This book is dedicated to my good friend and mentor,
Deborah K. Mayer, RN, PhD, AOCN®, FAAN, for her constant friendship
and encouraging challenges to my career as an oncology nurse.

And to my husband, Chuck Carpenter, for his endless support and belief in me.
And to my nephew, Aidan Joseph Brown, for reminding me that the future belongs
to those who dream.
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Management of the symptoms and problems that people experience as a result of cancer and its treatment is core to the role of oncology nurses. Advances in cancer treatment, including the advent of targeted therapies and personalized health care based on genetic profiles, have created new challenges in the field of symptom management. Moreover, in some cases, such as pain management, complex societal issues such as addiction, overdoses, and increased regulations have led to increased barriers to effective symptom management.

Management of symptoms is a problem the world over. In economically advanced countries, improved screening and early detection of cancer has resulted in higher cure rates. The growing population of cancer survivors, many of whom will live into old age, may experience lingering symptoms and develop new problems caused by delayed effects of cancer treatments. Yet paradoxically, as the burden of cancer has spread globally into low- and middle-income countries, many individuals still present with advanced disease and often die with unrelied symptoms. It is essential for nurses around the world to have the knowledge and skills to optimally manage the multitude of symptoms and other problems that patients and their caregivers experience.

This second edition of *A Guide to Oncology Symptom Management* is a comprehensive, evidence-based resource to guide oncology nursing practice, education, and research. An impressive array of well-qualified clinical and research experts have contributed to 25 chapters, each addressing a particular symptom, such as pain or fatigue, or an area of impact, such as spirituality or electrolyte imbalances. The text is holistic, addressing a range of common concerns—physical, emotional, social, and spiritual. Some chapters address specific populations that may have unique symptom experiences, including older adults and caregivers. New to this edition are chapters that address management of symptoms at the end of life, family caregiver burden, and distress. The latter is most timely, given new standards related to distress screening and management from the American College of Surgeons Commission on Cancer. Of particular note is the inclusion of emerging data related to the genomics of certain symptom phenotypes, for example, anticipatory nausea and vomiting.

All chapters are organized to consistently provide

- Definitions of relevant constructs and inclusion of useful theoretical perspectives
- A review of pathophysiology and etiology related to cancer and specific treatments
- A framework for symptom assessment, including diagnostic criteria
- An evidence-based review of pharmacologic and nonpharmacologic management
- Delineation of the expected outcomes
- Recommendations for future research.

In addition, the authors have provided a case study, patient teaching points, and links to useful resources, such as clinical practice guidelines, Oncology Nursing Society (ONS) Putting Evidence Into Practice (PEP) evidence reviews, and resources for patient teaching.
The text will be particularly beneficial to oncology clinicians, as it guides assessment, diagnosis, intervention, and patient and family teaching using an up-to-date, evidence-based, practical approach. Educators also will find useful tools, such as the case studies, to aid in teaching of nursing students at both undergraduate and graduate levels. The well-organized and thorough text is impressive in synthesizing the current state of our clinical and research knowledge related to caring for individuals with cancer and their caregivers and proposing directions for future inquiry. These features will be immensely valuable to novices and experienced nurse scientists.

This new resource from ONS advances the organization’s sustained and successful efforts to improve the quality of cancer care through providing evidence-based resources to oncology nurses. In the Foreword to the first edition, Dr. Dana Rutledge summarized this history, describing the evolution of ONS evidence-based initiatives, beginning with the Fatigue Initiative Through Research and Education (FIRE®), the subsequent Priority Symptom Management (PRISM) project, the development of the online Evidence-Based Practice Resource Area in 2002, and creation of a definition of oncology nursing-sensitive patient outcomes and an organizing framework, all culminating in the ONS PEP project. “Each sponsored effort has involved delineation of the current state of the knowledge on particular oncology-related topics and subsequently has supported education programs for oncology nurses and the public” (Rutledge, 2010, pp. xiii–xiv).

Since 2010, ONS has mobilized more than 175 national and international volunteer members to update the PEP evidence-based reviews of more than 450 discrete interventions. ONS is committed to more effectively disseminating this important work via a newly redesigned website (www.ons.org/practice-resources/pep) and publication of journal articles and books.

In the past five years, the ONS Quality Measures Initiative has built upon this foundational work. In collaboration with the Joint Commission and funded by the National Philanthropic Trust’s Breast Cancer Fund, ONS has developed and tested two sets of quality measures that address assessment and intervention for key symptoms (pain, fatigue, nausea and vomiting, sleep-wake disturbances, anxiety, depression, bone health risk, lymphedema, peripheral neuropathy, and menopausal symptoms) experienced by women with breast cancer during and following cancer treatment. Other components of the campaign included oncology nurse educational programs related to quality and a collaborative of participating organizations sharing their improvement experiences through communities of practice. The current ONS strategic plan focuses on dissemination and implementation of these measures, including collaboration with partner organizations (ONS, n.d.).

In summary, the new edition of *A Guide to Oncology Symptom Management* is a must-have resource for oncology nurse clinicians, educators, and scientists. Readers will find valuable and relevant information and tools to inform their efforts to improve the quality of care for individuals with cancer and their caregivers.

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Even with all of the progress being made in cancer symptom management and evidence-based practice, some patients with cancer still suffer distress in their symptom experience. Additionally, new patients are diagnosed every day and will experience new symptoms either from cancer or its treatment. While our care for patients with cancer has improved, many still grapple with symptoms such as pain, nausea, and mucositis. We know that very few patients experience just one symptom; usually patients have two or more symptoms, which often makes it even more difficult to establish good symptom control. Think about the patient who has nausea, pain, anxiety, depression, and distress from this compilation of symptoms.

In some instances, adequate interventions such as medications or other treatments are available that can alleviate or lessen those symptoms, but for whatever reason, sometimes patients suffer needlessly. As an example, treatment of cancer pain is greatly improved over the last decade, but some nurses and other healthcare providers for numerous reasons provide less than adequate pain management. Much literature has been conducted about the barriers to effective pain management, yet some patients still have unmanaged pain. Although we have made tremendous progress in the evidence-based management of symptoms, frankly, we can do better!

The second edition of this book rose out of that desire for us to do better for patients needing symptom management. In this new edition, the authors have improved upon the knowledge provided in the original chapters. For example, given the increased number of skin alterations deriving from many of the target-specific medications as a part of cancer treatment, information in that chapter has been expanded and includes additional photographs to aid in identification of these reactions. In addition, new chapters have been added in symptom management at the end of life, symptom distress, and caregiver burden. The ultimate goal of this textbook is to present an evidence-based practice approach to the management of many symptoms provided in an accessible yet comprehensible format.

This book is dedicated to every patient who has or will experience one or more symptoms related to cancer and to those incredible oncology nurses who care for them so expertly. I’ve cared for thousands of patients with cancer in my 25 years as an oncology nurse, and their journeys remind us all of the work that needs to be done. Perhaps someday a book like this will no longer be necessary. Until that day, we will continue to work tirelessly to care for patients and families with cancer and to alleviate or lessen all associated symptoms.

A special thanks to Amy Nicoletti, Lisa George, Judy Holmes, John Zaphyr, and all of the publishing staff at the Oncology Nursing Society. And a warm thank you to the amazing authors of these chapters who worked to bring this textbook to fruition.

Carlton G. Brown, PhD, RN, AOCN®, FAAN
Chapter 1

Age-Related Challenges in Symptom Management

Cheryl Lacasse, MS, RN, OCN®

Case Study

M.F. is a 73-year-old man with recurrent colorectal cancer with metastases to the small bowel, liver, lungs, and thoracic spine. He is admitted for pneumonia in the right lower and middle lobe with pleural effusion. His medical history includes osteoarthritis diagnosed 12 years ago, cardiovascular disease (hypertension and congestive heart failure after a myocardial infarction two years ago), type 2 diabetes diagnosed seven years ago, and postoperative deep vein thrombosis after a colectomy. Past cancer history includes prostate cancer diagnosed three years ago, treated with radical retroperitoneal prostatectomy with lymph node dissection and follow-up radiation therapy, and colon cancer diagnosed four months ago, treated with a total colectomy. He is currently receiving oxaliplatin and 5-fluorouracil, but his treatment has been complicated by bone marrow suppression and altered nutrition. Current medications include ceftriaxone IV, gentamicin IV, prednisone for five days, digoxin, furosemide, potassium chloride, lisinopril, atenolol, Humalog® insulin subcutaneous injection on a sliding scale, citalopram, vitamin K, and a multivitamin. Medications prescribed as needed include acetaminophen, hydrocodone and acetaminophen combination, albuterol nebulizers, and ibuprofen. A comprehensive symptom assessment reveals achy pain in the thoracic and lumbar spine area rated as a 7 on a 0–10 pain scale, an occasional sharp pain in his right knee, headache, nausea, dyspnea on exertion, sharp pain with inspiration, fatigue rated as a 6 on a 0–10 scale, insomnia, petechiae on the abdomen and lower extremities, anorexia with a 30-pound weight loss since the diagnosis of colon cancer, and sadness because of the diagnosis, disease progression, and loss of previous good health and active lifestyle. M.F. has been married for 47 years, and his wife is his primary caregiver and has several comorbidities herself.

Overview

Adults age 60 and older account for an estimated 60% of all cancer survivors in the United States (American Cancer Society, 2014). It is projected that by 2030, 20% of the U.S. popula-
tion will be age 65 and older as the baby boomer generation ages (Federal Interagency Forum on Aging-Related Statistics, 2012). The group of older adults age 85 and older is projected to grow rapidly after 2030 as the baby boomers enter the oldest-old population group (Federal Interagency Forum on Aging-Related Statistics, 2012). Older adults are one of the most vulnerable and rapidly growing populations of cancer survivors. More than three-quarters of all cancers are diagnosed in individuals age 55 and older (Howlader et al., 2014). Cancer and heart disease are the leading causes of death in adults age 40 and older (Siegel, Ma, Zou, & Jemal, 2014). Men age 70 and older have a one-in-three probability of developing cancer, with the most common cancers being prostate, lung and bronchus, colon and rectum, and urinary bladder (Siegel et al., 2014). Women age 70 and older have a one-in-four chance of developing cancer, with the most common cancers being breast, lung and bronchus, colon and rectum, and uterine (Siegel et al., 2014). Many issues are unique to the aging population and may have an overall effect on symptom management in this population. These include the changes of normal aging; common health issues in the aging population such as chronic illnesses, frailty, and polypharmacy; and complex symptom relationships, which include groups of symptoms attributed to aging and chronic illness.

Normal Aging

Many individuals age 65 and older experience normal physiologic changes that may affect the recognition of cancer-related symptoms (Tabloski, 2014). Table 1-1 includes normal physiologic changes of aging and considerations for symptom assessment and management in older adults. Aging skin has thinner layers because of the loss of cutaneous and subcutaneous tissue, fewer blood vessels and nerves, and less elasticity. Bone loss is a common occurrence in aging individuals and may result from altered calcium metabolism. Loss of soft tissue function, including muscle atrophy and slowing of the nervous system, may affect overall physical functioning and independence. Sensory loss and altered cognitive functioning may have an impact on overall functioning and successful pharmacologic and nonpharmacologic symptom management modalities.

An altered hematopoietic system in older adults may lead to a delayed response of bone marrow to therapy-induced bone marrow suppression and may increase the risk of infection and anemia (Tabloski, 2014). Older adults may have altered production and metabolism of intrinsic factor and iron. Alterations in the cardiopulmonary system may increase the adverse effects of symptom management medications. Alterations in the gastrointestinal system may affect multiple systems, such as vitamins D and B₁₂ and folic acid absorption; bowel elimination; and hepatic metabolism of pharmacologic agents (Tabloski, 2014). Changes in urinary elimination may have a major impact on drug metabolism via the kidneys, hydration status, and urinary continence. Cognitive changes usually are subtle and affect short-term memory acuity.

Common Health Issues in the Aging Population

Chronic Illnesses and Conditions

More than 75% of older cancer survivors have at least one chronic illness or condition at the time of cancer diagnosis (Deckx et al., 2012). About one-half of older cancer survivors may experience three or more comorbidities when compared to the general older adult
**TABLE 1-1  Physiologic Changes of Aging and Their Relationship to Symptom Management**

<table>
<thead>
<tr>
<th>Physiologic Change</th>
<th>Potential Impact on Symptom Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased cutaneous layers and thinned sub- cutaneous tissue</td>
<td>Can increase risk for effects of anorexia and cachexia</td>
</tr>
<tr>
<td>Decreased blood vessels</td>
<td>May alter absorption of transdermal medications; may decrease ability to use IV route for symptom management</td>
</tr>
</tbody>
</table>
| Decreased neurons and diminished nerve functioning | May alter pain sensation  
May increase sleep disturbances  
May decrease short-term memory and diminish coping abilities, leading to depression and mood disorders |
| Decreased elasticity                       | Increases risk for skin tears                                                                           |
| **Bones**                                 |                                                                                                        |
| Altered calcium metabolism leading to bone loss | Increases risk for bone instability with metastatic bone disease                                      |
| Tooth loss                                | Increases risk for malnutrition during therapy and subsequent nutrition-related symptoms such as anemia, mucous membrane and skin breakdown, and electrolyte disturbances |
| **Soft Tissue**                           |                                                                                                        |
| Muscle atrophy                            | Decreases strength and endurance, which may increase fatigue                                           |
| Nervous system slowing                     | Decreases fine motor control, which may have an impact on implementing symptom management strategies     |
| Increased body fat                        | May have an impact on drug metabolism                                                                    |
| **Sensory Loss**                          |                                                                                                        |
| Hearing                                   | May have an impact on communication of patient education information for symptom management               |
| Vision                                    | May have an impact on communication of patient education information for symptom management               |
| Smell and taste                           | May have an impact on successful treatment of anorexia or cachexia                                        |
| Touch                                     | May reduce the patient's ability to hold reading materials or turn pages; may also reduce ability to prepare healthy food for self or open medication bottles |
| **Hematology and Immunology**             |                                                                                                        |
| Decreased bone marrow reserve             | May have delayed response to infection and anemia                                                       |

*(Continued on next page)*
<table>
<thead>
<tr>
<th>Physiologic Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia related to decreased intrinsic factor production and decreased iron metabolism</td>
</tr>
<tr>
<td>Increased clotting caused by increased platelet adhesion</td>
</tr>
<tr>
<td><strong>Circulation</strong></td>
</tr>
<tr>
<td>Enlargement of heart</td>
</tr>
<tr>
<td>Slowling of electrical activity</td>
</tr>
<tr>
<td>Changes in collagen in arteries, causing stiffness and thickening</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
</tr>
<tr>
<td>Decreased oxygen and carbon dioxide exchange because of decreased elasticity of lung tissue and alveoli enlargement</td>
</tr>
<tr>
<td>Decreased cough reflex and ciliary function</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
</tr>
<tr>
<td>Decline in small intestinal absorption of vitamins D and B&lt;sub&gt;12&lt;/sub&gt; and folic acid</td>
</tr>
<tr>
<td>Thinning of intestinal lining, decreased mucus production, and weaker intestinal muscles</td>
</tr>
<tr>
<td>Diminished liver function because of circulatory and metabolic changes</td>
</tr>
<tr>
<td><strong>Urinary</strong></td>
</tr>
<tr>
<td>Decreased renal perfusion beginning at age 40</td>
</tr>
<tr>
<td>Decreased number of nephrons and glomeruli with decreased glomerular filtration rate</td>
</tr>
<tr>
<td>Decreased adaptability of kidneys to handle stress</td>
</tr>
<tr>
<td>Decreased bladder capacity and tone; decreased tone of pelvic floor</td>
</tr>
<tr>
<td><strong>Cognitive</strong></td>
</tr>
<tr>
<td>Decrease in short-term memory</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Potential Impact on Symptom Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>May contribute to cancer-related fatigue</td>
</tr>
<tr>
<td>May contribute to perfusion issues and lead to vague, noncancer-related symptoms</td>
</tr>
<tr>
<td>Caution should be used with symptom management drugs that may affect cardiac function, such as medications used for treating neuropathic pain.</td>
</tr>
<tr>
<td>Caution should be used with medications that have a direct effect on pulmonary functioning such as benzodiazepines or opioids.</td>
</tr>
<tr>
<td>May increase risk of decreased airway clearance</td>
</tr>
<tr>
<td>Increases risk for developing anemia and bone loss</td>
</tr>
<tr>
<td>Increases risk for constipation</td>
</tr>
<tr>
<td>May have an impact on drug metabolism by slowing drug metabolism and leading to increased drug toxicity</td>
</tr>
<tr>
<td>Increases risk for developing drug toxicity, especially with nonsteroidal anti-inflammatory drugs and diuretics</td>
</tr>
<tr>
<td>May increase risk for dehydration or fluid overload</td>
</tr>
<tr>
<td>Altered potassium regulation</td>
</tr>
<tr>
<td>May lead to urinary incontinence</td>
</tr>
<tr>
<td>Eventually leads to lower urinary tract symptoms</td>
</tr>
<tr>
<td>May decrease the patient's ability to remember details of symptom onset, duration, and treatment</td>
</tr>
</tbody>
</table>

Note. Based on information from Tabloski, 2014.
population (Mohile et al., 2011). The most prevalent chronic conditions found in older adults, in addition to cancer, are hypertension, arthritis, heart disease, diabetes, and chronic respiratory illnesses (Deckx et al., 2012; Federal Interagency Forum on Aging-Related Statistics, 2012). Cancer survivors commonly experience the following chronic diseases: diabetes, venous thrombosis, osteoporosis, chronic obstructive pulmonary disease, heart failure, dyslipidemia, hypothyroidism, obesity, and dementia (Deckx et al., 2012; Edgington & Morgan, 2011).

Individuals age 65 and older have trouble hearing (46% of men, 31% of women), trouble seeing (13% of men, 15% of women), and issues with dentition, with about 24% having no natural teeth (Federal Interagency Forum on Aging-Related Statistics, 2012). Comorbidities and their symptoms add to the complexity of cancer-related symptom identification and treatment. For example, an older adult with significant cardiac disease and lung cancer may have overlapping symptoms of chest pain, shortness of breath, fatigue, and cough, which may require simultaneous oncology- and cardiopulmonary-related treatments.

Older cancer survivors may correlate the “normal” symptom experience of cancer with aging or chronic illness, not with cancer or its treatment. The traditional retirement age (typically 65 years old) has been suggested to be a developmental marker for changes in symptom perception from abnormal to a normal expectation that comes with age (Williamson & Schulz, 1995). If symptoms are perceived to be part of the aging process or attributable to comorbidities, this altered symptom perception may obstruct the “normal signals” that would prompt a person to seek treatment. For example, an older adult experiencing chronic fatigue may attribute it to old age or heart disease, when in fact it is a serious symptom of chronic leukemia or multiple myeloma. Recently, Cheung, Le, Gagliese, and Zimmermann (2011) compared the reported symptom intensity of 1,358 outpatients with advanced cancer to determine age and gender differences. They found that adults age 61 and older did not experience clinically significant differences in symptom severity and symptom distress than those age 60 and younger, except for loss of appetite, which was increased in the older group (Cheung et al., 2011). Further research is needed to determine the factors that may influence symptom distress in older adults, such as the burden of multiple morbidities or polypharmacy.

In addition to redefining normal functioning within the context of aging and comorbidity, older adults may have a tendency toward a positive perception of their health. The Federal Interagency Forum on Aging Statistics (2012) reported that 76% of adults age 65 and older report their health as good to excellent. This positive perspective may be explained by the positivity effect, which is a preference for positive over negative perspectives during information processing about health, illness, and symptoms (Reed & Carstensen, 2012). When assessing symptoms of older adults using self-report, healthcare providers should determine the context of the symptom experience such as the perception of a person’s overall health and wellness, actual physical functioning, impact of symptoms on daily life, and normalization of symptoms due to age or chronic illness. Further research is needed to determine if older adults perceive symptoms the same way as younger populations.

**Polypharmacy**

Polypharmacy generally refers to the use of multiple medications to treat health-related conditions; however, multiple definitions are used in the literature (Maggiore, Gross, & Hurria, 2010). Maggiore et al. (2010) listed several dimensions that are integrated into the definition of polypharmacy, including increased number of medications, potentially inappropriate medications, and medication underuse and duplication. A study of 975 community-dwelling women age 65 and older found a mean of 3.9 prescription medications used per person, 1.9
over-the-counter medications being taken used per person, and an 8% increase in the number of medications taken per each additional illness diagnosis. Cancer was associated with a 13% increase in medication use (Crentsil, Ricks, Xue, & Fried, 2010). Many factors contribute to the cause of polypharmacy, including (a) multiple chronic conditions, (b) age-related physiologic changes, (c) lack of knowledge about the use of multiple medications, (d) increased use of complementary therapies, (e) self-medication with over-the-counter medications, (f) recommended treatment guidelines, (g) hospitalization for acute illness, and (h) use of multiple healthcare providers (Maggiore et al., 2010; Sergi, De Rui, Sarti, & Manzato, 2011). The issue of polypharmacy has major implications with regard to the use of pharmacologic and herbal methods of symptom management in older cancer survivors.

Adverse drug reactions are a concern with older adults with multiple chronic conditions and symptoms who are taking multiple medications. For example, an 82-year-old with metastatic breast cancer, hypertension, congestive heart failure, and gastroesophageal reflux disease may be on multiple medications to manage her chronic conditions and their symptoms, such as multiple antihypertensives, a proton pump inhibitor, a diuretic, and oral chemotherapy. Pain management that includes a nonsteroidal anti-inflammatory drug may be contraindicated because of the risk for increased gastrointestinal irritation, increased risk of renal toxicity, and altered therapeutic effect of antihypertensives. Generally, the potential for an individual to have adverse drug reactions increases with the number of medications taken.

Budnitz and colleagues studied emergency department visits of older adults age 65 and older who had a diagnosis of adverse drug reactions (Budnitz, Lovegrove, Shehab, & Richards, 2011). Of those studied, 48.1% were age 80 or older. This study found that 54.8% of patients requiring hospitalization were taking more than five different medications. The medications found to cause the highest likelihood of adverse drug reactions leading to an emergency department visit were antineoplastic agents (51%), hematologic agents such as warfarin and antiplatelet drugs (44.6%), cardiovascular drugs (42.3%), and endocrine-related drugs such as insulin and oral hypoglycemic agents (42.1%).

Older adults taking multiple drugs are at increased risk for adverse drug reactions, which have an atypical presentation described by many patients as “feeling off.” Often these adverse drug reactions present as changes in functional status (activities of daily living, instrumental activities of daily living), mental status changes, or falls (Pretorius, Gataric, Swedlund, & Miller, 2013). One approach that may be helpful in assessing and planning future management of older adults with multiple drug therapies and the need for symptom control is the ARMOR (Assess, Review, Minimize, Optimize, and Reassess) tool. This tool uses a stepwise approach to working with older adults who are taking nine or more medications and are at high risk for adverse drug events (Haque, 2009).

In addition to adverse drug reactions, many negative outcomes may result from polypharmacy, including drug-drug or drug-food interactions that either enhance a drug’s potency or diminish its therapeutic effect, thus leading to further symptoms (Nobili, Garattini, & Mannucci, 2011). Multiple drugs may cause a cumulative toxic effect on the chemoreceptor trigger zone, leading to nausea, vomiting, and altered nutritional intake (Tracy & Morrison, 2013). Another complication of polypharmacy is the increased prevalence of poor adherence to a pharmacologic regimen (Nobili et al., 2011).

**Frailty**

Older adults with cancer and multiple medical illnesses may experience loss of organ function, decrease in physical function reserve, and overall health decline. The term *frail elders* has been applied to older populations who have decreased physical, cognitive, and social
functioning leading to overall disability (Anderson, 2010; Golden, Martin, da Silva, & Roos, 2011). Frailty has been defined as a multidimensional phenomenon that includes a decline in daily physical functioning, imbalanced nutrition, cognitive decline, and sensory impairment (Ferrucci et al., 2003; Strawbridge, Shema, Balfour, Higby, & Kaplan, 1998). The concept of frailty may be defined as a clinical syndrome that includes the following characteristics: decreased physiologic and psychological homeostasis, chronic malnutrition (unintentional weight loss of 10 pounds or more in the past year, self-report of exhaustion, weakness), and sarcopenia (leading to slow walking speed and minimal physical activity) (Fried et al., 2001; Rodríguez-Mañas et al., 2013). Using a comprehensive geriatric assessment (CGA) tool to screen for frailty in the older adult oncology population may yield valuable information for healthcare providers to use when making treatment-related decisions (Pal, Katheria, & Hurria, 2010). Symptom assessment and management in the frail elder population is challenging and requires careful consideration of appropriate pharmacologic and nonpharmacologic approaches and their overall impact on patient functioning and quality of life.

Cancer-Related Symptom Issues

Assessment

Because most cancers occur in the older adult population, symptom assessment needs to include a broad approach, as members of this population are likely to have complex medical histories that include multiple chronic illnesses with concurrent symptoms and their treatments (Howlader et al., 2014). The presence of oncology-related symptoms should be explored in context with patients’ medical and surgical histories and current medical and surgical treatments.

A recent systematic review of 83 articles addressing the use of geriatric assessment in the oncology setting suggested that a multidisciplinary CGA is instrumental in collecting valuable data for determining specific clinical interventions and their practical outcome endpoints for older cancer survivors (Puts et al., 2012). Typically, a CGA includes a medical history, physical and cognitive functional assessment (focused on activities of daily living, instrumental activities of daily living, and sensory function), psychological and social functioning, socioeconomic environment, nutrition, and polypharmacy (Ellis, Whitehead, O’Neill, Langhorne, & Robinson, 2011; Tabloski, 2014). The CGA screens older cancer survivors for the presence of geriatric syndromes, including pressure sores, sensory impairment, history of falls, incontinence, delirium, depression, dementia, and functional decline (Mohile et al., 2011; Puts et al., 2012; Tabloski, 2014). Commonly used CGA screening tools are listed in Table 1-2 and can be found online at the Hartford Institute for Geriatric Nursing’s ConsultGeriRN website (www.consultgerirn.org/resources), which provides evidence-based online resources for nurses to enhance the clinical care of the older adult population with a variety of complex needs.

Heidrich, Egan, Hengudomsub, and Randolph (2006) studied symptoms, beliefs about symptoms, and quality of life in older breast cancer survivors (n = 18) compared to older women without breast cancer (n = 24). Women in both groups reported more than 10 symptoms, and no significant difference was noted between cancer survivors and those with no history of cancer. Study results indicate that all participants reporting symptoms mostly attributed their symptoms to aging and chronic health problems. Symptoms most frequently attributed to aging included memory problems (69%), decreased sex drive (35.7%), fatigue (33.3%), stiffness (28.6%), poor hearing (26.2%), and hair thinning (26.2%). Symptoms most fre-
Commonly attributed to chronic illness included pain (45.2%), joint pain (40.5%), stiffness (26.2%), and aching (26.2%). Individuals who did not know the cause of their symptoms had poorer social functioning ($r = -0.33$), poorer mental health (depression [$r = 0.45$] and anxiety [$r = 0.38$]), increased fatigue ($r = -0.35$), and decreased purpose in life ($r = -0.42$). This study suggested that broad symptom assessment and CGA may be important for planning comprehensive symptom management in older cancer survivors (Heidrich et al., 2006).

In a review of adult cancer survivors, Ganz (2009) suggested that symptoms in older cancer survivors may be multicausal and include late effects of surgical intervention, chemotherapy, radiation, and hormonal therapy and preexisting and post-treatment comorbidities. A study of 863 long-term cancer survivors by Zucca, Boyes, Linden, and Girgis (2012) assessed the quality of life and clusters of patient-reported symptoms in cancer survivors five to six years after diagnosis. Seventy-three percent of the study population was age 50 or older and included survivors of mostly breast, prostate, and large bowel cancers and melanoma of the skin who had received multimodality cancer treatments. Although 18% of survivors reported two or more symptoms in the past month, the reported symptoms formed a cluster including fatigue, insomnia, cognitive impairment, pain, dyspnea, loss of appetite, and gastrointestinal symptoms. The results of this study suggest that many symptoms experienced beyond cancer treatment may be attributed to noncancer-related comorbidities and aging. Clinicians must consider the symptoms of chronic illnesses, the primary cancer, and treat-

<table>
<thead>
<tr>
<th>Focus of Assessment</th>
<th>Assessment Tools</th>
</tr>
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<tbody>
<tr>
<td>Caregiver burden</td>
<td>Caregiver Strain Index*</td>
</tr>
<tr>
<td>Cognitive</td>
<td>The Mini-Cog*</td>
</tr>
<tr>
<td></td>
<td>Confusion Assessment Method*</td>
</tr>
<tr>
<td></td>
<td>Mini-Mental State Examination</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Number of comorbid conditions</td>
</tr>
<tr>
<td></td>
<td>Charlson Comorbidity Index</td>
</tr>
<tr>
<td>Elder abuse</td>
<td>Elder Mistreatment Assessment*</td>
</tr>
<tr>
<td>Falls</td>
<td>Hendrich II Fall Risk Model*</td>
</tr>
<tr>
<td>Incontinence</td>
<td>Urinary Incontinence Assessment*</td>
</tr>
<tr>
<td>Independent living skills</td>
<td>Lawton Instrumental Activities of Daily Living*</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Mini Nutritional Assessment*</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>Chart review and medication count</td>
</tr>
<tr>
<td>Psychological</td>
<td>Geriatric Depression Scale*</td>
</tr>
<tr>
<td>Physical</td>
<td>Katz Index of Independence in Activities of Daily Living*</td>
</tr>
<tr>
<td>Skin breakdown</td>
<td>Braden Scale*</td>
</tr>
</tbody>
</table>

* These tools are available with a brief description on the “Try This: Best Practices in Nursing Care to Older Adults” website (http://www.consultgerirn.org/resources), by the Hartford Institute for Geriatric Nursing, New York University College of Nursing.

Note. Based on information from Hartford Institute for Geriatric Nursing, n.d.; National Comprehensive Cancer Network, 2014b; Puts et al., 2012.
ments when performing a comprehensive symptom assessment on older adults. Oncology nurses have the opportunity to detect potential cancers or cancer-related complications in older adults by recognizing that symptoms may be intertwined with chronic illness and perceived changes of normal aging.

Oncology nurses can provide comprehensive symptom assessment and assess older survivors’ perceptions regarding potential causes of symptoms. That data can identify valuable information on which to base a patient-centered symptom management plan.

**Symptom Perception**

Symptoms in older adults may be complex in origin, and symptom perception of chronic illness, presenting symptoms of cancer, symptoms of disease exacerbation, and symptoms caused by treatment of disease may be blurred. Table 1-3 lists presenting symptoms of the most common cancers in older adults and common chronic conditions in older adults that have overlapping symptoms. Bender et al. (2008) suggested that symptom clusters (discussed in the following section) in older adults may be unique to chronic health problems and comorbidities within the context of the cancer experience.

**Symptoms and Their Relationships**

Researchers have explored the relationships among symptoms, referred to as symptom clusters, including pain and fatigue, physical functioning, psychological and social well-being, and depression in older adults. Molassiotis, Wengström, and Kearney (2010) defined a symptom cluster as having the following characteristics: (a) the cluster has two or more symptoms that are related to each other at a given time, (b) symptoms occur together and share a significant variance with their cluster, (c) core symptoms within the cluster are stable over time, and (d) nondefining symptoms may be part of the cluster episodically based on the population and associated clusters. For example, an older adult cancer survivor experiencing a symptom cluster of pain, fatigue, insomnia, and anorexia that persists nine months after multimodal cancer may experience additional symptoms including decreased physical functioning, depression, anxiety, and spiritual distress that may be related, in part, to several comorbidities. Bellury et al. (2013) found that in older breast cancer survivors, multiple comorbidities (r = 0.45) and high levels of symptom bother (r = -0.49) were significantly related to decreased physical functioning. The implications for nursing symptom management include focusing on symptoms that have a negative impact on physical functioning, such as pain or fatigue, and current comorbidities and treatments; using client-centered goal setting to plan care; and critically evaluating the impact of symptom management strategies on patients’ quality of life. Exploration of symptom clusters in individuals with chronic diseases and cancer may further illuminate the complexity of symptoms in older adults with multiple chronic illnesses.

The symptom of pain is well studied in the older adult population. The pain experience for older adults with cancer includes physiologic, psychological, spiritual, affective, and contextual dimensions and requires careful assessment (Molton & Terrill, 2014). The contextual meaning of pain includes sociocultural values and beliefs and perceptions of disease (both cancer and other chronic illnesses) (Molton & Terrill, 2014). Hadjistavropoulos et al. (2007) conducted an interdisciplinary review of pain assessment in older adults and reported a comprehensive consensus statement including recommendations for physical evaluation, use of self-report, assessment of older adults with dementia, functional status evaluation, emotional functioning evaluation, and medication history. This multidisciplinary group represented medicine, nursing, pharmacy, psychology, occupational therapy, physiotherapy, neurology,
and gerontology. They provided a critical review of the most common assessment tools in pain management of older adults and suggested that the patient’s ability to report pain is an important factor in selecting a pain assessment method and tool (Hadjistavropoulos et al., 2007). Figure 1-1 presents a summary of these recommendations.

Scientific knowledge has begun to expand the understanding of differences in pain perception between younger and older individuals. Farrell (2012) suggested that pain perception may be affected by changes that occur in the normally aging brain, such as loss of brain...
volume in the prefrontal cortex and the hippocampus. In addition, pain perception may be altered because of reduced functioning of dopaminergic neurons in the basal ganglia (Farrell, 2012). Emerging evidence suggests that older people may have altered pain sensitivity, are less tolerant of pain, and may experience pain due to tissue injury for a longer period of time (Farrell, 2012). Oncology nurses need to carefully assess the current pain of older adults within the context of physiologic age and condition and general pain experience. Pain has been studied in relationship to other cancer-related symptoms, including fatigue and depression (Geerlings, Twisk, Beekman, Deeg, & van Tilburg, 2002; Kurtz, Kurtz, Stommel, Given, & Given, 2001), and fatigue (Bennett, Stewart, Kayser-Jones, & Glaser, 2002; Given, Given, Azzouz, Kozachik, & Stommel, 2001; Hodgson & Given, 2004), along with their contribution to decline in physical functioning.

### Evidence-Based Interventions

#### Pharmacologic Management

Pharmacologic intervention for symptom management in older adults with cancer requires the consideration of current health status, including physical and mental functioning, and the medical treatment regimen. For example, a 78-year-old with metastatic colon cancer to the liver and a history of stroke and multi-infarct dementia may be challenging to assess for symptom presence and distress, treat with appropriate medications for symptom control, and then evaluate as to the outcome of the symptom management. Clinicians should take care to avoid the use of medications that may cause severe toxicities in older adults. The American Geriatrics Society (AGS) convened an interdisciplinary panel of nationally recognized experts in geriatric care, clinical pharmacology, and psychopharmacology to reach a consensus about potentially inappropriate medications for older adults (AGS 2012 Beers Cri-
teredia Update Expert Panel, 2012). These consensus data were used to revise one of the current tools, the Beers Criteria, which guides care providers when prescribing medications for adults age 65 and older.

Table 1-4 displays a comprehensive list of medications and their potential toxicities related to oncology symptom management in the older adult population. When determining the appropriate pharmacologic management for cancer-related symptoms in older adults, clinicians should consider the individual’s clinical condition, functional status (both physical and cognitive), current comprehensive drug list (both oncology-related and general), and overall prognosis (AGS 2012 Beers Criteria Update Expert Panel, 2012).

Symptoms in older adults can be managed effectively with conservative pharmacologic therapies (Nobili et al., 2011). Adult dosing of medications is generally safe for older adults, but clinicians must seriously consider the patient’s size, nutritional status (e.g., serum albumin level, as some drugs are protein bound), renal and hepatic function, lifestyle and life responsibilities, and economic issues. The general rule of “start low and go slow” with regard to dosing of symptom management medications is especially important in the older adult population. Comprehensive evidence-based clinical guidelines for treating older adults with cancer and complex symptoms such as pain are available to clinicians and can assist in critical clinical decision making about the application of symptom management strategies (AGS Panel on the Pharmacological Management of Persistent Pain in Older Persons, 2009; National Comprehensive Cancer Network®, 2014b).

Two additional tools are available to safely treat symptoms in older cancer survivors. The Screening Tool of Older Persons’ Prescriptions (STOPP) criteria provides detailed assessment criteria, using a physiologic systems approach, to determine potentially inappropriate medications within the context of chronic illness and its treatment (Gallagher & O’Mahony, 2008; Pretorius et al., 2013; Ryan, O’Mahony, Kennedy, Weedle, & Byrne, 2009). The Screening Tool to Alert doctors to the Right Treatment (START) criteria (Barry, Gallagher, Ryan, & O’Mahony, 2007) uses a systems approach to the assessment of delivery of appropriate treatments for com-

### TABLE 1-4 Potentially Inappropriate Symptom Management Medications for Older Adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potential Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonopioid Analgesics</strong></td>
<td></td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs (NSAIDs)</td>
<td>May cause or exacerbate gastric or duodenal ulcers*</td>
</tr>
<tr>
<td></td>
<td>Prolonged clotting time and international normalized ratio*</td>
</tr>
<tr>
<td></td>
<td>Decreased platelet function*</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Central nervous system (CNS) effects (highest of all NSAIDs)*</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Asymptomatic gastrointestinal conditions*</td>
</tr>
<tr>
<td>Aspirin (&gt; 325 mg)</td>
<td>Asymptomatic gastrointestinal conditions*</td>
</tr>
<tr>
<td></td>
<td>Decreased platelet function</td>
</tr>
<tr>
<td></td>
<td>May cause or exacerbate gastric or duodenal ulcers*</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Gastrointestinal bleeding*</td>
</tr>
<tr>
<td></td>
<td>Renal failure*</td>
</tr>
<tr>
<td></td>
<td>High blood pressure*</td>
</tr>
<tr>
<td></td>
<td>Heart failure*</td>
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</tbody>
</table>

(Continued on next page)
### TABLE 1-4 Potentially Inappropriate Symptom Management Medications for Older Adults (Continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potential Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioids</strong></td>
<td></td>
</tr>
<tr>
<td>Meperidine</td>
<td>Intense side effect profile for adverse effects; most critical in individuals with renal compromise*&lt;br&gt;CNS effects such as seizures</td>
</tr>
<tr>
<td>Morphine, hydromorphone, fentanyl</td>
<td>Intense side effect profile at higher doses, especially CNS effects such as somnolence, respiratory depression, and delirium*</td>
</tr>
<tr>
<td><strong>Adjuvant Drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Muscle relaxants (methocarbamol, carisoprodol, chlorzoxazone, metaxalone, cyclobenzaprine, baclofen)</td>
<td>Anticholinergic effects†&lt;br&gt;Sedation*&lt;br&gt;Weakness*&lt;br&gt;Cognitive impairment*</td>
</tr>
<tr>
<td>Tricyclic antidepressants (amitriptyline and amitriptyline compounds, doxepin)</td>
<td>Strong anticholinergic effects†&lt;br&gt;May lead to ataxia, impaired psychomotor function, syncope, and falls&lt;br&gt;Cardiac arrhythmias (QT interval changes)<em>&lt;br&gt;May produce polyuria or lead to urinary incontinence</em>&lt;br&gt;May exacerbate chronic constipation</td>
</tr>
<tr>
<td>Antihistamines (diphenhydramine, hydroxyzine, promethazine)</td>
<td>Potent anticholinergic properties†&lt;br&gt;May lead to confusion and sedation</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Increased sensitivity at higher doses with prolonged sedation and increased risk for falls</td>
</tr>
<tr>
<td>• Short-acting (lorazepam ≥ 3 mg, oxazepam ≥ 60 mg, alprazolam ≥ 2 mg)</td>
<td>May produce or exacerbate depression&lt;br&gt;Smaller doses may be both effective and safer.</td>
</tr>
<tr>
<td>• Long-acting (diazepam)</td>
<td>CNS effects*&lt;br&gt;May cause or exacerbate respiratory depression in chronic obstructive pulmonary disease*&lt;br&gt;May produce polyuria or lead to urinary incontinence*</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitor antidepressants (fluoxetine, citalopram, paroxetine, sertraline)</td>
<td>May produce CNS stimulation, sleep disturbances, and increased agitation*&lt;br&gt;May exacerbate or cause syndrome of inappropriate secretion of antidiuretic hormone or hyponatremia</td>
</tr>
<tr>
<td>Decongestants</td>
<td>High level of CNS stimulation, which may lead to insomnia*</td>
</tr>
<tr>
<td>CNS stimulants (methylphenidate)</td>
<td>Altered CNS function, leading to cognitive impairment*&lt;br&gt;Appetite-suppressing effect*</td>
</tr>
</tbody>
</table>

*High severity rating<br>† Anticholinergic effects include some of the following symptoms: blurred vision, constipation, drowsiness, sedation, dry mouth, tachycardia, urinary retention, confusion, disorientation, memory impairment, dizziness, nausea, nervousness, agitation, anxiety, facial flushing, weakness, and delirium.

mon chronic illnesses and conditions based on best treatment practices (Pretorius et al., 2013; Ryan et al., 2009). The combined use of the Beers criteria (AGS 2012 Beers Criteria Update Expert Panel, 2012) and the STOPP (Gallagher & O’Mahony, 2008) and START (Barry et al., 2007) criteria can assist clinicians in safely managing complex symptoms in older cancer survivors while balancing pharmacologic treatment for multiple comorbidities (O’Mahony et al., 2010).

**Nonpharmacologic Management**

Many of the nonpharmacologic techniques generally used for cancer symptom management can be used with the older adult population. Clinicians must adapt these interventions to the physical and cognitive limitations of patients and their individualized responses. Physical activity (exercise and strength training) is one evidence-based intervention that is effective in many chronic illness populations and in older adults with cancer (Speck, Courneya, Mâsse, Duval, & Schmitz, 2010). A systematic review and meta-analysis of 60 studies was conducted to determine the extent of effectiveness of physical activity on improved healthcare outcomes of cancer survivors during and after treatment (Speck et al., 2010). Increased physical activity in cancer survivors was found to have a positive small to moderate effect on upper (r = 0.99) and lower (r = 0.90) body strength, fatigue (r = 0.54), and general symptoms (r = 0.30). This suggests that increased physical activity may be an important nonpharmacologic intervention for managing symptoms in older cancer survivors and improving overall healthy aging. The conclusions from this review support an earlier integrative review on the impact of physical activity on older adults with cancer and comorbidity, which found that physical activity interventions decrease fatigue, elevate mood, improve physical functioning, decrease role limitations, decrease falls, and modify cardiovascular risk factors (Penedo, Schneiderman, Dahn, & Gonzalez, 2004).

Integrative therapies such as acupuncture, acupressure, Tai Chi, yoga, and Qigong also have been reported to have a positive effect on symptoms in older cancer survivors. A recent review of current literature examined the treatment of cancer-related stress with complementary and alternative medicine such as tailored exercise, Tai Chi Chuan, and yoga (Chandwani et al., 2012). The review concluded that carefully tailored exercise, Tai Chi Chaun, and yoga may have a positive effect on the physical and mental health of older cancer survivors by improving their physical strength and balance, mood, and overall quality of life. Campo et al. (2014) conducted a 12-week randomized controlled trial to study the feasibility of using Qigong to improve fatigue and distress levels in 40 older prostate cancer survivors. The results of this study demonstrated significant improvement of fatigue levels and distress levels in the Qigong group (69%) versus the comparison group (31%), who did stretching only. Further research is needed to determine the overall impact of integrative therapies on older adults across the cancer survivorship continuum.

Older adults are reported to use multiple nonpharmacologic methods to control pain, and many perceive these therapies to be effective in managing their pain (Barry, Gill, Kerns, & Reid, 2005; Jakobsson, Hallberg, & Westergren, 2004). Frequently used nonpharmacologic techniques include physical therapies (heat, massage, stretching, muscle release), cognitive behavioral therapies (distraction, imagery, relaxation exercises), assistive devices (canes, walkers, raised toilet seats and chairs, large-grip utensils), and complementary therapies (therapeutic touch, music therapy, exercise, reminiscence therapy) (AGS Panel on the Pharmacological Management of Persistent Pain in Older Persons, 2009; Barry et al., 2005; Coyle & Derby, 2006; Jakobsson et al., 2004). Many of these techniques may be used for the management of other cancer-related symptoms, such as fatigue, depression, anxiety, and functional decline; however, current evidence for use of these interventions in the older adult cancer population is minimal.
Expected Patient Outcomes

Quality symptom management is key to enhancing the overall quality of life and optimal functioning of older adults with cancer-related symptoms. General cancer symptom management principles may be safely applied to the gero-oncology population using a multidisciplinary team approach with careful consideration of the physiologic changes of aging. The incorporation of an abbreviated CGA for all individuals with cancer who are age 65 and older may provide valuable insights into the most appropriate holistic symptom management to implement. Having general knowledge of the normal changes that occur with aging may assist members of the healthcare team to be more vigilant in assessing for positive and negative patient responses to therapy. This knowledge will aid in the planning and implementation of age-specific education about symptom management therapies. Maintaining a caring partnership with older adults with cancer and their families will provide the best possible symptom management outcomes and will lead to higher levels of functioning and better overall quality of life.

Need for Future Research

Clinical research on symptom management interventions for older adults with cancer is sparse, and studies need to be done to examine the symptoms of older cancer survivors with multiple chronic illnesses. Generally, symptoms that are common in the oncology population are also common in the older adult population, but more research is needed regarding the appropriate assessment of symptoms, prevalence of these symptoms, distress and intensity of symptoms, overlap with common symptoms in chronic illness, and symptom management within the older population.

Conclusion of Case Study

The nurse conducts a screening of the functional status of M.F., which indicates that he is at risk for functional decline because of symptoms related to cancer and other comorbidities, nutritional deficits, chemotherapy-related bone marrow depression, and reactive depression. The patient is currently at risk for falls due to spine pain and its effect on safe movement and skin breakdown due to nutritional deficits, diabetes, and prednisone therapy. An assessment of laboratory values reveals decreased renal and hepatic function beyond the expected decline with aging and chemotherapy-induced pancytopenia. Functional decline may be the most important factor in achieving optimal symptom control. M.F. clearly verbalizes that quality of life is more important than quantity of life. He defines quality of life as having enough symptom control to have clear thinking and spend time with his close friends and family.

Collaborative goal setting is a key component in achieving optimal symptom management outcomes, which is defined by the patient as quality of life. Pharmacologic management requires careful consideration of comorbidities and drug-drug interactions with cardiac, pulmonary, arthritis, diabetes, and pneumonia-related medications. The symptom of pain may be the most challenging to treat because there are multiple sources of pain caused by the cancer and acute and chronic illnesses. Although acetaminophen is the drug of choice for pain management in older adults, this patient reports significant pain, which
Ibuprofen may be the drug of choice for bone pain, but it may cause renal impairment, exacerbate nausea, increase the risk of bleeding (especially gastrointestinal bleeding), and decrease the therapeutic effect of the patient’s antihypertensives (Tracy & Morrison, 2013). Opioids such as morphine may be an alternative to treat this patient’s pain and dyspnea; however, low doses should be used, and the patient should be monitored carefully for adverse effects such as delirium (Molton & Terrill, 2014; Nobili et al., 2011). Nausea should be treated by a medication with a low adverse effect profile such as low doses of a selective 5-HT₃ receptor blocker (e.g., ondansetron). Fatigue may be treated by using nutritional support and hematopoietic growth factors (National Comprehensive Cancer Network, 2014a). The nurse considers all of the data for this complex case and develops a collaborative care plan, which includes the use of a 5-HT₃ antagonist, low-dose oxycodone, supplemental oxygen, fatigue management strategies such as short daily walks and establishing a sleep routine, and nutritional supplements.

The nurse also recommends appropriate nonpharmacologic therapies for this patient, which include patient and family education, relaxation exercises such as music therapy, and gentle physical activity when the patient has recuperated from the pneumonia. Progressive physical activity is important in assisting M.F. to treat his fatigue and attain his maximum level of functioning and may improve his ability to cope with the disease process (Speck et al., 2010).

After completing the assessment and developing the symptom management plan, the nurse evaluates the symptom management plan and implementation with respect to their effect on the symptoms, the stability of the patient’s chronic illnesses, the caregiver’s perspective, and the patient’s overall quality of life as he defines it.

**Conclusion**

Approximately 20% of the U.S. population will be age 65 and older by 2030, and nurses will be challenged to care for a population with multiple complex healthcare needs, including cancer (Federal Interagency Forum on Aging-Related Statistics, 2012). The intertwined nature of symptoms related to cancer and its treatment, chronic illnesses, and an individual’s perception of normal aging presents a challenge for optimal symptom management in the gero-oncology population. Nurses must utilize evidence-based practices in oncology and geriatric care to ensure quality care for older adults with cancer. These practices include comprehensive assessment of health issues that are common to older patients with cancer, such as frailty, polypharmacy, and physical, cognitive, and social functioning, along with comprehensive management of each. Nurses are essential members of the interdisciplinary cancer care team and are responsible for ensuring the best possible symptom management outcomes without compromising the quality of life of the gero-oncology population.

**References**


CHAPTER 2

Alopecia

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Case Study

P.W. is a 47-year-old woman diagnosed with node-positive breast cancer. She underwent a left mastectomy with immediate reconstruction and is scheduled to begin chemotherapy. The regimen begins with doxorubicin 60 mg/m² IV plus cyclophosphamide 600 mg/m² IV every 21 days for four cycles. While she was waiting for her postoperative healing to reach the level where she could begin chemotherapy, P.W. attended a chemotherapy orientation class. The progress note in her chart from the nurse who led the class indicates that P.W. was very concerned about hair loss and had difficulty focusing on any of the other topics discussed. Ten days after the class, P.W. returns to the outpatient clinic for her first chemotherapy treatment.

Overview

Hair loss is a common side effect of many chemotherapy drugs used in cancer treatment. It also occurs in areas of the body treated with radiation and can be a result of treatments that alter the body’s hormone environment. Despite the high rate of alopecia with commonly used chemotherapy drugs and radiation (Paus, Haslam, Sharov, & Botchkarev, 2013; Yeager & Olsen, 2011), there is little research on the mechanisms of hair loss, human responses to potential or actual hair loss, strategies for preventing hair loss, and approaches to promoting hair regrowth in people with cancer. This chapter reviews each of these topics and summarizes current clinical practice recommendations for the care of people who are at risk for or are experiencing alopecia.

The characteristics, functions, and patterns of distribution of mammalian hair vary by species. Compared to the hair of most mammals, human hair provides little protection from the cold and is dense on only a few areas of the body. In humans, the primary use of hair is to communicate social and sexual identity (Messenger, 2003). In other mammals, hair has additional functions relevant to survival, such as hiding the animal from predators, serving as a sensory organ used in communication or locating predators and prey, and deterring predators (e.g., quills) (Messenger, 2003). Although humans do not depend on hair for personal protection, hair is an important element of appearance and identity. Over the course of human history, images of war, plague, crime, and poverty have associated complete loss of scalp hair with disease, louse infestation, submission, incarceration, and loss of self. In contrast, contemporary images of completely shaved heads in Western society may be associated with specific
political views, rebellion against authority, physical strength and toughness, and reluctance of men to have male-pattern baldness create a rim of hair around the lower portion of the scalp.

Pathophysiology

Hair Growth Phases

Each hair develops within a hair follicle that provides the environment for the initiation, maturation, shedding, and eventual replacement of the hair. The life of an individual hair has three phases: anagen, catagen, and telogen (Paus et al., 2013). The length of the active growth phase, the anagen phase, determines the maximum hair length. During the catagen phase, the hair is no longer growing, the base of the hair shaft becomes firm, and the bottom of the hair follicle moves closer to the surface of the skin. At this point, the base of the shaft is basically free of the follicle. In the telogen, or resting, phase, the hair shaft can be shed, but it may not fall out until the anagen phase is reestablished and the new hair pushes the firm base of the original hair to the skin surface. Both the anagen and telogen phases overlap the catagen phase, so the catagen phase usually is not addressed separately from the anagen and telogen phases of hair growth (Paus et al., 2013).

In humans, both the duration of the anagen phase and the proportion of hairs in the anagen phase at any given time vary by anatomic location. Scalp hair is in the anagen phase for two to six years, and 85%–90% of scalp hairs are in the anagen phase at any one time (Trüeb, 2010). In contrast, eyebrow hairs have a much shorter anagen phase of one to two months, with 6%–15% of hairs estimated to be in this phase at any one time (Messenger, 2003). Because the scalp has the highest percentage of hairs in the anagen phase at any single time, it is the first area of the body to show the effects of systemic cancer treatments that interfere with hair growth (Ganguly & Karnik, 2012).

Control of Hair Growth

Researchers have explored the control of hair growth in animal and human studies, but the precise mechanism responsible for switching hair growth on and off has not been identified. Much research has been done on the role of androgen in stimulating both hair growth and hair loss. Many molecular mediators of the hair growth cycle have been identified, including estrogen receptors, tumor protein p53, vascular endothelial growth factor, epidermal growth factor, tumor necrosis factor-alpha, mast cells, and interleukin-1 (Botchkarev et al., 2000; Paus et al., 2013). Specific cells, such as the cells of the dermal papilla at the base of the hair follicle and hair follicle stem cells alone or in interaction with other cells, also may contribute to the control of hair growth (Botchkarev et al., 2000; Messenger, 2003; Nathan & Tomlinson, 2010; Paus et al., 2013; Sharov et al., 2003; Wyatt, Leonard, & Sachs, 2006).

Hair Loss During Cancer Treatment

Types of Hair Loss

Anagen hair loss is caused by disruption in hair growth and is the type of hair loss induced by cancer chemotherapy and radiation because both treatment modalities target rapidly dividing cells. Exposure to a drug or to radiation interferes with hair growth, producing a weak
or narrowed area in the hair shaft where the hair breaks off or causes cells surrounding the hair root to die so that the hair is able to fall out. Cyclic chemotherapy causes successive areas of narrowing on hair that does not break at the first exposure to the treatment. These hairs exhibit a second area of narrowing following the second treatment (Paus et al., 2013; Sinclair, Grossman, & Kvedar, 2003).

With repeated doses of radiation delivered five days per week, hair in the irradiated area becomes progressively narrower and eventually breaks (Sinclair et al., 2003). High radiation doses delivered over short periods of time can permanently destroy hair follicles (Kondziolka, Niranjan, Flickinger, & Lunsford, 2005). A patient may experience temporary or partial hair loss after receiving 30 gray (Gy) within the treatment field, with permanent hair loss occurring after receiving 55 Gy (Iwamoto, Haas, & Gosselin, 2012).

Several acute, long-lasting, and late effects of cancer treatment, as well as complications of cancer, can cause hair loss during the telogen phase. Hypothyroidism, cessation or initiation of hormonal contraceptives in women, some hormone replacement therapy in women, decreased caloric intake, protein-calorie deficiency, iron deficiency (e.g., dietary, blood loss), essential fatty acids deficiencies, zinc deficiency, biotin deficiency, liver disease, fever, and injuries or medical procedures that lead to pressure-induced ischemia are all believed to cause hair loss during the telogen phase (Fiedler & Gray, 2003; Karakunnel & Berger, 2011).

Some drugs used in cancer treatment, cancer supportive care, or the management of comorbid conditions also are associated with telogen hair loss (Fiedler & Gray, 2003). Methotrexate, interferon alfa, and interferon gamma are examples of cancer treatments that cause telogen hair loss. Supportive care drugs that produce telogen hair loss include high doses of some antifungals, octreotide, amphetamines, and androgens. Anticoagulants, propranolol, allopurinol, and cimetidine are examples of drugs that may be used in the management of comorbid illnesses in adults with cancer and cause telogen hair loss (Fiedler & Gray, 2003; Tipton, 2011). When the drug causing hair loss is discontinued or the underlying deficiency state is corrected, telogen hair loss resolves.

**Pattern of Hair Loss and Regrowth**

The severity and incidence of hair loss associated with specific cancer treatment regimens are established during treatment trials through the documentation of side effects using toxicity rating instruments such as the Common Terminology Criteria for Adverse Events (National Cancer Institute Cancer Therapy Evaluation Program [NCI CTEP], 2010). Unlike other side effects, which are scored on a five-point (1–5) scale with the highest score indicating a life-threatening event, alopecia is scored using a more restricted range: hair loss of up to 50% that is not obvious from a distance (grade 1) to loss of more than 50% that is readily apparent to others (grade 2) (NCI CTEP, 2010).

The incidence rate and severity of drug-induced hair loss are reported in the studies used to support U.S. Food and Drug Administration (FDA) approval of new cancer treatment drugs and new indications for existing drugs. When new drugs are tested in combination with established chemotherapy drugs rather than as single agents, the new drug’s contribution to hair loss is seen in the difference between the rate and severity with the established regimen compared to the rate and severity of hair loss reported for the new combination regimen. When the established regimen includes chemotherapy drugs that cause high rates of hair loss, the new drug’s potential to cause hair loss if used alone or in a different combination may be obscured by the effects of other drugs in the treatment regimen.

The variation in the proportion of individual hairs in the anagen phase in the different types of body hair explains the pattern of hair loss during cancer chemotherapy. Generally,
scalp hair disappears first, body hair follows, and eyebrow hairs are lost last. Scalp hair may begin to grow between treatments depending on the drug, dose, frequency of treatment, and characteristics of the individual’s hair. Some people experience patchy hair loss initially; others may retain isolated hairs on the scalp and never lose all of their body hair; and some may lose all of the hair on their body. Chemotherapy-induced hair loss with standard-dose therapies is usually temporary, and extensive regrowth is apparent within the first months after completion of treatment. Patchy hair regrowth and permanent alopecia have been reported following bone marrow or stem cell transplantation and may be seen with some hormonal therapies that begin or continue following the completion of chemotherapy. Permanent alopecia has also been reported with standard-dose adjuvant therapy for breast cancer and with cranial radiation (Kluger et al., 2012; Miteva et al., 2011; van Dijk et al., 2013). Hair loss is also associated with some targeted therapies (Chan & Tan, 2011; Shaw et al., 2013; Toda et al., 2011; Zhang, Zhou, Ma, Wu, & Wang, 2011). It is not clear whether hair regrows following the cessation of targeted therapies because many patients are receiving long-term therapy and long-term follow-up data on people who have received many of these newer therapies are lacking.

Hair loss during external radiation treatment is limited to the treatment field. The area of hair loss follows the shape of the treatment field. Regrowth depends on the dose; higher doses (greater than 55 Gy) increase the likelihood of permanent hair loss (Iwamoto et al., 2012; Kondziolka et al., 2005; van Dijk et al., 2013). People who have had mantle field irradiation for Hodgkin lymphoma often have a higher than normal, perfectly straight hairline at the base of their skull. This unusual hairline corresponds with the upper border of the treatment field. When hair regrows in a treated area, regrowth may be concentrated along the outer edge of a treatment field and may gradually decrease in intensity so that the definition of the edge of the field softens over the years and less regrowth occurs in the central part of the field. Whether this is a result of dose variation at the edge of the treatment field or is caused by some sort of biologic process linked to nearby unaffected hair follicles is unclear.

Prevention of Hair Loss

Decreasing Blood Flow to the Scalp

A variety of strategies for preventing or delaying hair loss have been proposed, and a few have been studied. In the 1980s, interest emerged in restricting blood flow to the scalp by using scalp cooling (hypothermia) or scalp tourniquets alone or in combination. The rationale for this practice was that decreasing blood flow would decrease the amount of cytotoxic drug exposure at the hair follicle and, in the case of scalp cooling, would decrease biochemical activity in the scalp and consequently decrease susceptibility to damage from cancer chemotherapy (Christodoulou, Tsakalos, Galani, & Skarlos, 2006; Grevelman & Breed, 2005). The use of scalp tourniquets was abandoned because of patient discomfort. Because of the concern about the possibility of increasing the risk of scalp metastases or recurrence if cancer cells were among the cells protected and the lack of support for efficacy, no scalp cooling devices have received FDA approval for prevention of chemotherapy-induced alopecia (U.S. FDA Center for Devices and Radiological Health, n.d.). Scalp cooling continues to be studied and used outside the United States. Yeager and Olsen (2011) noted that interest in scalp cooling is increasing in the United States as a result of an observational study showing no differences in rates of scalp metastases following cancer chemotherapy between
patients who did and did not receive scalp cooling during treatment (Lemieux, Amireault, Provencher, & Maunsell, 2009).

Reviews of research on scalp cooling include Grevelman and Breed’s (2005) analysis of 53 published reports and three personal communications, as well as the analysis of 58 studies and three personal communications reported by Breed, van den Hurk, and Peerbooms (2011). In both papers, the authors concluded that scalp cooling is helpful in preventing hair loss but that the quality of the studies was low with few randomized trials included in the reviews (six and seven, respectively) and that scalp cooling was contraindicated for patients receiving treatment for hematologic malignancies. They identified several important issues requiring further research in multicenter studies, including safety, efficacy, the optimum approach to scalp cooling, the duration of cooling following the completion of chemotherapy infusion, patient tolerance of the procedures, and the extent to which the categorization of results as “good” reflected the patient’s report of acceptability of hair preservation rather than an estimate of the proportion of hair follicles remaining at the time of measurement (Grevelman & Breed, 2005). Recent studies of scalp cooling compared patients who received scalp cooling to historic controls (van den Hurk et al., 2012) or to concurrent controls who refused scalp cooling (Kargar, Sarvestani, Khojasteh, & Heidari, 2011). In both designs, the lack of random assignment to treatment is a major threat to the internal validity of the research design.

Pharmacologic Therapies

A wide range of pharmacologic approaches to chemotherapy-induced hair loss have been tried, but few have progressed to human trials. Topical minoxidil, which is indicated for treating androgenic hair loss and alopecia areata, was not effective in preventing chemotherapy-induced alopecia but did shorten the time for regrowth of hair in women following chemotherapy in breast cancer and gynecologic cancer (Wang, Lu, & Au, 2006; Yeager & Olsen, 2011). Because of changes in the chemotherapy regimens used since the minoxidil studies were completed, it is not clear if the same effect on hair regrowth would be seen with newer chemotherapy agents or with targeted therapies in use today. Topical minoxidil does not have an approved indication for hair regrowth following chemotherapy.

Topical antibodies to specific chemotherapy drugs, such as doxorubicin, have shown promise in animals for single-agent chemotherapy but are not expected to be useful in combination chemotherapy because each antibody only targets one drug. Initial animal studies using several different cytokines or growth factors to prevent hair loss from cytarabine and cyclophosphamide showed an effect for cytarabine only, again raising concern about its usefulness in multidrug regimens (Karakunnel & Berger, 2011; Yeager & Olsen, 2011). Cyclosporin A, an immunosuppressant that stimulates hair growth, has shown positive results when used topically or systemically in rodent tests of several different cancer chemotherapy drugs, but increasing immunosuppression poses safety issues that argue against pursuing this approach in humans (Wang et al., 2006).

Topical calcitriol (vitamin D₃) showed positive effects with a variety of commonly used chemotherapy agents in animal models. Enthusiasm for using topical calcitriol, however, decreased when it was ineffective in preventing hair loss caused by 5-fluorouracil, doxorubicin, and cyclophosphamide in women with breast cancer and also caused contact dermatitis in some study participants (Bleiker, Nicolau, Traulsen, & Hutchinson, 2005; Yeager & Olsen, 2011). Additional approaches tested for preventing hair loss in cancer chemotherapy include the use of parathyroid hormone and parathyroid hormone–related peptide agonists and antagonists, tumor protein p53 inhibitors, selenium, and a mushroom extract (Agaricus blazei Murill Kyowa), but none of these has yielded viable results (Ahn et al., 2004; Sieja & Talerczyk, 2004; Wang et al., 2006).
Radioprotectors (drugs that protect normal cells from radiation damage) are expected to protect against hair loss in patients receiving radiation to the scalp, but few studies have been done of alopecia prevention strategies in whole brain radiation or other forms of external radiation treatments that include scalp hair in the treatment field. None of the radioprotectors tested are currently used for preventing radiation-induced alopecia (Kouloulias et al., 2004; Metz et al., 2004).

Hair Care Techniques

Many self-care strategies for preventing or delaying chemotherapy-induced scalp hair loss appear in the patient education and professional literature. These include cutting hair short prior to beginning treatment, using a satin pillowcase on the bed pillow, brushing hair gently, not using high heat on hair dryers, avoiding straightening or curling irons and curlers, avoiding hair dyes and permanent waves or relaxers, not braiding the hair or wearing hair bands, and using a neutral pH shampoo (NCI, 2007). Many of these suggestions, such as brushing hair gently, cutting hair short, avoiding braiding, and using a satin pillowcase, appear to decrease traction on hair to preserve damaged hairs that could be susceptible to breaking with higher traction. Other suggestions, such as avoiding exposing the hair and scalp to high temperatures and chemicals, suggest that the recommendation is based on concern about skin irritation around the hair shaft. None of the suggested self-care strategies have a research base.

Human Responses to Hair Loss

Many studies have documented the distress associated with both the anticipation of scalp hair loss and the experience of living with scalp hair loss as a side effect of cancer chemotherapy (Bernard et al., 2011; Borsellino & Young, 2011; Erol, Can, & Aydiner, 2012; Zannini et al., 2012). Most of these studies explored the experience of cancer treatment in general. Although responses to hair loss are not a specific focus of most work, results are consistent: The loss of scalp hair is feared; the likelihood of scalp hair loss is considered during treatment decision making; a variety of concrete strategies are used to deal with hair loss (going bald, using a wig, using other head coverings); and scalp hair loss may be viewed as a stigma (Boehmke & Dickinson, 2005; Carpenter & Brockopp, 1994; Cash, 2001; Fallowfield, McGurk, & Dixon, 2004; Frith, Harcourt, & Fussell, 2007; McGarvey, Baum, Pinkerton, & Rogers, 2001; Münstedt, Manthey, Sachsse, & Vahrson, 1997; Rosman, 2004). In the study by Rosman (2004), men reported less distress from hair loss than women and were less likely than women to use a wig or head covering.

Few data exist on the responses of others to an individual’s hair loss. Reports of qualitative studies suggest that women who elect to display a bald head consider the decision carefully and that family members, including children, become accustomed to the change in appearance over time (Williams, Piamjariyakul, et al., 2006). However, the responses of others to unexpected baldness are often shock. Women have reported feeling as though people view them differently because of their hair loss and have expressed concern about the impact of hair loss on the way people think about and act toward them (Erol et al., 2012; Rosman, 2004; Snöbohm, Friedrichsen, & Heiwe, 2010).

The research focusing on hair loss reveals a wide range of responses to both the prospect of and the reality of hair loss. For some, hair loss is the concrete evidence of cancer, whereas others view it as a sign that they are moving forward by being treated (McGarvey et al., 2001). Cultural differences in the meaning of hair and hair loss are critical to the meaning that people ascribe to the experience. For example, some Native Americans view long hair as a sign of
respect for motherhood. Some collect shed hairs in a pillow for their entire lifetime as part of a practice of keeping one’s body intact. Others view the loss of hair as shameful (Native American Cancer Research, n.d.).

Whether one’s interpretation of the hair loss drives decisions about what action to take in managing it is unknown, and the range of behaviors used to camouflage hair loss is broad (Forrest, Plumb, Ziebland, & Stein, 2006; Frith et al., 2007; McGarvey et al., 2001; Rosman, 2004; Ucok, 2007). Some people experiencing scalp hair loss with cancer treatment choose to make a statement of identity by going bald. Others have created one or more “new” identities based on wigs, scarves, hats, and going bald. A few have had their scalps adorned with tattoos (permanent or temporary). Those who want to look about the same as they always have seek out wigs that match their own hair color and style, whereas others seek out new colors and styles. Some people find that wearing a wig is not tolerable because it is too hot, too itchy (even with a wig cap placed on the scalp before the wig is put on), does not fit well, or is burdensome to care for, while others wear a wig at all times, even while asleep (Nail & Lee-Lin, 2013). Children with cancer treatment–related alopecia often wear baseball caps or go bald, whereas female adolescents may use the same range of behaviors as adult women (Paus et al., 2013; Williams, Schmideskamp, Ridder, & Williams, 2006; Yeager & Olsen, 2011).

Some people clip or shave off their scalp hair when it becomes apparent to others that they are losing their hair or before they begin to lose hair to avoid having to deal with shedding and thinning (Borsellino & Young, 2011; Roe, 2011; Zannini et al., 2012). A family member, friend, or group of supporters may be recruited to participate in the clipping, with some approaching this event as a formal rite of passage with a celebratory component (Nail & Lee-Lin, 2013).

The process of dealing with scalp hair regrowth is less apparent in the research literature, clinical literature, and reports of personal experiences with cancer treatment. Some people have difficulty acknowledging their new hair and show the same reluctance to expose the new hair as they had in showing their bald head (Rosman, 2004). Although some patient education materials suggest that regrown scalp hair will differ from the original scalp hair in color and texture, this concept has limited research support. Whether the characteristics of regrown hair vary according to the type of cancer treatment or other variables, such as shifts in the hormone environment or damage to hair follicles, is unclear.

Almost no research has been done on the impact of hair loss in anatomic locations other than the scalp in people undergoing cancer treatment. Pubic hair is part of adult identity and sexual identity, and the loss of pubic hair can produce feelings of regression to a childlike state (Frith et al., 2007; Münstedt et al., 1997). The loss of visible body hair may be viewed as a positive or negative aspect of the cancer treatment experience depending on individual body image beliefs, gender, and cultural norms. Responses to loss of hair other than scalp hair have not been studied and rarely are addressed in educational materials for cancer care providers or people with cancer.

Although some people may elect to have temporary or permanent makeup tattoos, applying a permanent tattoo is not recommended for patients receiving cancer treatment because of the risk of infection. Prosthetic eyelashes, eyebrows, and beards secured with adhesive also present a risk of infection because of chemical or mechanical damage to the skin.

**Clinical Practice Recommendations**

In research addressing satisfaction with information and support about treatment-induced hair loss, a common finding is that some subjects were dissatisfied with the information and
support received from professionals (Borsellino & Young, 2011) and that care providers may not appreciate the level of distress associated with hair loss (Yeager & Olsen, 2011). Clinicians need to be aware of the variation in responses to hair loss along with the need for adequate preparation. They must correct misconceptions and avoid minimizing the concerns expressed by people facing or experiencing hair loss.

**Preparing People for Hair Loss**

Accurate information about the likelihood and nature of hair loss is a key element of preparing people for cancer treatment. Public awareness of hair loss as a side effect of treatment is widespread and has produced misconceptions about who is likely to experience hair loss. People beginning radiation treatment to an anatomic site other than the head commonly think that they will lose their scalp hair. Similarly, people making a treatment decision may assume that they will lose their hair, when in fact the treatment they are considering is not associated with hair loss. Clinicians must clarify what is expected for specific treatments while acknowledging that individual variation exists.

Only one published trial of a specific preparatory intervention for chemotherapy-induced hair loss exists. McGarvey et al. (2010) evaluated the efficacy of a computer-imaging program to simulate baldness and use of wigs in a randomized trial comparing the computer-imaging program to standard care, which was referral to a resource area for women with chemotherapy-induced hair loss and provision of an NCI educational booklet and list of places to buy wigs. The experimental group (n = 25) demonstrated a trend for lower levels of hair loss distress from baseline to three months following hair loss compared to the standard care group (n = 20), but the differences were not statistically significant (group x time; p = 0.079). The intervention was evaluated as being feasible and acceptable for use by women as a preparatory intervention for chemotherapy-induced hair loss, but further research is needed to determine if it decreases hair loss distress.

Preparation for hair loss is often incorporated into general support and information programs in cancer care settings. Zannini et al. (2012) used interpretative phenomenology to describe perceptions of the effects of an aesthetic care program for women (N = 20) who were beginning chemotherapy in a rural area of Sicily. The program included information, expression of feelings, the opportunity to select a wig, wig fitting and styling by a hairstylist, and support by a social worker during the wig selection and fitting visit if desired. The themes that emerged from the interviews described perceptions of the experience of hair loss, the impact of the wig on social interactions, and women’s approaches to the cancer experience. The investigators concluded that the integrated aesthetic care program created a supportive relationship during the cancer treatment experience in addition to providing tangible assistance in dealing with chemotherapy-induced hair loss (Zannini et al., 2012).

When systemic treatment likely to cause hair loss will be given, being clear that all hair, not just scalp hair, may be lost and that these losses may not occur at the same time will help patients to plan for and interpret their experience. Providing information about the variety of management options available, including the information that a bald head can get cold (wear a fleece cap) and that a runny nose may drip more suddenly than usual (carry tissues), helps people to prepare responses for these new experiences. Acknowledging that hair loss can be distressing, that it may have special meaning to an individual that others do not appreciate, and that it will have an impact on family members and friends, as well as providing information about resources for dealing with these concerns, are important elements in preparing people for the experience of hair loss.
Resources available, such as support groups, vary widely by institution/practice and area of the country. Local programming should be included in the referral to resources. No studies have been performed on the effects of pairing “chemo buddies” (survivors who have experienced hair loss) with patients facing hair loss on hair loss–specific distress.

**Preventing Scalp Problems**

Specific instructions for preventing scalp problems vary according to the type of treatment and should be provided to all patients. Scalp care during whole brain radiation therapy often includes institution-specific restrictions on and suggestions for the use of lotions, creams, and ointments (Iwamoto et al., 2012). Scalp care during cancer chemotherapy is less complicated and addresses a few general principles, including protecting the skin from the sun and preventing injury to the scalp because of the loss of local protection from scalp hair (Tipton, 2011). Instructions to inspect the scalp, including the back of the head, for rashes, sunburn, and scratches or blisters from wigs, hats, or decorations on scarves are important as part of the general recommendations for preventing and recognizing infection and maintaining skin integrity (NCI, 2007).

**Head Coverings**

People who want a wig that matches their own hair color and style should select the wig while they still have their hair to achieve the best possible match. Some may choose to use a scarf or hat in combination with hairpieces designed as bangs, ponytails, sideburns, or long hair on the sides and back of a hat or scarf, whereas others may use scarves or hats without any hairpiece. Cancer care providers need to recognize that most head-covering strategies result in some out-of-pocket expense and maintenance challenges. Health insurance may cover at least part of the expense of a wig if the patient has a prescription for a hair prosthesis. High-quality synthetic wigs, which are easier to care for than a human hair wig, cost approximately $200, and high-quality human hair wigs generally are more expensive (Roseborough, 2008). A simple cotton or silk head scarf or covering may cost $35–$50, and hats can range in cost from a few dollars for a simple baseball cap to more than $500 for luxury items. Those who want variety in color or style of scarves and hats can easily spend more than the cost of a high-quality wig.

Appearance programs for people with cancer include the Look Good Feel Better program (http://lookgoodfeelbetter.org) as well as local programs developed by individual healthcare systems as part of their cancer program or by retailers who stock products used by people with cancer. Look Good Feel Better is a brand-neutral program that addresses a combination of skin care, makeup, and head-covering strategies and targets women as the primary audience (Personal Care Products Council Foundation, n.d.). A companion self-help brochure and website are available for men (www.lookgoodfeelbetterformen.org).

**Conclusion of Case Study**

The nurse who will be performing P.W.’s prechemotherapy assessment and administering her chemotherapy identifies P.W. as the well-dressed woman in a business suit sitting alone at the far end of the waiting room and staring at the other people in the room. The nurse introduces herself to P.W. and escorts her to a private room in the treatment area. As part of the pretreatment assessment, the nurse asks P.W. what questions she
has about chemotherapy and offers to review the information presented in the class. P.W. replies that she thinks the chemotherapy regimen that has been prescribed is the wrong one for her. She tells the nurse that she knows that some people with cancer do not lose their hair, and she wants the treatment they are getting rather than either of the chemotherapy options that were presented to her.

The nurse clarifies that there are different regimens of chemotherapy that are very specific to an individual’s type of cancer. The nurse checks the chemotherapy with the patient and shares with the patient that she will very likely have some level of alopecia because it is commonly associated with the chemotherapy drugs she is scheduled to receive. The nurse encourages P.W. to get a wig or other head covering for appearance purposes and to help keep her head warm. The nurse suggests that P.W. attempt to match a wig to her hair color as soon as possible before her hair begins to fall out. The nurse arranges for the patient to attend a Look Good Feel Better program and encourages P.W. to verbalize her concerns about potential hair loss.

Conclusion

Hair loss continues to be part of the treatment experience for many people with cancer. The impact of new cancer treatments, such as targeted therapies, on this side effect is unclear. Recent interest in understanding the basic biology of hair loss as a side effect of cancer treatment may lead to translational studies of novel prevention strategies. Current clinical practice recommendations focus on acknowledging the importance of the problem to people with cancer, respecting the concerns and responses of individuals who are anticipating or experiencing hair loss, delivering appropriate education and preparation for the experience of hair loss, and providing support to people dealing with changes in self-image and identity as a result of hair loss.

References


Anemia

Case Study

T.C. is a 62-year-old woman with a two-month history of dry cough, mild dyspnea with exertion, and complaint of fatigue rated as a 6 on a scale of 0–10 where 0 is no fatigue and 10 is the worst fatigue (Oncology Nursing Society, 2000). T.C. states that she believes she has lost weight in the past few months. She is a nonsmoker but reports that her spouse smokes one pack per day. T.C. is retired and cares for her two young grandchildren two days a week.

T.C.’s medical history includes coronary artery disease and controlled hypertension. Baseline laboratory values reveal the following: white blood cell count is 4,000/mm$^3$, absolute neutrophil count is 2,400/mm$^3$, red blood cell (RBC) count is $5.1 \times 10^6$/mm$^3$, hemoglobin (Hgb) is 10.5 g/dl, hematocrit is 34%, ferritin is 120 ng/ml, and serum iron, vitamin B$_{12}$, folate, and chemistry are within normal limits. Computed tomography (CT) scan reveals a 4 cm mass in the right upper lung. Needle biopsy confirms an adenocarcinoma, non-small cell lung cancer. Mediastinoscopy reveals stage N2 disease (single-level ipsilateral mediastinal node involvement). T.C. is scheduled for neoadjuvant chemoradiation followed by surgical resection. Is T.C. at risk for anemia?

Overview

Anemia is a problem common to patients with cancer and one that oncology nurses encounter almost daily in practice. The risk and incidence of anemia vary widely with the type of malignancy, as well as the duration and extent of disease (Wu, Aravind, Ranganathan, Martin, & Nalysnyk, 2009). The prevalence of anemia is high (30%–90%) in patients with cancer who are not receiving treatment and even higher in patients who are undergoing chemotherapy or radiation therapy (Knight, Wade, & Balducci, 2004).

A review of the available literature reveals a significant incidence of chemotherapy-induced anemia (CIA) across many tumor types. The European Cancer Anemia Survey (ECAS) studied the prevalence and incidence of anemia in more than 15,000 patients with cancer. Of the 14,520 patients with Hgb levels available at the time of enrollment, 39% were anemic. Among 2,732 patients who were not anemic at enrollment, 53.7% of participants became anemic while receiving treatment for their cancer, with the highest incidence of anemia occurring among patients receiving chemotherapy (n = 2,101, 62.7%), greater than in those receiving combination chemotherapy and radiation therapy (n = 117, 41.9%) or radiation therapy...
alone (n = 514, 19.5%) (Ludwig et al., 2004). Incidence of CIA increases as the number of chemotherapy cycles increases (Cheng et al., 2012; Pirker et al., 2013).

A retrospective, observational cohort study of adult patients who received care at U.S. oncology practices between 2000 and 2007 revealed that 21% of patients were anemic at baseline (Hgb less than 11 g/dl), and 39% had Hgb less than 12 g/dl (n = 47,159) (Wu et al., 2009). Overall, 46%–59% of the patients in this study population experienced anemia at some point while receiving chemotherapeutic regimens containing a platinum (50.7%, n = 17,825), anthracycline (50.8%, n = 10,506), taxane (46.4%, n = 4,132), or gemcitabine (59%, n = 3,276) (Wu et al., 2009).

Knight et al. (2004) found a high incidence of anemia across numerous tumor types, including lung (8%–84%), colon (30%–67%), breast (41%–82%), head and neck (16%–65%), gynecologic (26%–85%), bone (78%), brain (59%), pancreatic (93%), and hematologic (32%–100%) malignancies. Wu et al. (2009) described the incidence of pretreatment anemia across several cancer types including hematologic malignancies (30.6%) and solid tumors such as ovarian (25.7%), colorectal (21.8%), non-small cell lung (16.1%), breast (12.2%), and head and neck cancer (11.2%). Of these, RBC transfusion was most common among patients with hematologic malignancies (14.5%), ovarian cancer (13.3%), and non-small cell lung cancer (10.6%).

Low Hgb levels have been associated with adverse clinical outcomes, including resistance to cancer treatment (Hoff et al., 2011) and decreased survival (Wan et al., 2013). In a study of 6,675 patients with solid tumors, Wan et al. (2013) showed that those patients who demonstrated greater absolute change in Hgb level within the first six months after diagnosis also exhibited poorer overall survival compared with patients who exhibited a low change in Hgb level (95% confidence interval [1.31, 1.50], \( p = 4.5 \times 10^{-22} \), \( p_{\text{log rank}} = 1.6 \times 10^{-39} \)) (Wan et al., 2013).

Anemia has been identified as an independent factor affecting mortality (Habib, Sultan, & Salman, 2012). Caro, Salas, Ward, and Goss (2001) completed a review of the literature and found a 20%–43% reduction in median survival in patients with cancer who were diagnosed with anemia. All of the 60 studies in the review reported a longer median survival in patients who were not anemic. For example, the relative risk of death in patients with lung cancer who were anemic increased by 19% compared to those without anemia. For anemic patients with head and neck cancer, the risk of death increased by 75%, and for those with lymphoma, by 67% (Caro et al., 2001). Greater changes in Hgb level after an anemia diagnosis have also been adversely associated with patient survival (Wan et al., 2013).

Although the incidence of anemia in patients with cancer has driven progress in toxicity management, anemia nonetheless often is underdiagnosed and undertreated (Hurter & Bush, 2007). There is no single, universal definition of anemia, and the vast variability in Hgb levels among the general, healthy population makes identifying a “normal” Hgb level challenging (National Comprehensive Cancer Network® [NCCN®], 2014a; Wan et al., 2013). Because symptoms often develop slowly, healthcare professionals are accustomed to placing great importance on quantitative laboratory assessments (e.g., Hgb and hematocrit levels) to drive assessment and management of anemia (Wan et al., 2013). The impact of anemia and its symptoms is profound and may negatively affect patients’ quality of life (QOL); physical, social, and emotional function; and survival (Doni et al., 2011; Kleinman et al., 2012; Wan et al., 2013).

**Pathophysiology**

Anemia is defined as a reduction in the number or volume of circulating RBCs, the amount of Hgb, or volume of hematocrit, which reduces the oxygen-carrying capacity of the blood,
causing hypoxia (Faiman, 2014; Walker, 2014). In patients with cancer, anemia may result from a number of causes including blood loss, increased RBC destruction, or decreased RBC production (Faiman, 2014; NCCN, 2014a). To fully appreciate the pathophysiology of anemia requires an understanding of the normal process of erythropoiesis.

In adults, RBCs are produced in the bone marrow of the vertebrae, sternum, ribs, pelvis, and proximal femurs (Waite, 2013; Walker, 2014). RBCs develop and mature in approximately five to seven days and are then released into the bloodstream, where they typically survive for 100–120 days (Quigley, Means, & Glader, 2014). Erythroblasts develop into RBCs after a series of divisions, but it is during erythroid differentiation that Hgb synthesis begins, and it continues into the orthochromatic stage (Quigley et al., 2014). Mature RBCs, or erythrocytes, serve mainly as a vehicle for Hgb transport, carrying oxygen to the tissues and binding carbon dioxide for transport from the tissues to the lungs (Chow & Frenette, 2014). Mature RBCs have a biconcave disc shape to allow greater surface area for gases to cross the cell membrane, but they can change shape as needed to pass through small capillaries (Quigley et al., 2014).

The production of RBCs is regulated by tissue oxygen needs. Anemia can lead to hypoxia, which triggers the body processes that lead to production of new RBCs. The kidneys release erythropoietin (EPO) in response to hypoxia, sending a signal to erythroid progenitor cells to produce more RBCs (Bunn, 2013). The resultant increase in the oxygen-carrying capacity of the blood functions to downregulate further EPO production (Bunn, 2013). RBCs senesce at a rate of approximately 20 ml daily (Fried, 2009). The old cells are destroyed and eliminated predominantly (80%–90%) by phagocytic cells in the spleen (Quigley et al., 2014).

Hypoxia has been found to play roles in angiogenesis, tumor progression, and resistance to cancer therapies (Hoff et al., 2011; Rankin & Giaccia, 2008).

Anemia caused by relative loss of RBCs and circulating volume can result from surgical blood loss, acute or chronic gastrointestinal hemorrhage, excessive diagnostic phlebotomy, or disseminated intravascular coagulation. Increased RBC destruction can cause various types of hemolytic anemia and cold agglutinin disease (a syndrome in which antibodies adhere to RBCs at low temperatures, causing hemolysis). Anemia resulting from decreased RBC production can be caused by treatment-induced myelosuppression, renal impairment, nutritional deficiencies, anemia of chronic disease (ACD), or tumor infiltration of the bone marrow (Dicato, Plawny, & Diederich, 2010; Rodgers et al., 2012). Risk factors for the development of anemia include a lower baseline Hgb level (12.9 g/dl or lower in females, 13.4 g/dl or lower in males), certain cancer types (i.e., lung or gynecologic cancers), older age, treatment with platinum-based chemotherapy regimens, increased number of chemotherapy cycles, and female gender (Barrett-Lee et al., 2006; Cheng et al., 2012; Spivak, Gascón, & Ludwig, 2009).

The size of the RBCs is important in the morphologic assessment of anemia and can give clues as to the cause (Pagana & Pagana, 2013; Rodgers et al., 2012). The RBC indices reveal the size of the RBCs and their Hgb content; these include the mean corpuscular volume (MCV), mean corpuscular Hgb concentration, and the red cell size distribution width. The MCV identifies the average size of the RBC and directs the classification of anemia as microcytic (low MCV, less than 80 femtoliters [fL]), normocytic (normal MCV, 80–100 fL), or macrocytic (high MCV, greater than 100 fL) (NCCN, 2014a; Walker, 2014). The mean corpuscular Hgb measures the average Hgb weight in each RBC. The level is increased in macrocytic anemia and decreased in microcytic anemia. The mean corpuscular Hgb concentration measures the amount of Hgb in each RBC and leads to further classification of anemia as hypochromic, normochromic, or hyperchromic and is useful for monitoring response to anemia treatment. The red cell size distribution width confers information about RBC size and may help to differentiate the type of anemia (Pagana & Pagana, 2014).
Standard tests in the laboratory workup for anemia include Hgb and hematocrit, reticulocyte count, and iron studies. A reticulocyte is an immature RBC, and the reticulocyte count measures the effectiveness of the bone marrow in producing RBCs. A low reticulocyte count denotes decreased production of RBCs in the bone marrow (e.g., ACD, iron deficiency, aplastic anemia). In contrast, a high reticulocyte count reflects the loss or destruction of RBCs (e.g., hemolysis) (Walker, 2014). Table 3-1 lists the classifications of common cancer-related anemias.

Iron studies are important in the differential diagnosis of anemia, as iron is essential for Hgb production. Iron deficiency can promote anemia or be its primary cause, and it can reduce the effectiveness of anemia treatment. Serum ferritin, transferrin saturation (TSAT), and total iron-binding capacity are included in iron studies (Adamson & Longo, 2012). Together, they measure the body’s ability to store and transport iron. Serum ferritin alone is an insufficient measure, as ferritin may be elevated because of inflammation or liver cell damage (as can occur in the context of certain malignancies). Therefore, a normal ferritin does not necessarily confirm that iron stores are adequate (Aapro, Österborg, Gascón, Ludwig, & Beguin, 2012; Cullis, 2011).

Vitamin B₁₂ and folate are necessary for the production of RBCs, and folate is essential for normal blood cell function. They often are tested in conjunction to determine if a macrocytic

<table>
<thead>
<tr>
<th>Anemia Type</th>
<th>Description</th>
<th>Differential Diagnosis</th>
</tr>
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<tbody>
<tr>
<td>Microcytic</td>
<td>Decreased mean corpuscular volume (MCV) (&lt; 80 fL) Red blood cells (RBCs) small in size</td>
<td>Iron deficiency Anemia of chronic disease Thalassemia minor Sideroblastic anemia</td>
</tr>
<tr>
<td>Normocytic</td>
<td>Normal MCV (80–100 fL) RBCs normal in size</td>
<td>Anemia of chronic disease Hemolytic anemia Aplastic anemia Renal failure</td>
</tr>
<tr>
<td>Macrocytic</td>
<td>Increased MCV (&gt; 100 fL) RBCs large in size</td>
<td>Vitamin $B_{12}$ deficiency Folate deficiency Myelodysplastic syndromes Alcohol abuse Hypothyroidism Drug-induced (e.g., chemotherapy)</td>
</tr>
<tr>
<td>Low reticulocyte count</td>
<td>Decreased RBC production</td>
<td>Anemia of chronic disease Aplastic anemia Iron deficiency Vitamin $B_{12}$ deficiency Folate deficiency Bone marrow suppression or infiltration</td>
</tr>
<tr>
<td>High reticulocyte count</td>
<td>Increased RBC destruction</td>
<td>RBC destruction (e.g., hemolysis) Chemotherapy-induced Autoimmune disorder</td>
</tr>
</tbody>
</table>

Note. Based on information from Pagana & Pagana, 2014; Perkins, 2010; Walker, 2014.

anemia is present. Elevated vitamin $B_{12}$ levels can be caused by certain leukemias, such as chronic granulocytic leukemia and myelomonocytic leukemia, as well as cancers with liver metastasis. Decreased vitamin $B_{12}$ levels can occur as a result of decreased gastric secretion of intrinsic factors (e.g., gastrectomy syndrome, gastric bypass, gastritis), insufficient dietary intake, autoimmune disorders, or drug activity (e.g., proton pump inhibitors, colchicine, metformin, cholestyramine) (Faiman, 2014). Vitamin $B_{12}$ deficiency is associated with macrocytic anemia and often coexists with iron and folic acid deficiencies. Decreased folate levels are associated with macrocytic, normochromic, or megaloblastic anemia (Moran, 2014a). The underlying folic acid deficiency results from inadequate intake or absorption or an increased bodily requirement (Moran, 2014a). See Figure 3-1 for a decision-making guide for identifying sources of anemia.

ACD is thought to be the most common cause of anemia in patients with chronic illness, including cancer (Cullis, 2011). It is a state of impaired iron utilization in which Hgb is decreased but ferritin is normal or high. ACD is a condition of insufficient EPO production, weakened bone marrow response to EPO, iron-restricted RBC production, or decreased cellular response to EPO. In ACD, the reticulocyte count is low, signaling a decreased production of RBCs. Reduced levels of iron and TSAT occur in normocytic, normochromic ACD (Cullis, 2011).

Several factors contribute to the development of ACD. The peptide hormone hepcidin, which functions in the regulation of iron balance, has an integral role in ACD (Cullis, 2011). The development of malignant cells leads to activation of T cells and monocytes, which drive immune effector functions. This results in the production of cytokines (i.e., interferon, tumor necrosis factor, interleukin [IL]-1, and IL-6), which stimulate the liver to produce hepcidin. Iron absorption in the duodenum is decreased, the release of iron stores from macrophages and hepatocytes is inhibited, and the net effect is a decrease in serum iron concentration and renal production of EPO (Cullis, 2011; Spivak et al., 2009). Inflammatory cytokines have additional direct deleterious effects, including promotion of erythroid cell death in the absence of EPO (Spivak et al., 2009).

Assessment

The NCCN (2014a) anemia guidelines offer evidence-based strategies for the screening, assessment, and management of patients with cancer- and chemotherapy-related anemia. Clinicians should always check for the most up-to-date guidelines, as NCCN updates its recommendations frequently. Although the NCCN guidelines serve as an excellent resource, they should be customized to meet the needs of each patient. The American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO) originally adopted joint guidelines for anemia in 2002, which were updated in 2010 (Rizzo et al., 2010).

Although objective findings are essential to the differential diagnosis of anemia, subjective information is beneficial in planning interventions to enhance patient QOL. Anemia can cause a wide range of symptoms that can affect the function of almost every organ and tissue in the body. The degree and extent of symptoms depend on the severity of the anemia, rapidity of onset, the body’s ability to compensate, comorbidities, and the physiologic status of the patient (Means & Glader, 2014; NCCN, 2014a). NCCN (2014a) recommends assessment of the cause when the Hgb level is 11 g/dl or less or drops by 2 g/dl or more in patients with a high baseline Hgb. Note that in slow-onset anemia, clinical symptoms may not prompt patients to pursue medical care until their Hgb and hematocrit levels become quite low (Means & Glader, 2014).

A comprehensive assessment of anemia includes a detailed history and physical examination. The history begins with a risk assessment. Barrett-Lee et al. (2006) identified indepen-
dent risk factors including low baseline Hgb, lung or gynecologic malignancies, treatment with platinum chemotherapy, and female gender. Additional considerations include prior chemotherapy or radiation therapy. When taking a patient’s history, the clinician must include the medical, surgical, and oncologic history. Cancer diagnosis, stage, treatment, response, and treatment-related side effects are important details. The patient’s current health status, including elements such as comorbid conditions, recurrent illnesses or infections, medica-
tions, clinical symptoms, diet, alcohol intake, and functional changes (i.e., ability to complete activities of daily living), is vital to a differential diagnosis of anemia (Faiman, 2014; Means & Glader, 2014).

The physical examination should be exhaustive, as cancer-related anemia can affect the whole body (Spivak et al., 2009). Many of the symptoms of anemia arise from the body’s inability to compensate adequately for chronic oxygen deficiency; this is more pronounced in acute-onset anemia or in patients with physiologic impairment in the compensatory systems (NCCN, 2014a). Anemia often develops gradually, and the body’s compensatory mechanisms may adjust to the lower oxygen-carrying capacity of the blood so well that symptom presentation is blunted (NCCN, 2014a). However, patients may still be aware of subtle changes in their ability to tolerate activity and may notice fatigue or mild shortness of breath following activity (Means & Glader, 2014). The nurse’s detailed history and physical examination may reveal these subtle changes. In addition, the Oncology Nursing Society has identified a number of clinical assessment tools to assist in the quick identification and longitudinal monitoring of symptoms such as fatigue (Eaton, 2009).

Physical examination in a patient with mild to moderate anemia may reveal pallor, shortness of breath on exertion, headache, syncope, abnormal menstruation in female patients, and manifestations of fatigue (NCCN, 2014a). In patients with severe anemia, dyspnea may occur at rest, cardiovascular symptoms may manifest, and debilitating fatigue often is present. These symptoms are a result of the decreased oxygenation of Hgb, which leads to hypoxia and increased cardiac output. The reduction in the number of RBCs affects the blood’s consistency and volume, thus causing the blood to flow faster and more fiercely. Systolic murmurs can occur with anemia (Means & Glader, 2014). Figure 3-2 illustrates the signs and symptoms of anemia.

A number of standard toxicity criteria for anemia exist, the most common of which is the National Cancer Institute Cancer Therapy Evaluation Program (NCI CTEP, 2010) grading scale (see Table 3-2). Clinical trials often focus on identification and management of severe toxicities (grades 3 and 4) while placing less emphasis on those that are mild to moderate (grades 1 and 2). The NCI CTEP grading system relies solely on the objective measure of Hgb level to assess for anemia, whereas clinical measurement tools for anemia take patient-reported symptoms and QOL into account.

Validated assessment tools such as the Functional Assessment of Cancer Therapy–Anemia (FACT-An) subscale (Cella, 1997), the Brief Fatigue Inventory (BFI), and the Linear Analog Scale Assessment (LASA) (Gough, Furnival, Schilder, & Grove, 1983; Locke et al., 2007; Schwartz, 2007) can be used to help providers assess patients with anemia and subjectively reported symptoms that affect QOL. The FACT-An is a scale with 55 questions specific to cancer, including 13 questions regarding fatigue and 7 related to anemia. The BFI includes four questions and asks patients to rate the impact of fatigue on their daily functioning in the past 24 hours. Patients can use the LASA scale to self-measure energy level, ability to complete activities of daily living, and QOL using a range of 0–100 where 0 is “as low as could be” and 100 is “as high as could be” (Gough et al., 1983; Schwartz, 2007). More recently, Locke et al. (2007) have validated a single-item LASA scale that is shorter and potentially easier to use. This LASA also assesses fatigue; activities of daily living; and emotional, spiritual, and intellectual well-being on a 0–10 scale, where 0 is “as bad as it can be” and 10 is “as good as it can be.”

Assessment of fatigue is essential when completing a comprehensive assessment of anemia. Fatigue continues to be a common and troublesome symptom of cancer and cancer treatment and is a frequently reported symptom of cancer-related anemia (NCCN, 2014b; Spivak et al., 2009). Fatigue is multidimensional, and treatment hinges upon the assessment and identification of treatable contributing factors (NCCN, 2014b). See Chapter 15 for a more detailed discussion of fatigue.
### FIGURE 3-2  Signs and Symptoms of Anemia

<table>
<thead>
<tr>
<th><strong>General</strong></th>
<th><strong>Fatigue, lethargy, apathy, fever</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Immune System</strong></td>
<td></td>
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<tr>
<td>Weakened macrophage and T-cell function</td>
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<tr>
<td><strong>Central Nervous System</strong></td>
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<tr>
<td>Headaches</td>
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<tr>
<td>Vertigo, dizziness</td>
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<tr>
<td>Irritability</td>
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<td>Confusion, impaired judgment</td>
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<tr>
<td>Ataxia, weakness</td>
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<tr>
<td>Retinal hemorrhage</td>
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<td>Loss of sensation or proprioception</td>
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<tr>
<td>Spasticity</td>
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<td><strong>Respiratory System</strong></td>
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<tr>
<td>Tachypnea</td>
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<td>Dyspnea</td>
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<td>Pulmonary edema</td>
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<td><strong>Genitourinary System</strong></td>
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<tr>
<td>Proteinuria</td>
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<td>Water retention</td>
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<td>Menorrhagia</td>
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<td>Amenorrhea</td>
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<td>Reduced libido</td>
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<td>Impotence</td>
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<tr>
<td><strong>Hematologic System</strong></td>
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<tr>
<td>Generalized lymphadenopathy</td>
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<tr>
<td><strong>Cardiovascular System</strong></td>
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<tr>
<td>Tachycardia</td>
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<tr>
<td>Angina, palpitations</td>
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<tr>
<td>Dysrhythmias</td>
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<tr>
<td>Systolic murmur</td>
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<tr>
<td>Bruit</td>
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<td>Postural hypotension</td>
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<td><strong>Gastrointestinal System</strong></td>
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<tr>
<td>Indigestion</td>
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<td>Irregular bowel movements</td>
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<tr>
<td>Stomatitis</td>
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<td>Occult blood loss</td>
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<td>Ascites</td>
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<tr>
<td>Hepatosplenomegaly</td>
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<tr>
<td>Abdominal distention</td>
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<tr>
<td><strong>Peripheral Vascular System</strong></td>
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<tr>
<td>Cold skin</td>
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<tr>
<td>Swelling in calves, legs, feet</td>
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<tr>
<td><strong>Musculoskeletal System</strong></td>
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<tr>
<td>Decreased muscular resistance</td>
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<tr>
<td>Bone pain</td>
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<tr>
<td><strong>Integumentary System</strong></td>
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<tr>
<td>Pallor</td>
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<tr>
<td>Blue, pale, or white sclera</td>
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<tr>
<td>Brittle, broken nails</td>
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<tr>
<td>Poor skin turgor</td>
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<tr>
<td>Dry, brittle, and thinning hair</td>
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<tr>
<td>Ecchymosis, petechiae, nasal/gingival bleeding</td>
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<tr>
<td>Poor wound healing, skin ulcerations</td>
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</tbody>
</table>

*Note. Based on information from Ludwig & Strasser, 2001; Means & Glader, 2014; Perkins, 2010.*
Evidence-Based Interventions

The primary treatments for cancer-related anemia include blood transfusions and erythropoietin. Iron supplementation may be a necessary adjunct to treatment with an erythropoiesis-stimulating agent (ESA). The expected outcomes of treatment are an increase in Hgb, the prevention or reduction of symptoms, an increase in the patient’s QOL, and the ability to complete the treatment course without interruption.

Blood Transfusions

Transfusions of packed RBCs typically are administered when immediate and rapid correction of anemia is needed because of a low Hgb level or the presence of severe symptoms (Faiman, 2014; NCCN, 2014a) and is particularly indicated for patients receiving myelosuppressive chemotherapeutic drugs who require immediate correction of anemia (Rodgers et al., 2012). In general, an Hgb rise of approximately 1 g/dl and hematocrit rise of approximately 3% can be expected after transfusion of one unit of packed RBCs in adult patients (NCCN, 2014a; Schrijvers, 2011).

NCCN (2014a) guidelines recommend that if the cause of the anemia is likely cancer- or chemotherapy-related, the anemia should be categorized to direct initial need for transfusion: (1) asymptomatic anemia without comorbidity indicates observation and ongoing reassessment, (2) asymptomatic anemia with comorbidity (i.e., cardiac, chronic pulmonary, or cerebral vascular issues) or high-risk anemia (i.e., progressive Hgb decline following recent chemotherapy or radiation therapy) indicates consideration of transfusion, and (3) symptomatic anemia indicates administration of transfusion. AABB recommends a restrictive threshold strategy, with an Hgb threshold of 7–8 g/dl for transfusion in hemodynamically stable adults, depending on the patient population, underlying disease, and presence of symptoms (Carson et al., 2012).

The risks associated with RBC transfusion for patients with cancer must be considered. The most common transfusion risk is a delayed hemolytic reaction, followed by transfusion-related acute lung injury (TRALI) (Spivak et al., 2009). TRALI is a serious syndrome of acute respiratory distress, with symptoms including acute-onset hypoxemia and pulmonary edema, fever,
tachypnea, and hypotension. With aggressive respiratory support, which includes mechanical ventilation, most patients will recover within 96 hours. However, in some cases, TRALI may be fatal (AABB, 2013; Spivak et al., 2009). The use of leukoreduced blood products from male donors has reduced the number of reported TRALI cases (AABB, 2013).

Transfusion of RBCs has also been associated with immunosuppressive risks (e.g., depression of natural killer cell function), which may leave patients vulnerable to infection and may even increase the risk of cancer recurrence (Spivak et al., 2009). When clinicians are considering transfusions, understanding the process of RBC storage and how this may impact the clinical benefit to the patient is important. When blood is donated for clinical use, it typically is stored for 35–42 days depending on the anticoagulant-preserve solution (AABB, 2013). The shelf life of irradiated RBCs is a maximum of 28 days (AABB, 2013). The regulatory requirement for maximum storage time is based on the 24-hour survival rate of the transfused RBCs and does not reflect the oxygen-carrying capacity of the product (Lelubre & Vincent, 2013). It is important for nurses to be aware of the changes that RBCs undergo during storage and how they may ultimately affect clinical benefit of transfusion.

During storage, RBCs change from their normal shape to a dented or shriveled structure. They undergo cell membrane changes that make them more susceptible to phagocytosis (Lelubre & Vincent, 2013; Van de Watering & Brand, 2008). In addition, RBCs contain the metabolite 2,3-diphosphoglycerate (DPG). The oxygen-delivering function of RBCs is impaired when 2,3-DPG levels are low. Within two weeks of storage, RBCs almost completely lose 2,3-DPG, and, although this is reversible, it may take up to three days for 2,3-DPG levels to be restored (Van de Watering & Brand, 2008). Together, these storage-related changes in RBCs may impair the functional capacity of the blood product.

An important nursing-sensitive risk involved with RBC transfusion is human error, which is thought to be the most common cause of acute hemolytic transfusion reactions (Spivak et al., 2009). For example, Patient A and Patient B have the same last name but different blood types, and both are receiving two units of packed RBCs on the oncology unit on the same day. The unit of blood intended for Patient B is administered to Patient A. Maskens et al. (2014) reported the results of a Transfusion Error Surveillance System implemented at a 1,212-bed tertiary care center in Toronto, Canada, between 2005 and 2010. A median of 19,000 blood products were transfused during that time, and 15,134 errors were reported, 40% of which were made by the clinical service. Of that 40%, 84% was on the part of the nurse or phlebotomist. Of the top “high-severity” clinical team errors, 12% were due to sample collection error. Twenty-one (0.35%) of clinical service errors resulted in patient harm (i.e., transfusion-associated circulatory overload, TRALI, transfusion reaction, delayed control of hemostasis), and all of these were the result of “inappropriate ordering of blood products outside of hospital guidelines” (Maskens et al., 2014, p. 69).

These data highlight the importance of understanding and adhering to expert group and institutional guidelines and the critical role that nurses play in the safe management and treatment of patients with anemia. Implications for nurses with regard to the administration of blood include the recognition that transfusions provide a temporary benefit and may be detrimental for patients with cancer. Nurses should be aware that the most serious risk associated with blood transfusion is mistransfusion, of which the most common issue is improper patient identification. Institutional policy usually dictates the procedure for patient identification regarding blood transfusion. An active blood type and crossmatch result must be available, the patient must provide written informed consent for transfusion of blood products, and an order must be written. A minimum of two patient identifiers should be used at the bedside (e.g., patient name, date of birth, medical record number), with the patient verbalizing these identifiers to be checked against the order and the patient’s wristband. A two-
nurse check to confirm the blood product unit identification number, type of blood product (e.g., packed RBCs, platelets), ABO blood type and rhesus factor, and expiration date and time for the blood product should be conducted prior to administration.

Transfusions are beneficial for patients who require rapid correction of Hgb, but in light of the risks, alternatives should be considered whenever feasible.

**Erythropoietin Therapy**

As an alternative to blood transfusion, two ESAs are available in the United States: epoetin alfa and darbepoetin alfa. The U.S. indications for epoetin alfa include the treatment of patients with nonmyeloid malignancies experiencing anemia secondary to myelosuppressive chemotherapy, with a minimum of two additional months of such treatment planned; anemic patients with chronic kidney disease with or without concurrent dialysis; anemic zidovudine-treated patients with HIV; and patients with perioperative anemia undergoing elective, non-cardiac, nonvascular surgery (Amgen Inc., 2013b; Janssen Products, LP, 2013). Darbepoetin alfa is indicated in the United States for the treatment of anemia associated with chronic kidney disease with or without concurrent dialysis, and in patients with nonmyeloid malignancies experiencing anemia secondary to myelosuppressive chemotherapy, with a minimum of two additional months of such treatment planned (Amgen Inc., 2013a).

Recent randomized controlled trials demonstrated that treatment with ESAs increases Hgb concentration, resulting in a reduced need for RBC transfusion in patients with chemotherapy-induced anemia, although not without significant risks (Glaspy et al., 2010; Grant et al., 2013; Rizzo et al., 2010). The U.S. Food and Drug Administration (FDA) revised the labeling of ESAs after studies revealed a greater possibility of serious to life-threatening side effects (e.g., serious cardiovascular and thromboembolic events, tumor progression) or death when using epoetin alfa and darbepoetin alfa (U.S. FDA, 2007). An important note is that patients participating in these studies were not receiving chemotherapy. Concerns included an increased risk of serious cardiovascular events in patients with chronic renal failure receiving erythropoietic therapies dosed to target an Hgb level of greater than 12 g/dl, risk of thrombosis in patients treated with erythropoietic therapies before surgery, and possible enhancement of tumor growth rate in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers with the use of erythropoietic therapies dosed to achieve an Hgb level greater than 12 g/dl (Lappin, Maxwell, & Johnston, 2007).

Since that time, additional label changes and warnings have been issued based on data demonstrating increased mortality, tumor progression, and increased risk for thromboembolic events, cardiovascular reactions, and stroke in patients receiving ESAs (Amgen Inc., 2013a, 2013b; Janssen Products, LP, 2013; Rizzo et al., 2010). Bohlius et al. (2009) completed a meta-analysis of data from 13,933 patients across 53 clinical trials and found that treatment with ESAs caused an estimated 17% increase in mortality during the on-study period in patients with cancer and a 10% increase in patients undergoing chemotherapy when compared with control groups. This is the reason that the FDA-approved indication is for patients with anemia secondary to myelosuppressive chemotherapy used for palliative, not curative, intent (Rizzo et al., 2010).

Only providers enrolled in the ESA APPRISE (Assisting Providers and Cancer Patients With Risk Information for the Safe Use of ESAs) Oncology Program may prescribe or dispense ESAs to patients with cancer (Amgen Inc. & Janssen Products, LP, n.d.). The NCCN (2014a) guidelines cite the FDA requirement for patient informed consent under the risk evaluation and mitigation strategy, or REMS, guidelines prior to treating patients with ESAs. In the 2010 updated ASH/ASCO recommendations, providers are reminded to perform a thorough his-
tory, physical examination, and laboratory evaluation to ensure that the decision to consider ESA therapy is consistent with labeled indications and that all clinical risks and benefits are carefully considered and discussed with the patient (Rizzo et al., 2010).

Treatment with ESAs should only be initiated in patients with cancer if they are experiencing CIA with Hgb less than 10 g/dl and at least two more months of myelosuppressive chemotherapy are planned at the start of ESA therapy (Amgen Inc., 2013a, 2013b; Janssen Products, LP, 2013). Only the lowest required ESA dose to avoid blood transfusion should be used, and if an immediate increase in Hgb is indicated, then transfusion should be considered (Amgen Inc., 2013a, 2013b; Janssen Products, LP, 2013; NCCN, 2014a). NCCN (2014a) guidelines provide dosing recommendations for both epoetin alfa and darbepoetin alfa. Initial dosing, following the package insert dosing schedule, is a choice of epoetin alfa 150 units/kg administered subcutaneously (SC) three times weekly or epoetin alfa 40,000 units SC every week. Doses are titrated to 300 units/kg or 60,000 units, respectively, if no response (Amgen Inc., 2013b; Janssen Products, LP, 2013; NCCN, 2014a). Darbepoetin initial dosing is 2.25 mcg/kg SC weekly, titrated to 4.5 mcg/kg for subtherapeutic response, or darbepoetin 500 mcg SC every three weeks, with no titration for Hgb increase of less than 1 g/dl (Amgen Inc., 2013a; NCCN, 2014a). Currently the most common dosing schedule of epoetin alfa for patients who are receiving chemotherapy is 40,000 units SC once weekly. The dose of darbepoetin alfa commonly used in the oncology setting is 500 mcg SC every three weeks.

Alternative ESA regimens for patients with cancer were added to the NCCN guidelines in 2007. NCCN (2014a) lists regimens for darbepoetin alfa as
- 100 mcg SC fixed dose every week, titrated to 150–200 mcg for no response
- 200 mcg SC fixed dose every two weeks, titrated to 300 mcg for no response
- 300 mcg SC fixed dose every three weeks, titrated to 500 mcg for no response.

NCCN (2014a) lists the alternative regimens for epoetin alfa as
- 80,000 units SC every two weeks
- 120,000 units SC every three weeks.

If the patient experiences less than 1 g/dl rise in Hgb after four weeks of therapy with epoetin alfa or six weeks of therapy with darbepoetin alfa, a dose increase is indicated (NCCN, 2014a). If no Hgb response occurs by eight to nine weeks despite iron supplementation, ESAs should be discontinued and transfusion should be considered. If dose titration produces a response, erythropoietic therapy should be continued at the minimum dose required to avoid transfusion until chemotherapy is completed and anemia has resolved (usually within six weeks after the completion of chemotherapy), at which time it should be discontinued. If Hgb levels exceed a level at which RBC transfusion is not indicated, or if an Hgb rise of 1 g/dl or more in a two-week period if achieved, the ESA dose should be reduced by 25% for epoetin alfa and by 40% for darbepoetin alfa (Amgen Inc., 2013a, 2013b; NCCN, 2014a). In comparing the available data on these two therapies, they appear to be equivalent in regard to clinical benefits and risks (Grant et al., 2013; Rizzo et al., 2010; Ross et al., 2006).

Nursing implications for the administration of erythropoietic agents include the need for nurses to keep abreast of current research, labeling indications, dosing schedules, and associated risks and benefits of ESA therapy. Nurses must advocate for patients to receive the lowest dose possible that is able to increase the Hgb level and avoid transfusion, remain vigilant in monitoring Hgb at least weekly to ensure stabilization of Hgb, and diligently advocate to withhold erythropoietic therapy if it is ineffective after eight or nine weeks of therapy despite iron supplementation (NCCN, 2014a).

Some patients report discomfort from the SC injection of epoetin alfa, which results from the citrate buffer in single-dose vials of the drug. Epoetin alfa should be warmed to room tem-
perature before administration to decrease the likelihood of stinging with injection. Other strategies include using a smaller-gauge needle to administer epoetin alfa and rotating injection sites to alleviate discomfort (Buchsel, Murphy, & Newton, 2002).

Patient safety is imperative when prescribing ESAs. The orders must be clear and accurate and avoid the use of abbreviations (i.e., SC, SQ, sub q) (Institute for Safe Medication Practices, 2013). Preprinted or computerized (electronic) entries of ESA orders provide common dosing and titration schedules, enhancing the safe use of ESAs. Institutional policy will determine which method of ordering medications is best for the individual setting.

Iron Supplementation

Iron supplementation is necessary in iron-deficiency anemia and also in many patients receiving erythropoietic therapy because of the eventual development of functional iron deficiency. In functional iron deficiency, the release of stored or bound iron cannot be activated at a rate fast enough to keep up with erythropoiesis, whereas in absolute iron deficiency, patients have deficient iron stores (NCCN, 2014a). Reduction in iron stores may result from ACD, nutritional deficiencies, or chronic blood loss (Moran, 2014b). Supplementation with usable iron may be required in patients with functional iron deficiency to enhance their response to erythropoietin therapy (NCCN, 2014a), although it is not currently a standard-of-care adjuvant therapy to ESA treatment per ASH/ASCO recommendations (Rizzo et al., 2010).

Once erythropoietic therapy is warranted, baseline iron studies should be completed before initiating therapy. If the patient has absolute iron deficiency, defined as serum ferritin less than 30 ng/ml or TSAT less than 20%, iron supplementation is indicated without the use of ESAs (NCCN, 2014a). If the Hgb does not increase, the patient should be evaluated for functional iron deficiency. The initial method of pharmacologic iron supplementation should be oral therapy. If insufficient response is observed after four weeks, a trial of IV iron should be considered (NCCN, 2014a). In patients receiving ESAs, a ferritin level of 30–100 ng/ml and TSAT of 20%–50% will result in the development of functional iron deficiency, and the nurse should anticipate the need for administration of IV iron (NCCN, 2014a).

Oral iron supplementation for iron-deficiency anemia often consists of 200–325 mg oral ferrous sulfate (approximately 130 mg elemental iron) twice daily for six months (Moran, 2014b). Multiple preparations of oral iron are available with varying amounts of elemental iron in each tablet. Gastrointestinal side effects, such as abdominal pain, nausea, vomiting, and constipation, are common with oral iron treatment and can result in a lack of patient adherence to the prescribed iron supplementation schedule. Taking the supplement with food may reduce the severity of side effects, but it also can reduce iron absorption (Alleyne, Horne, & Miller, 2008). Other factors that may affect the absorption of oral iron include drugs (e.g., antacids, tetracycline antibiotics), beverages (e.g., tea, milk, phosphate-containing or carbonated beverages), and health conditions (e.g., ACD, which is prevalent in patients with cancer) (Alleyne et al., 2008; Moran, 2014b).

Available parenteral iron preparations include iron dextran, ferric gluconate, ferric carboxymaltose, and iron sucrose. Most adverse events are associated with high-molecular-weight iron dextran; therefore, the low-molecular-weight formulation is recommended (NCCN, 2014a). Hypersensitivity to iron dextran usually occurs within the first few minutes of administration in 2.5% of patients and causes anaphylaxis in less than 1% of patients (Drugs.com, 2014). Symptoms of hypersensitivity may include urticaria, skin rash, allergic purpura, pruritus, fever, chills, dyspnea, arthralgia, and myalgia, while respiratory collapse quickly manifests in anaphylaxis (Drugs.com, 2014). The NCCN (2014a) guidelines require test doses
when administering iron dextran and strongly recommend them for ferric gluconate or iron sucrose in patients who are sensitive to iron dextran or who have allergies to other medications. It is recommended to avoid IV iron in patients with active infection (Aapro et al., 2012; NCCN, 2014a).

The NCCN recommendations for parenteral iron administration (NCCN, 2014a, p. ANEM-D 2 of 3) include the following.

- **Iron dextran**: A test dose of 25 mg slow IV push is required; the clinician must wait one hour prior to administering the remainder of the dose. Treatment is 100 mg IV over five minutes once weekly for 10 doses (total dose of 1 g). Alternatively, the total dose can be given over a few hours.

- **Ferric gluconate**: A test dose of 25 mg slow IV push or infusion is recommended. Treatment is 125 mg IV injection or infusion over 60 minutes once weekly for eight doses. Doses greater than 125 mg at a time are not recommended.

- **Iron sucrose**: A test dose of 25 mg slow IV push is recommended. Treatment is 200 mg IV injection or infusion over 60 minutes every two to three weeks. Alternatively, 200 mg IV may be given over two to five minutes and repeated every one to four weeks. Doses greater than 300 mg at a time are not recommended.

Henry, Dahl, Auerbach, Tchekmedyian, and Laufman (2007) conducted a study of 187 patients with CIA to determine the safety and efficacy of IV ferric gluconate, oral ferrous sulfate, or no iron to improve the Hgb level in anemic patients with cancer receiving chemotherapy and epoetin alfa. IV ferric gluconate significantly improved the response to epoetin alfa (p = 0.0092). The Hgb response rate for patients receiving IV ferric gluconate was 73%, compared to 45% and 41% for patients receiving oral iron and no iron, respectively. Of the 50 patients in this study with a baseline TSAT below 20%, the Hgb response rate for patients receiving IV ferric gluconate was 81%, compared to 37% and 27% in those receiving oral iron or no iron, respectively. The response rates for the oral iron and no-iron groups were so similar that it raised the question of whether oral iron should even be an option for patients with cancer who are receiving erythropoietic therapy (Henry et al., 2007).

Bastit et al. (2008) conducted a study of 396 patients with CIA to determine the hematopoietic response in patients receiving darbepoetin alfa either with or without IV iron (200 mg IV every three weeks). Hematopoietic response rates were significantly greater in the IV iron group than in the standard practice group (86% vs. 73%, p = 0.011). Patients in the IV iron group demonstrated a faster hematopoietic response, lower transfusion requirement, and similar incidence of adverse events, suggesting improvement in clinical benefit from ESAs with the use of concomitant iron supplementation (Bastit et al., 2008). Nausea was the most common adverse event reported by participants in both treatment groups (19% in each), whereas fatigue (11% vs. 19%) and diarrhea (7% vs. 17%) differed between the IV iron and standard practice groups, respectively (Bastit et al., 2008). Iron-related adverse events occurred in 3% of the IV iron arm, with the most common being hypotension (n = 3), abdominal pain (n = 3), nausea (n = 3), and vomiting (n = 3).

Nursing implications for the administration of iron supplementation include continuous monitoring of iron status and appropriate patient teaching based on the route of administration. Patients should be taught to take oral iron supplements on an empty stomach, to separate doses from antacid medications, and to report gastrointestinal symptoms promptly so that interventions can be implemented. Common side effects include nausea, constipation (or diarrhea), and black stools; therefore, patient education should review pharmacologic and nonpharmacologic strategies to manage such toxicities and parameters for when patients should notify their doctor of persistent, bothersome, or severe side effects. In administering IV iron, nurses should be cognizant of the importance of test doses and monitoring
for signs and symptoms of hypersensitivity reactions (Alleyne et al., 2008; NCCN, 2014a). Patients should be instructed to report any new or worsened symptoms during the course of an infusion to their nurse immediately.

### Expected Patient Outcomes

The goals of anemia management are to increase the Hgb level to the patient’s normal level, resolve symptoms, improve the patient’s QOL, and allow the patient to complete the treatment course uninterrupted. Cleeland et al. (1999) conducted an incremental analysis that is now a classic study of the Hgb level at which the greatest effect on QOL is realized. They found that the largest improvement in QOL occurred when the patient’s Hgb level increased from 11 g/dl to 12 g/dl and that QOL benefits were more significant in patients with mild anemia than in those with moderate to severe anemia. Crawford et al. (2002) confirmed these results, finding the greatest gain in QOL to occur at an Hgb level of 11–13 g/dl upon analyzing the same community-based studies as Cleeland et al. (1999). Lyman and Glaspy (2006) conducted a systematic literature review of 11 studies to detect whether benefits existed for early intervention with erythropoietic therapy to treat CIA. They concluded that patients received the greatest clinical benefit, defined as an Hgb level greater than 10 g/dl, from erythropoietic therapy when treatment was begun early.

These studies were important in identifying strategies to enhance patients’ QOL, including initiating interventions early and maintaining the Hgb level at 11–12 g/dl. Oncology nurses should strive to identify anemia early and begin treatment promptly to prevent the development of moderate to severe anemia. Anticipating anemia, comprehensively assessing its impact on patients, and advocating for evidence-based treatments are key strategies for oncology nurses in providing high-quality patient care.

### Patient Teaching Points

One of the most crucial roles of oncology nurses is to instruct patients with regard to their care. Patients must be fully educated about anemia. The American Cancer Society’s website (www.cancer.org) offers patient information on cancer symptoms, including anemia (see American Cancer Society, 2012). This resource discusses the condition of anemia, treatment options, and other relevant information for the oncology nurse.

At diagnosis, nurses can define anemia for patients, discuss risk factors for and causes of anemia, list the symptoms, and explain blood counts. They should offer strategies for managing fatigue, such as energy conservation, sleep routines, distraction, exercise, and keeping a symptom journal (Mitchell, Beck, Hood, Moore, & Tanner, 2009). Nurses should provide nutrition information, including suggestions for energy-boosting foods and information on vitamin deficiencies. For patients taking iron supplements, education regarding the prevention and management of constipation is essential (Woolery et al., 2008). See Chapter 5 more information on managing constipation and Chapter 15 for a more detailed discussion of fatigue management strategies.

Education fosters patient compliance with treatment and allows patients to actively participate in their care. Knowledge empowers patients and provides a sense of control during a time in which they may be experiencing significant losses and fears. Education ideally should begin prior to the development of symptoms. Nurses should encourage patients to report all symptoms promptly to facilitate early intervention.
Need for Future Research

A number of questions and issues remain pertaining to anemia and its treatment. First, with regard to classification, the current grading systems do not consider gender differences. Because the normal Hgb level for men is higher than that for women, the optimal time to begin treatment may vary with gender.

Second, erythropoietin receptors have been found on tumor cells, such as head and neck and breast tumor cells (Glaspy et al., 2010). Studies have reported decreased survival in patients treated with ESAs while receiving chemotherapy or radiation therapy (Henke et al., 2003; Leyland-Jones et al., 2005). The package inserts for darbepoetin alfa and epoetin alfa warn that ESAs have been shown to adversely affect overall survival and disease progression in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers (Amgen Inc., 2013a, 2013b; Janssen Products, LP, 2013).

Another issue that has been addressed in historic studies but needs revisiting is whether a correlation exists between cancer recurrence and blood transfusion (Jahnson & Andersson, 1992; Vamvakas, 1996). Immunosuppression resulting from blood transfusion and tumor hypoxia associated with anemia are two explanations for this possible connection (Hellings & Blajchman, 2009; Vaupel, 2012). In light of the correlation between erythropoietic therapy and decreased survival, future studies designed with the primary endpoints of overall survival and progression-free survival are warranted.

Future research is also needed to determine the ideal time to begin IV iron supplementation during chemotherapy when an erythropoietic agent is being administered. In addition, the optimal total IV iron dose must be further explored (Henry et al., 2007). Finally, as anemia assessment and management typically have focused on objective measures (Hgb and hematocrit levels), nursing research exploring subjective measures of anemia is needed. Monitoring patient-reported outcomes and nursing response to issues related to anemia may help to determine anemia patterns, potentially resulting in new strategies in the assessment and management of anemia.

Conclusion of Case Study

T.C. demonstrates several risk factors for anemia during the treatment of her cancer. These include a mild baseline anemia, female gender, a diagnosis of lung cancer, upcoming myelosuppressive chemotherapy, and planned surgical resection, which carries the risk of blood loss (Barrett-Lee et al., 2006; Cheng et al., 2012). T.C. presented with symptoms including dyspnea on exertion and fatigue, which could be related to her cancer, her mild anemia, or both. Vigilant ongoing nursing assessment will be critical in monitoring her for new or worsened symptoms of cancer- or chemotherapy-induced anemia and initiating prompt intervention.

Conclusion

Anemia is prevalent in oncology populations and negatively affects patients’ QOL, daily functioning, and survival. Determining the differential diagnosis of anemia may pose a challenge for the healthcare team. Oncology nurses are in an ideal position to identify symptoms of anemia and initiate treatment early to improve the Hgb level, resolve symptoms, enhance
patients' QOL, and afford patients the opportunity to complete their treatment course without interruption. In light of concerns about potential serious adverse effects of ESAs, oncology nurses must keep abreast of current research in this area and vigilantly monitor the Hgb level of patients who are receiving erythropoietic therapy. Anticipation of anemia, comprehensive symptom assessment, and evidence-based interventions are essential to ensure high-quality patient care.

The author would like to acknowledge Sheryl Miller, RN, MSN, MBA, OCN®, for her contribution to this chapter that remains unchanged from the first edition of this book.

References


Case Study

E.M. is a 47-year-old woman with a two-year history of multiple myeloma. When E.M. first came to the oncology center two years ago, she did not want her family (other than her husband) or her colleagues at work to know about her diagnosis and treatment. She had been receiving oral steroids and a bisphosphonate (zoledronic acid) every month to stabilize her bones. Her immunoglobulin G started climbing rapidly, and she developed systemic symptoms, including fevers and rigors. She failed to respond to treatment with thalidomide. The oncologist determined that autologous stem cell transplantation would offer the best treatment option at the present time. E.M. came to visit the oncology nurse after seeing the oncologist. After hearing the doctor’s recommendation, she was crying. She said she does not know how to tell her college-age daughters about this, and she is scared about the transplantation and unsure of how she is going to pay for the treatment. The nurse provided her reassurance and support, discussing her relationship with her daughters and her concerns. The nurse arranged for a visit from the social worker to discuss the financial arrangements and insurance coverage. To help prepare E.M. for the transplantation, the nurse offered ongoing assistance and provided teaching materials.

One week later, E.M.’s husband called the nurse because E.M. had been very upset, and he did not know what to do to help her. She was talking rapidly and saying she was so worried that she had not been able to sleep or eat all week. The nurse suggested that she come into the center to see the oncology nurse practitioner. When E.M. and her husband came into the office, E.M. was pacing around the room and talking at a quick pace. Her thoughts moved from the transplantation to her daughters to work issues in rapid sequence. Her weight was down four pounds since a week ago.

Overview

Anxiety disorders include those defined by a response of excessive fear or worry in anticipation of an event. Anxiety is a subjective state characterized by emotional discomfort and apprehension that stimulates a physiologic adaptation to a perceived threat (American Psychiatric Association [APA], 2013). It can be a protective mechanism by motivating an individual to reduce or avoid the perceived threat. In this way, anxiety is adaptive and helps a person to function appropriately by responding to the threat and reducing its danger (Levin & Alici,
For example, a woman who finds a lump in her breast experiences fear, which motivates her to seek medical care; this is adaptive anxiety. Anxiety becomes maladaptive when a person responds to stress or a threat in a way that is disproportionate to the threat—either overblown, chronic, or inappropriate (APA, 2013). A woman with a lump in her breast may experience fear to such a degree that she is unable to make a medical appointment; this is maladaptive anxiety.

Factors associated with a risk for anxiety include female sex (approximately a 2:1 ratio), younger age, lower socioeconomic status, and divorced or widowed marital status (APA, 2013; Hulbert-Williams, Neal, Morrison, Hood, & Wilkinson, 2012; Levin & Alici, 2010). Anxiety disorders usually last longer than six months and are differentiated by the type of situations that create the excessive fear response, as well as by the associated thoughts and beliefs (APA, 2013). The anxiety disorder subtypes are described in Table 4-1. A number of patient disorders have a high prevalence for anxiety comorbidity (APA, 2013), but APA does not classify these as anxiety disorders. They include post-traumatic stress disorder, anticipatory nausea and vomiting, and obsessive-compulsive disorder. The anxiety component is managed as an anxiety disorder concurrently with treatment for the primary diagnosis (National Comprehensive Cancer Network® [NCCN®], 2014). These disorders are also described in Table 4-1.

Anxiety is a common problem in patients with a cancer diagnosis. Oncology nurses may spend extended periods of time with patients with cancer, creating opportunities for patients to disclose their fears. During routine care, patients may reveal their feelings about their diagnosis and treatment, allowing nurses to carefully explore and assess the perception of threat and the degree of associated fear. How nurses respond to patients’ expressions of fear affects further assessment (Fortin, Dwamena, Frankel, & Smith, 2012) and consequently the identification and treatment of anxiety for patients.

A person’s response to stressors, such as a cancer diagnosis, will depend on many factors. Patients react based on previous life experiences, prior coping strategies, age, maturity, culture, gender, and the presence of support systems, including family, friends, and spiritual sources of support (Li, Hales, & Rodin, 2010). Anxiety may occur as part of a preexisting anxiety disorder or at different periods during the course of a cancer diagnosis and treatment.

High levels of anxiety are common with a new diagnosis of cancer before patients have had an opportunity to integrate these new experiences into their frames of reality (Brocken, Prins, Dekhuijzen, & van der Heijden, 2012). During this initial period of shock and turmoil, patients may experience fear and worry about the future, confused and scattered thinking, and difficulty concentrating. They may have disruptions in sleep and appetite and may experience difficulty carrying out normal roles and responsibilities, such as work and family obligations. With the support of families and friends, attentive healthcare providers, counseling, and sometimes medications, patients usually move forward through this crisis period, make the necessary decisions, and pursue treatment for their cancer. In addition to the diagnostic phase, anxiety disorders occur at various times throughout the cancer trajectory into survivorship and have a pervasive effect over time (Hulbert-Williams et al., 2012; Shuster, 2013). Overall incidence rates of anxiety in patients with cancer have been reported as 10%–30% (Brintzenhofe-Szoc, Levin, Li, Kissane, & Zabora, 2009; Mitchell et al., 2011; So et al., 2009). The presence of prolonged or recurrent anxiety after the initial stage of crisis supports the need for ongoing assessment. Numerous assessment strategies are available to understand and quantify the patient’s experience. Additional members of the resource team, such as social workers, mental health specialists, and pastoral care providers, may be recruited to assist patients and provide the necessary interventions to decrease their anxiety and improve their quality of life (NCCN, 2014).

This chapter will present and discuss the assessment and treatment of anxiety disorders in patients with cancer. The term distress often is used instead of anxiety because it has less social
<table>
<thead>
<tr>
<th>Subtype</th>
<th>Description</th>
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<tbody>
<tr>
<td>Generalized anxiety disorder</td>
<td>Chronic, uncontrollable nervousness, fearfulness, or a sense of worry that lasts 6 months or longer; usually preexisting but may be exacerbated by illness</td>
</tr>
<tr>
<td>Anxiety due to medical conditions</td>
<td>Symptoms are a direct physiologic consequence of an underlying medical condition</td>
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<tr>
<td>Separation anxiety</td>
<td>Developmentally inappropriate or excessive fear of separation from those to whom the individual is attached; is recurrent and persistent</td>
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<tr>
<td>Social anxiety disorder (phobia)</td>
<td>Fear that social situations may expose one to scrutiny and resulting embarrassment or humiliation</td>
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<tr>
<td>Substance-/medication-induced anxiety</td>
<td>A direct physiologic effect of a drug, medication, or toxin</td>
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<tr>
<td>Panic disorder</td>
<td>An abrupt surge of intense fear and/or discomfort that reaches a peak in minutes and has 4 or more associated physical symptoms (such as sweating, palpitations, light-headedness, chills or heat, shaking, shortness of breath); may recur during illness</td>
</tr>
<tr>
<td>Phobic disorder</td>
<td>Excessive fear of a specific object or situation (such as needles, hospitals, claustrophobia in medical imaging machines)</td>
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**Comorbid Anxiety Disorders**

<table>
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<tr>
<th>Subtype</th>
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<tbody>
<tr>
<td>Anticipatory nausea and vomiting</td>
<td>A conditioned response induced by prior cancer treatments</td>
</tr>
<tr>
<td>Post-traumatic stress disorder</td>
<td>A state of psychological distress following exposure to a traumatic or stressful event</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>Presence of obsessions (recurrent, persistent thoughts and images that are intrusive and unwanted and are attempted to be ignored or suppressed by another thought or action) and compulsions (repetitive behaviors aimed at reducing a perceived threat that are either not connected with the threat or are excessive); usually preexisting</td>
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<tr>
<td>Adjustment disorder</td>
<td>A psychological response within 3 months of introducing a stressor; occurs directly in response to that stressor and is marked by either anxiety or a mixed anxiety and depressed mood; similar to generalized anxiety disorder although due to a specific stressor</td>
</tr>
</tbody>
</table>

stigma attached to it and may be easier for patients to discuss (Holland, Kelly, & Weinberger, 2010; NCCN, 2014). For this chapter, anxiety will be considered a part of a cluster of symptoms that cause distress. See Chapter 11 for a more detailed discussion of distress.

Incidence

Anxiety, depression, and distress often are clustered when describing the experience of patients with cancer, and some overlap exists between anxiety and depression in many patients (So et al., 2009). The actual incidence of anxiety often has been combined with depression in studies that evaluate psychiatric disorders in patients with cancer (Mitchell et al., 2011). In one of the most quoted historical studies, the Psychosocial Collaborative Oncology Group found that 47% (n = 101) of patients (N = 215) with cancer had psychiatric disorders (Derosgatis et al., 1983). Of the 101 patients with cancer who also had psychiatric diagnoses, 68% had adjustment disorders with depressed, anxious, or mixed mood features, and 16% met the criteria for an anxiety disorder.

In their meta-analysis of studies comparing anxiety and depression prevalence in patients with cancer with healthy controls, Mitchell and colleagues found the prevalence of anxiety significantly higher (p = 0.039) in patients with cancer (17.9%, n = 48,964) than in the healthy controls (13.9%, n = 226,467) (RR = 1.27, 95% CI [1.08, 1.50]) (Mitchell, Ferguson, Gill, Paul, & Symonds, 2013). Notably, the authors found that this higher prevalence of anxiety was long lasting, persisting for up to 10 years after a cancer diagnosis. In historical studies, 20%–40% of patients with cancer experienced distress and anxiety (Carroll, Kathol, Noyes, Wald, & Clamon, 1993; Zabora, BrintzenhofeSzoc, Curbow, Hooker, & Piantadosi, 2001). Uncontrolled pain is particularly associated with anxiety, making pain management a significant need for many patients with prolonged distress after an initial cancer diagnosis (Syrjala et al., 2014).

When it occurs across the cancer spectrum, anxiety is one manifestation of emotional distress that people with cancer frequently experience. NCCN included the management of anxiety within its guidelines for distress management (NCCN, 2014). According to the guideline authors, anxiety occurs along a continuum from normal feelings of sadness and vulnerability to problems that may become disruptive. The guidelines identify specific periods of increased vulnerability that may put patients with cancer at risk for developing distress and anxiety. These points of care are described in Chapter 11 (see Table 11-1). During these times, clinicians need to assess patients more thoroughly so that interventions to alleviate anxiety and distress and thus improve quality of life are instituted in a timely manner.

Certain patients are more at risk for anxiety disorders during the course of their cancer treatment (see Figure 4-1). Patients with a previous history of adjustment disorders with anxiety or panic attacks, sexual abuse, or major depression are at risk for maladaptive anxiety associated with a cancer diagnosis (Levin & Alici, 2010). Patients with depression may have anxiety disorders and often are predisposed to more anxiety during times of stress (APA, 2013).

Pathophysiology

Although the symptoms of anxiety may be both behavioral and physical, they often present as somatic symptoms, as the case study illustrated. Feeling anxious is precipitated by stimulation of a general adaptation to stress including both the sympathetic and autonomic nervous systems (APA, 2013). Patients with high anxiety often present with physical symptoms
related to activation of the autonomic nervous system (Dahlin, 2014). In the case study, E.M. had lost weight, was restless and pacing, and was unable to eat or sleep. Stimulation of the autonomic nervous system may produce sweating, tachycardia, cold and clammy hands, dizziness, and diarrhea. Symptoms in the musculoskeletal system include shakiness and jumpiness, trembling, inability to relax, restlessness, and fidgeting (APA, 2013; Dahlin, 2014). The most common physical symptoms of anxiety are listed in Figure 4-2.

The experience of anxiety varies among patients, and symptoms may be more subjective in nature in some patients than in others. In the case study, E.M. was worried about finances, worried about the transplant, was restless, and suffered insomnia. Patients experiencing increased levels of anxiety often present with both physical and psychosocial symptoms that are exhibited more days than not and interfere with important areas of daily functioning (APA, 2013). Examples of behavioral, cognitive, and affective symptoms of anxiety are detailed in Figure 4-2.

Medical conditions and certain drugs may cause a subtype of anxiety. Use of steroids, neuroleptics, or stimulants, as well as withdrawal from sedatives, benzodiazepines, or alcohol, may contribute to a state of anxiety (APA, 2013). Clinicians also must consider the possibility of comorbid medical conditions causing the feelings of anxiety in a patient and explore this carefully while instituting anxiety-reducing interventions. Medical conditions that may cause anxiety are listed in Figure 4-3.

**Assessment**

A thorough assessment is the cornerstone of care for patients with cancer experiencing anxiety. Determining what is appropriate (adaptive anxiety) and what is disabling (maladaptive anxiety) and the etiology of these symptoms may be difficult. If anxiety is affecting the patient’s ability to function in normal roles, make decisions, or continue with treatment, then further assessment of the physical and subjective symptoms of anxiety is warranted.

Good communication skills will help nurses to assess anxiety and explore patients’ experiences and concerns. When a patient says “I can’t stop worrying,” “I am so nervous about this treatment that I can’t sleep,” or “I can’t concentrate at work because I’ve been worrying about the test results,” the nurse needs to hear these phrases as cues to the patient’s anxiety.
In contrast, a nurse may conduct a symptom assessment with a single question such as “Are you worried?” (Levin & Alici, 2010) or “How anxious have you felt this week?” (Jacobsen & Jim, 2008). Although not comprehensive, this questioning is rapid and may lead to further exploration of the presence of anxiety and the impact of these feelings on the patient’s ability to function and make decisions.

**FIGURE 4-2** Common Symptoms of Anxiety

<table>
<thead>
<tr>
<th>Physical Symptoms</th>
<th>Behavioral Symptoms</th>
<th>Cognitive Symptoms</th>
<th>Affective Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tachycardia or palpitations</td>
<td>• Avoidance</td>
<td>• Recurrent thoughts or worries</td>
<td>• Nervous behaviors: pacing, picking, unable to sit still</td>
</tr>
<tr>
<td>• Fainting or light-headedness</td>
<td>• Compulsion</td>
<td>• Apprehension</td>
<td>• Scared, alarmed, worried</td>
</tr>
<tr>
<td>• Tachypnea</td>
<td>• Flight-or-fight response</td>
<td>• Focusing on the threat at the exclusion of other details (“tunnel vision”)</td>
<td></td>
</tr>
<tr>
<td>• Perception of dyspnea or shortness of breath</td>
<td>• Inability to speak</td>
<td>• Hypervigilance</td>
<td></td>
</tr>
<tr>
<td>• Sweating</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Loss of appetite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Headaches</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Restlessness or fidgeting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Startle reflex; twitching muscles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Abdominal distress, butterflies in stomach</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note. Based on information from American Psychiatric Association, 2013; Dahlin, 2014; Levin & Alici, 2010.*

**FIGURE 4-3** Medical Conditions That May Cause Anxiety

- Cancers with hormone-secreting tumors such as pheochromocytoma
- Cardiovascular conditions such as angina, congestive heart failure, mitral valve prolapse, or new-onset severe hypertension or dysrhythmias
- Endocrine disorders such as hyperthyroidism, hypothyroidism, diabetes, and hyper- and hypoglycemia, carcinoid syndrome, or Cushing syndrome
- Respiratory disorders such as asthma, emphysema, hypoxia, pneumonia, or pulmonary embolus
- Neurologic conditions such as brain lesions, seizure disorder, cerebrovascular accident, and encephalopathy, or dementia
- Withdrawal from drugs or alcohol
- Immune or autoimmune conditions such as HIV, AIDS, or lupus
- Uncontrolled pain or other symptoms related to cancer treatment
- Hereditary predisposition to developing anxiety

*Note. Based on information from Dahlin, 2014; National Comprehensive Cancer Network, 2014.*
Specific communication skills by nurses may facilitate patient disclosure, provide psychosocial support, and assess patients’ anxiety. Communication skills will also direct patient assessment and identify anxiety that requires further intervention or referral to mental health providers (Lein & Wills, 2007). The following communication skills may facilitate patient disclosure while providing psychosocial support (Fortin et al., 2012).

• Active listening—an interactive process that begins with the nurse positioned, physically and emotionally, to hear the patient’s experience

• Open-ended questions—questions often beginning with who, what, when, why, or how that cannot be answered with a yes or no. These are used to explore the patient’s experience.

• Closed-ended questions—questions that require brief responses such as yes or no. They are facilitative if used to enhance the accuracy of information. They are a barrier to communication if they discourage patient discussion and can place the patient in a defensive position.

• Responses—responses that acknowledge the patient’s experience and contain messages of understanding and support
  – Clarifying responses use simplification and summarization to make concise statements about the patient’s experience and demonstrate that the patient has been heard.
  – Reflective responses restate the patient’s words with the implied emotional undertones. These are used to understand the patient’s responses to the situation.
  – Empathetic responses convey the meaning of the patient’s experience and the nurse’s support and interest.
  – Nonverbal responses including nodding, leaning forward, and facial expressions urge the patient to continue talking. They create a more comfortable interaction than silence and also demonstrate active listening.

The nurse’s assessment should explore current support systems and prior coping methods that have been successful for the patient. Support systems may include significant others such as family and friends, spiritual sources of support, colleagues, community members, and pets.

The risk for suicide in patients with cancer is twice that of the general public (Misono, Weiss, Fann, Redman, & Yueh, 2008). An association exists between a diagnosis of anxiety and a risk for suicide. Thus, nurses must assess for suicidal ideation, as well as risk factors for suicide, in all patients with cancer, including those who exhibit anxiety (Cooke, Gotto, Mayorga, Grant, & Lynn, 2013). The risk factors for suicide include (Cooke et al., 2013; Fang et al., 2012)

• Older age
• Male gender
• Unmarried
• Advanced cancer and/or high-fatality cancer (e.g., lung, head and neck, and stomach cancers)
• Time immediately after cancer diagnosis or recurrence
• Presence of pain
• Decreased physical functioning
• Preexisting depression, anxiety, or substance abuse
• Family history of suicide.

The presence of suicide risk factors warrants referral of the patient to a mental health professional. Other clinical indications also require referral to a mental health professional, social worker, or pastoral counselor (NCCN, 2014), such as

• Score of 4 or higher on the NCCN Distress Thermometer
• Excessive worries and fears
• Excessive sadness
• Unclear thinking
• Despair and hopelessness
• Severe family problems
• Spiritual crises
• Suicidal ideation.

Measurement

Many tools are available to evaluate patient anxiety and distress (see Table 4-2). Although traditional nursing assessments usually include questions regarding the patient’s psychosocial condition, they may not address or measure the severity of anxiety specifically. Specific tools are available to rate patient anxiety and identify specific areas of concern. Mental health professionals frequently use the Structured Clinical Interview for DSM (Diagnostic and Statistical Manual of Mental Disorders) Disorders, known as the SCID (Spitzer, Williams, Gibbon, & First, 1992), but this tool is lengthy, requires special training, and may be best utilized by mental health experts. Shorter tools are available to nurses, and some are brief enough to be used during routine assessment at the bedside or chairside. Some are visual scales that are appropriate for all literacy levels, such as the NCCN Distress Thermometer (NCCN, 2014), whereas others use paper questionnaires or handheld interactive electronic devices to capture information about the patient’s experience.

The Distress Thermometer is a simple screening tool that allows patients to rate their distress on a scale of 0–10, with 0 being no distress and 10 being extreme distress (NCCN, 2014). It is accompanied by a problem checklist that indicates sources of distress, including anxiety.

<table>
<thead>
<tr>
<th>TABLE 4-2</th>
<th>Self-Report Tools to Measure Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tool</td>
<td>Number of Items</td>
</tr>
<tr>
<td>Anxiety Sensitivity Index (Reiss et al., 1986)</td>
<td>16</td>
</tr>
<tr>
<td>Beck Anxiety Inventory (Beck &amp; Steer, 1993)</td>
<td>21</td>
</tr>
<tr>
<td>Brief Symptom Inventory (Derogatis &amp; Melisaratos, 1983)</td>
<td>53</td>
</tr>
<tr>
<td>Depression Anxiety Stress Scales (Lovibond &amp; Lovibond, 1995)</td>
<td>42</td>
</tr>
<tr>
<td>Distress Thermometer with problem checklist (National Comprehensive Cancer Network, 2014)</td>
<td>1 (0–10)</td>
</tr>
<tr>
<td>Generalized Anxiety Disorder Assessment (Spitzer et al., 2006)</td>
<td>7</td>
</tr>
<tr>
<td>Hospital Anxiety and Depression Scale (Zigmond &amp; Snaith, 1983)</td>
<td>14</td>
</tr>
<tr>
<td>State-Trait Anxiety Inventory (Spielberger, 1983)</td>
<td>20</td>
</tr>
</tbody>
</table>
symptoms (see Chapter 11, Figure 11-1). NCCN (2014) recommends incorporating the Distress Thermometer assessment scale into the initial patient visit and at appropriate intervals and referring patients with a score of four or higher for psychosocial services. The guidelines also recommend screening for medical causes of anxiety, patient safety, decision-making ability, and an evaluation of the family and home environment (NCCN, 2014).

While the Distress Thermometer is a useful tool for ongoing distress screening (NCCN, 2014), it measures a more global symptom cluster rather than providing a measure of anxiety severity. In a recent review of outcome measures used in randomized controlled trials (RCTs) of interventions for anxiety in patients with cancer, the Hospital Anxiety and Depression Scale (HADS) scored highest on detection of anxiety treatment effects (Luckett et al., 2010). The American Society of Clinical Oncology (ASCO) endorsed the use of any validated tool for measuring anxiety in its ASCO clinical guideline for managing patients with anxiety (Andersen et al., 2014). Despite this broad allowance for clinicians to use their tool of preference, the Generalized Anxiety Disorder 7-item scale (GAD-7) is endorsed in the guideline. Regardless of which tool is employed for screening, patients who screen positive for anxiety should be referred for a structured clinical interview (Traeger, Greer, Fernandez-Robles, Temel, & Pirl, 2012). The ASCO guidelines (Andersen et al., 2014) provide an algorithm for screening and assessing for anxiety in adults with cancer (see Figure 4-4).

**Evidence-Based Interventions**

The evidence base for anxiety treatment and management strategies in the cancer setting has limitations. Most trials lack inclusion of patients with clinically significant anxiety and are fraught with methodologic limitations (Traeger et al., 2012). This has led to continued use of interventions for which the outcomes are not supported by evidence. The care of patients with anxiety has historically included interventions that are accessible to patients, low cost, and well intentioned; however, ineffective care may be “worse than no care at all” (Jacobsen & Jim, 2008, p. 214). Although further research is needed to measure anxiety intervention outcomes, recent systematic reviews provide support for several psychosocial, pharmacologic, and complementary therapy interventions (Shuster, 2013). With this growing body of knowledge, it is important for oncology nurses to evaluate recent data to support the interventions recommended to patients (Fulcher et al., 2014).

Treatment of anxiety in people with cancer begins with the development of an open, trusting relationship between the patient and the oncology team. Addressing patient distress, especially anxiety, at the time of cancer diagnosis sets the stage for ongoing communication between the patient and the oncology team through treatment and into a future of survivorship or palliative care. Anxiety is a normal human response, so eradicating it is not the goal of treatment; rather, the goal is for patients to learn to manage anxiety and use it for better problem solving and improved functioning (Levin & Alici, 2010).

Acknowledging that patients may need to express their concerns to their healthcare providers requires the creation of a receptive and welcoming environment. The setting needs to allow the privacy, time, and “regard” that promote open patient-provider communication. **Regard**, or *unconditional positive regard*, is a term that was first used by Carl Rogers (1951) to describe the ability to accept another person’s beliefs and responses regardless of one’s own personal feelings. This nonjudgmental approach is important when patients are experiencing a difficult time and may be concerned as to whether their feelings of anxiety, worry, and fear are normal and understandable reactions. When nurses and other healthcare providers accept patients’ experiences, they enrich their relationship with their patients, which then
FIGURE 4-4  Anxiety Screening and Assessment for Adults With Cancer

Screen at initial diagnosis/start of treatment, other times, and as is relevant

If at risk of harm to self and/or to others:
- If YES > referral for emergency evaluation by licensed mental health professional; facilitate safe environment; one-to-one observation; initiate interventions to reduce risk of harm to self and/or others (the presence of other symptoms [eg, psychosis, severe agitation, and confusion (delirium)] may also warrant emergency evaluation).
- If NO > continue with algorithm

7-item GAD-7

None/mild symptomatology if patient reports a total score of 0–4, 5–9

Moderate symptomatology if patient reports a total score of 10–14

Moderate to severe, severe symptomatology if patient reports a total score of 15–21

Identify pertinent history/specific risk factors for (generalized) anxiety
- History: Familial history of anxiety, w/wo prior treatment
- History: Persons with other comorbid psychiatric disorders (eg, mood disorders)
- History of alcohol or substance use or abuse
- Presence of alcohol or substance use or abuse
- Presence of other chronic illness(es)

None/mild symptomatology

- None or mild symptoms of anxiety
- No/minimal functional impairment
- Effective coping skills and access to social support

Moderate symptomatology

- May present as worries or concerns re: cancer but also worry, concern about multiple other areas
- Fatigue, sleep disturbances, irritability, and concentration difficulties may also be present
- Functional impairment from ‘mild’ to ‘moderate’
- Consider possible comorbid anxiety symptoms, such as panic, social phobia

Moderate to severe, severe symptomatology

- Symptoms interfere moderately to markedly with functioning
- Symptoms not responding to Pathway 2
- Referral to psychology and/or psychiatry for diagnosis and treatment
- Consider possible comorbid anxiety diagnoses such as panic disorder or social phobia

In this algorithm, the use of the word “anxiety” refers to GAD-7 scale scores and not to clinical diagnosis of anxiety disorder(s): (1) initial diagnosis/start of treatment, regular intervals during treatment, 3, 6, and 12 months after treatment, diagnosis of recurrence or progression, when approaching death, and during times of personal transition or reappraisal such as family crisis; (2) presence of symptom in the last 2 weeks (rated as 0 = “not at all,” 1 = “several days,” 2 = “more than half the days,” and 3 = “nearly every day”); (3) content of items: feeling nervous, anxious, on edge, cannot stop/control worry, worry too much, trouble relaxing, restlessness, easily annoyed, irritable, and feeling afraid. Final item regarding difficulty of the problems.

GAD-7—Generalized Anxiety Disorder-7 scale; w/wo—with or without

affects patient outcomes of greater satisfaction with their care and increased trust in their healthcare team (Fortin et al., 2012).

The role of the oncology nurse is to facilitate referrals to a trained behavioral specialist such as a social worker, creative therapist, psychologist, or psychiatrist. Choosing the best psychosocial intervention depends on the communication and assessment experience, as well as the oncology nurse’s training. Most oncology nurses have the ability to help patients in disclosing their concerns, respond empathetically, and offer psychosocial support. The NURS mnemonic often is used to describe the steps of empathetic responsiveness in patient-centered interviewing (Fortin et al., 2012). The steps help nurses and other healthcare providers in responding to patients’ emotional expressions such as anxiety and distress.

N—Name the feeling: “I can see that you are really worried about this test.”

U—Understand the patient’s experience: “Many patients feel concerned when waiting for test results.”

R—Respect the patient’s coping: “You are doing the best you can to deal with this situation and help your family, too.”

S—Support the patient: “I would like to help you get through this time.”

Responding empathetically allows patients to disclose their concerns in a nonjudgmental and respectful climate. By reflecting the emotional content and supporting patients’ coping strategies, nurses empower patients and may identify anxiety that requires further intervention. The establishment of a therapeutic and open nurse-patient relationship allows nurses to make referrals for psychosocial support to meet individuals’ needs (Fortin et al., 2012).

Treatment for anxiety begins with addressing the underlying fear, concern, or perceived threat (Shuster, 2013). This should include a review and appropriate streamlining of medications that may contribute to an anxiety state. Because of the significant effect of physical symptoms such as pain on anxiety levels, interventions to address any underlying or disease-related symptoms need to be employed in addition to initiating anxiety-specific treatment (NCCN, 2014).

The NCCN (2014) guidelines for distress management provide an evidence-based overview of anxiety along with clinical pathways for evaluation, treatment, and follow-up of anxiety disorders associated with a cancer diagnosis. After the appropriate evaluation, diagnostic studies, and adequate treatment of symptoms and other disease-related factors, patients with an anxiety disorder should be treated with psychosocial interventions, anxiolytics medications, and/or antidepressant medications (NCCN, 2014; Traeger et al., 2012). In addition to these approaches, several complementary therapies may be implemented to relieve anxiety and improve quality of life for people with cancer (Fulcher et al., 2014). In 2014, ASCO developed the organization’s first clinical practice guideline for the screening, assessment, and care of patients with anxiety and depression (Andersen et al., 2014). These guidelines endorse the pan-Canadian practice guidelines for anxiety that were developed by the Canadian Association of Psychosocial Oncology and the Canadian Partnership Against Cancer (Howell et al., 2010). These guidelines recommend the screening of patients with cancer for anxiety at diagnosis and at regular intervals thereafter. The ASCO guidelines recommend that the formal assessment and management of anxiety are shared responsibilities of the clinical team, although patients who may present a harm to themselves and others, have severe depression, or present with psychosis should be referred to a psychiatrictrained professional (Andersen et al., 2014). These guidelines provide a care map for managing anxiety in adults with cancer (see Figure 4-5) (Andersen et al., 2014).

**Psychosocial Interventions**

Supportive psychosocial interventions for anxiety that are likely to be effective include individual coaching, cognitive behavioral therapy (CBT), mindfulness-based stress reduc-
The evidence supports the use of behavioral therapies in the management of anxiety (Levin & Alici, 2010; Shuster, 2013; Traeger et al., 2012). CBT introduces patients to behavioral techniques with the goal of skill development to control the response to an anxiety-
provoking stimulus (Greer et al., 2012). Although some behavioral therapies can be self-administered, most are tools designed for use by a trained specialist. Levin and Alici (2010) advocated that a failed behavioral intervention may leave a patient more vulnerable to anxiety, and, therefore, behavioral interventions should be offered only with trained guidance and practice. When patients’ problems are spiritual or existential in nature, pastoral counseling may be more appropriate to address these issues and draw upon religious resources to facilitate patient coping and adaptation rather than employing a behavioral therapy (NCCN, 2014).

Sufficient evidence exists to recommend psychoeducational interventions to reduce levels of anxiety in patients with cancer (Andersen et al., 2014; Fulcher et al., 2014). Psychoeducational offerings rely on provision of information or education in combination with a counseling or psychosocial intervention to reduce uncertainty, a common source of anxiety. Studies of orientation programs are limited and do not support the use of exclusively educational interventions in the management of anxiety (Fulcher et al., 2014).

**Pharmacologic Interventions**

The evidence for the use of pharmacologic interventions in the treatment of anxiety has been mixed (Shuster, 2013). However, a recent review of anxiety treatment outcomes found evidence to support their use in the oncology setting (Traeger et al., 2012). If psychosocial interventions are not sufficient in treating a patient’s anxiety, pharmacologic treatments may be necessary. NCCN (2014) recommends combining pharmacologic agents with psychosocial interventions. Anxiolytic (antianxiety) medications are used to decrease anxiety in patients with situational anxiety and generalized anxiety disorders. They include benzodiazepines, antidepressants, azapirones, antipsychotics, and antihistamines (see Table 4-3) (Grassi, Caruso, Hammelef, Nanni, & Riba, 2014). Patients receiving pharmacologic interventions should be assessed for their satisfaction with symptom relief and for their compliance with the treatment regimen (Andersen et al., 2014). Tapering the patient from anxiolytic medications should be considered once symptom control is achieved or if the environmental stressors are removed (Andersen et al., 2014; Grassi et al., 2014).

**Benzodiazepines**

Benzodiazepines are the most commonly prescribed class of anxiolytics for the treatment of anxiety in patients with cancer (Levin & Alici, 2010). They generally are well tolerated, are effective in treating anxiety, and offer short- or long-acting therapeutic options (Grassi et al., 2014). Longer-acting benzodiazepines can be addictive and may lead to tolerance. Dosage should be carefully monitored in patients with respiratory depression or bradycardia and in older adults (Grassi et al., 2014).

**Azapirones**

Azapirones are a class of drugs that are effective in the short-term relief of generalized anxiety disorders and lack the sedative and cognitive side effects of the benzodiazepines (Levin & Alici, 2010). The most common azapirone is buspirone. Dosages may be increased over several days but may take two to four weeks to reach efficacy. Unlike benzodiazepines, the azapirones are not addictive (Grassi et al., 2014; Levin & Alici, 2010).

**Antihistamines**

Hydroxyzine is an antihistamine and central nervous system depressant used to treat anxiety disorders and relieve tension during stressful circumstances, such as before sur-
Antidepressants are a group of drugs used to treat depression and other mood disorders, including anxiety disorders. The antidepressants most commonly used in anxiety treatment include the newer classes of selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors (SNRIs), and noradrenergic and specific serotonergic antidepressants (NaSSAs). SSRIs include paroxetine, sertraline, and fluoxetine, whereas venlafaxine is a commonly used SNRI, and mirtazapine is a NaSSA. These newer classes of

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Route</th>
<th>Side Effects</th>
<th>Nursing Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>Start at 0.25–0.5 mg TID; titrate to maximum 4 mg/day (short acting)</td>
<td>PO</td>
<td>CNS depression, fatigue, impaired coordination and memory, changes in libido and/or appetite</td>
<td>Contraindicated in patients with open-angle glaucoma Use with caution in patients with suicidal ideation. Avoid abrupt cessation.</td>
</tr>
<tr>
<td>Clonazepam (not FDA-approved for anxiety)</td>
<td>0.25–1.0 mg/day BID (long acting)</td>
<td>PO</td>
<td>Nausea, drowsiness, impaired cognition, irritability, impaired coordination and balance</td>
<td>Contraindicated in older adults, those at risk for falls, and patients with schizophrenia Not recommended for those younger than 18 years old</td>
</tr>
<tr>
<td>Diazepam</td>
<td>2.5–10 mg 2–4 times daily; increase gradually (long acting; rapid onset)</td>
<td>PO, IV</td>
<td>CNS depression, impaired coordination, fatigue, changes in libido and/or appetite</td>
<td>Contraindicated in patients with acute narrow-angle glaucoma Use with caution in patients with substance or alcohol abuse and depression.</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.5–2 mg every 8–12 hours (short acting)</td>
<td>PO, IV, SL, IM</td>
<td>CNS depression, sedation, dizziness, weakness, transient memory impairment, disorientation, sleep disturbances, agitation, abuse potential</td>
<td>Contraindicated in patients with acute narrow-angle glaucoma Use with caution with opioids and other CNS depressants, including alcohol. Preferred for use when hepatic function is impaired</td>
</tr>
<tr>
<td>Azapirones</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buspirone</td>
<td>5–20 mg TID, max 60 mg/day</td>
<td>PO</td>
<td>Dizziness, nausea, headache, nervousness, dream disturbances, insomnia</td>
<td>Use caution with other CNS drugs and in patients with renal and hepatic failure. Do not use with concomitant MAOIs. Should not be taken with grapefruit juice Lag time to reach effect is similar to antidepressants.</td>
</tr>
</tbody>
</table>

(Continued on next page)
### TABLE 4-3  Medications for the Treatment of Anxiety (Continued)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Route</th>
<th>Side Effects</th>
<th>Nursing Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antihistamines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>25–50 mg every 4–6 hours PO, IV</td>
<td>Drowsiness, dry mouth, tremor, convulsions</td>
<td>Use with caution in older adults. Risk of anticholinergic side effects and delirium.</td>
<td></td>
</tr>
<tr>
<td><strong>Antidepressants: Selective Serotonin Reuptake Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>10–80 mg QD PO</td>
<td>Asthenia, sweating, decreased appetite, dizziness, somnolence</td>
<td>Likely to impair the effectiveness of tamoxifen. High potential for drug-drug interactions. Longest half-life among the selective serotonin reuptake inhibitors.</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10–60 mg QD PO</td>
<td>Asthenia, sweating, decreased appetite, dizziness, somnolence</td>
<td>Contraindicated in patients with seizure disorder, cardiovascular disease, and narrow-angle glaucoma. Likely to impair the effectiveness of tamoxifen. High potential for drug-drug interactions.</td>
<td></td>
</tr>
<tr>
<td><strong>Antidepressants: Serotonin and Norepinephrine Reuptake Inhibitors</strong></td>
<td></td>
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</tr>
<tr>
<td>Venlafaxine</td>
<td>37.5–300 mg QD PO</td>
<td>GI upset, dizziness, somnolence, insomnia, headache, sexual dysfunction</td>
<td>Use with caution in patients with high blood pressure, heart disease, hypercholesterolemia, or seizure disorders.</td>
<td></td>
</tr>
<tr>
<td><strong>Antidepressants: Tricyclic Agents</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>10–25 mg QD; max dose 200 mg/day PO</td>
<td>Anticholinergic side effects are common: constipation, dry mouth. Weight gain and sedation are frequent.</td>
<td>Use with caution in combination with opioids due to constipation side effect.</td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>15 mg/day 5–15 mg at night; max dose 45 mg/day PO</td>
<td>Visual hallucinations, increased appetite, nightmares, drowsiness, headache</td>
<td>Do not use with concomitant MAOIs. Patients should avoid alcohol consumption. Rare risk of agranulocytosis; monitor white blood count. Use with caution with benzodiazepines.</td>
<td></td>
</tr>
</tbody>
</table>

CNS—central nervous system; FDA—U.S. Food and Drug Administration; GI—gastrointestinal; IM—intramuscular; MAOI—monoamine oxidase inhibitor; QD—every day; SL—sublingual

Note. Based on information from Dahlin, 2014; Grassi et al., 2014; Shuster, 2013; Traeger et al., 2012.
antidepressants are generally better tolerated and have reduced number and severity of side effects compared to the older classes of antidepressants, such as the tricyclic antidepressants and monoamine oxidase inhibitors (Grassi et al., 2014).

SSRIs and SNRIs are considered first-line medications for the treatment of generalized anxiety disorders (Levin & Alici, 2010). Treatment may be needed for at least two weeks for the therapeutic benefit to become evident (Shuster, 2013). Side effects vary with the type of antidepressant; however, all patients using antidepressants to treat anxiety need to be monitored (see Table 4-3). SSRIs and SNRIs can alter the metabolism of some medications, such as tamoxifen (Grassi et al., 2014; Shuster, 2013).

If symptoms of anxiety persist or increase, patients may need further evaluation and interventions. Patients should be reassessed every three weeks to monitor their response to the medications and identify any side effects.

**Complementary Therapies**

Complementary therapies refer to a group of interventions not traditionally practiced by Western-trained physicians (Williams, Gierisch, McDuffie, Strauss, & Nagi, 2011). They include mind-body therapies, manipulative and body-based practices, and movement or energy therapies. Many of these therapies are purported to reduce patient anxiety. Increasingly, patients seek these additional therapies to improve their quality of life during cancer treatment (Boon, Olatunde, & Zick, 2007). However, the evidence supporting their use in achieving positive outcomes for patients with anxiety is limited (Williams et al., 2011). Complementary therapies likely to be effective in alleviating anxiety in patients with cancer include (Fulcher et al., 2014)

- Yoga (Buffart et al., 2012)
- Massage, including partner-delivered massage and aromatherapy massage
- Exercise
- Music/music therapy
- Progressive muscle relaxation.

Complementary therapies that may help decrease anxiety but for which effectiveness has not been established include (Fulcher et al., 2014)

- Reiki
- Homeopathy
- Virtual reality
- Art therapy.

A systematic review looking at homeopathy as a complementary therapy showed insufficient evidence to recommend it as an effective intervention for anxiety (Pilkington, Kirkwood, Rampes, Fisher, & Richardson, 2006). The evidence for massage is more compelling. Several recent studies found a short-term reduction in anxiety, most commonly occurring immediately after the massage intervention (Karagozoglu & Kahve, 2013; Wilkinson et al., 2007). This evidence supports the use of massage as an intervention likely to be effective in the short term.

A recent meta-analysis of RCTs examined the use of yoga in patients with cancer. In their review, Buffart et al. (2012) examined 13 RCTs (16 papers) involving a physical yoga intervention in one group and a group of participants who were wait-listed for the intervention. All trials included patients with cancer; 12 involved patients with breast cancer and one trial included patients with lymphoma. Participants in the trials were evaluated for both physical and psychosocial outcomes, including anxiety. The intervention group demonstrated a significant reduction in anxiety (d = –0.77; 95% CI [–1.08, –0.46]) (Buffart et al., 2012). This evi-
Evidence has limitations, but it supports the recommendation of yoga as an appropriate intervention for managing anxiety in patients with cancer.

Conflicting evidence exists for the use of creative therapies such as art and music for the management of anxiety. While most studies are small, lack randomization, and vary in their design, a recent review of RCTs evaluating outcomes of creative arts therapies noted a reduction in anxiety with art or music therapy interventions (Puetz, Morley, & Herring, 2013). Anxiety was significantly reduced after exposure to creative arts therapy as measured by the mean effect size for the studies measuring anxiety outcomes. However, it was not lasting, and a reduced effect size was detected in the studies that measured follow-up outcomes (Puetz et al., 2013). Therefore, the evidence supports the use of art and music therapy as short-term interventions for anxiety reduction in patients with cancer. While the evidence supporting music therapy is stronger than that for art therapy (Fulcher et al., 2014), a number of studies evaluated both art and music interchangeably as creative or arts therapies (Boehm, Cramer, Staroszynski, & Ostermann, 2014). This is a limitation of the evidence and makes the recommendation of individual arts therapies challenging.

Patient Resources

Ongoing patient support is needed from not only the oncology team but also other sources. The nurse should assess patients’ identified support systems and their current use of these psychosocial supports. Resources for additional information and support are available for patients with cancer both online and through community organizations. Resources for support include

- NCCN Guidelines for Patients®, available at www.nccn.org/patients
- American Cancer Society educational and support resources, available at www.cancer.org or at regional offices
- ASCO’s Cancer.Net treatment and support information and resources, available at www.cancer.net/coping
- Cancer Support Community educational and support resources, as well as distress screening, available at www.cancersupportcommunity.org or at local affiliates.

Expected Patient Outcomes

Psychosocial, pharmacologic, and complementary interventions are intended to bring emotional relief in the short term and decrease maladaptive anxiety responses in the long term (Traeger et al., 2012). Patient outcomes of effective treatment of anxiety include decreased distress, improved quality of life, better functioning in roles such as returning to work or resuming social activities, increased adherence to cancer treatment recommendations, and improved decision-making ability.

Patient Teaching Points

Working with patients who are experiencing anxiety requires nurses to assess and intervene with an individualized approach. Nurses can teach patients self-awareness regarding their physical and psychological manifestations of anxiety. Open, trusting relationships with the nurses and the oncology team allow patients to express their feelings, report changes in
functioning, and provide feedback regarding effective interventions. Nurses and patients can work collaboratively to find effective strategies to decrease anxiety and optimize functioning. Ongoing teaching and follow-up may be necessary as patients move through vulnerable points in their care, and teaching needs to be done at appropriate times when patients are receptive. Mild anxiety may heighten awareness; however, moderate to severe anxiety may be incapacitating, thus impairing a patient’s ability to focus, make decisions, and function (APA, 2013).

Patients should be taught to (Andersen et al., 2014; Fulcher et al., 2014)
- Understand the normalcy of stress in the context of cancer and to recognize the symptoms of maladaptive anxiety.
- Understand that anxiety can be managed and that symptoms should not be ignored.
- Learn how they respond to stress.
- Find techniques that reduce their stress or anxiety, such as progressive muscle relaxation, yoga, or music therapy, and use these techniques when symptoms appear or prophylactically before situations that produce anxiety.
- Identify people who can provide support during difficult and stressful times.
- Talk about their anxiety with their oncology team so that the team can understand their symptoms and plan interventions.
- Take medications as prescribed and not discontinue them without talking with their healthcare provider.
- Follow through with referrals to mental health professionals to learn anxiety management strategies.
- Consider joining a psychoeducational group if uncertainty is a source of anxiety.
- Understand sleep hygiene and the self-management of fatigue.

Need for Future Research

Although psychosocial support is the most recommended intervention and has evidence to support its effectiveness, it can be done in many different ways, including individual and group counseling and even Internet- or telephone-linked care. Further research could identify effective intervention delivery methods and the specific population characteristics of those who benefit from them. Additionally, the training of healthcare providers, including nurses, in delivering psychosocial interventions can vary significantly and requires further clarification.

Studies are needed to identify the effectiveness of pharmacologic and complementary therapies for patients with cancer. Most of the research regarding medications for anxiety has not been specific to the needs of patients with cancer. RCTs for anxiolytics, antidepressants, and other medications are needed to demonstrate the effectiveness of particular medications in patients with cancer who experience anxiety. Future research is needed to identify additional complementary therapies that may reduce anxiety and improve quality of life and functioning for people living with cancer. Complementary therapies such as massage may be effective for some patients, but larger studies are needed to identify which patients may benefit from them.

Conclusion of Case Study

E.M. is exhibiting symptoms of maladaptive anxiety, including excessive worry, pacing, and rapid thoughts and speech—all of which are affecting her ability to make decisions and function normally. Having just received news of failed treatment, she is at an
established time of heightened risk for anxiety development. Recognizing these symptoms, the nurse correctly arranges for an immediate evaluation by the oncology nurse practitioner. The nurse practitioner assesses E.M.’s psychosocial history, including prior anxiety, and her medical history for physiologic causes of her symptoms, as well as thoroughly reviewing her current medication profile. E.M. is taking zoledronic acid, a bisphosphonate whose side effects can include excessive worry, insomnia, and weight loss. In excluding this as the sole cause of E.M.’s symptoms, the nurse practitioner finds a history of untreated anxiety that resulted in E.M.’s inability to involve her family in her care and impaired decision making. The nurse practitioner conducts a suicide assessment that includes presence of ideation, a suicide plan, and weapons in the house. Had the assessment identified the presence of any of these elements of suicide risk, the nurse practitioner would have sought immediate mental health intervention for E.M. After concluding E.M. was not at risk for suicide, the nurse practitioner prescribes a benzodiazepine for E.M. to reduce her anxiety symptoms. E.M. is referred to an oncology clinical social worker to begin a CBT program where she will learn distraction and relaxation therapies. E.M. is instructed that anxiety is not cured, but managed. Therefore, the nurses caring for E.M. will include discussion and assessment of her anxiety symptoms and management as an element of their routine assessment. The nurse encourages E.M. to openly discuss her symptoms and their management with the healthcare team. Routine use of an anxiety screening or assessment tool would provide an automated method of detecting new problems as well as ascertaining E.M.’s current level of anxiety.

Conclusion

Anxiety is a common and pervasive issue in oncology care. Many interventions have been used to relieve anxiety in patients with cancer, but no gold standard for care exists. Because each patient is an individual with a unique personality and history, clinicians need to customize treatment approaches to the patient and the situation. The characteristics of patients who are at high risk for anxiety need to be identified to provide timely assessment and referral before the anxiety becomes debilitating.

Interventions are available to prevent and alleviate anxiety and distress in patients with cancer. Psychosocial, psychoeducational, and pharmacologic interventions are supported by evidence demonstrating their effectiveness in the prevention and treatment of anxiety. Newer treatments such as massage, exercise, music therapy, and relaxation breathing may prove useful in some patients. Oncology nurses are in the unique position to assess patients for symptoms of anxiety during routine care and at vulnerable points in their diagnosis and treatment, thereby diminishing its impact on patients’ quality of life.

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References


Bowel Dysfunction

Deborah M. Thorpe, PhD, APRN, AOCNS®, ACHPN, and Katherine L. Byar, RN, MSN, APN-BC, BMTCN™

Introduction

Bowel dysfunction in patients with cancer is a significant problem that can affect treatment outcomes throughout the illness trajectory. Constipation and diarrhea are two common problems encountered by nurses caring for patients with cancer (Ahmedzai & Boland, 2010; Shaw & Taylor, 2012; Shoemaker, Estfan, Induru, & Walsh, 2011), and appropriate management not only can affect the quality of life for individuals through control of the symptoms but also can make a difference in whether the patient receives adequate treatment for the cancer (Andreyev, Davidson, Gillespie, Allum, & Swarbrick, 2012). To adequately assess and choose appropriate interventions, nurses need a basic knowledge of normal bowel anatomy and physiology to serve as a basis for understanding the pathology of the dysfunction encountered in constipation and diarrhea.

Pathophysiology of the Lower Digestive Tract

Elimination of stool through defecation is a complex physiologic process involving both voluntary and involuntary nervous system mechanisms. Alterations in the nervous and endocrine systems can have a major impact on how the bowel functions (Huether, 2010; McCrea, Miaskowski, Stotts, Macera, & Varma, 2008; Sykes, 2006). Individual factors from dietary and fluid intake to physical activity, pathologic factors such as obstruction, and treatment-related factors such as a vast array of medications and therapies also affect elimination of stool through defecation (Huether, 2010; McCrea et al., 2008; Mercadante, 2013).

The small intestine consists of the duodenum, jejunum, and ileum and is principally responsible for absorbing nutrients from food. The large intestine, which consists of the ascending, transverse, and descending colon and the rectum, is principally responsible for absorbing water from digested food and forming the stool. Although times vary, gastric contents spend two to four hours in the small intestine and 24–48 hours traveling through the colon (Huether, 2010; McCrea et al., 2008; Sykes, 2006).

The gastrointestinal tract is regulated by input from the central nervous system via the autonomic nervous system, which produces the signals required to initiate the normal peristaltic contractions that propel the stool content forward in a rhythmic, segmental fashion as the circular muscles contract and relax. The gastrocolic reflex stimulates the process, usually following ingestion of food when the stool enters the colon from the distal ileum. Gastrin and chole-
cystokinin are involved in stimulating the reflex. The volume of stool entering the colon varies greatly from one individual to another. Approximately 8–9 L of fluid enters the intestines daily: 1–2 L represents food and liquid intake, and the rest is from endogenous sources such as salivary, gastric, pancreatic, biliary, and intestinal secretions (Huether, 2010; McCrea et al., 2008; Sykes, 2006). Most of the fluid, about 6–7 L, is absorbed in the small intestine, and only about 1–2 L are presented to the colon. Most of this fluid is absorbed as it passes through the colon, leaving an expected stool output of approximately 100–200 g daily. Water is absorbed passively in the gut, dependent on the osmotic gradient. Diarrhea results when there is an excess osmolality of the stool because of decreased absorption of nutrients and electrolytes, excess secretion of electrolytes, or both (Huether, 2010; McCrea et al., 2008). Constipation occurs when peristalsis is decreased, thus allowing an increase in transit time, which results in increased reabsorption of fluid (Haylock, Curtiss, & Massey, 2014; Huether, 2010; McCrea et al., 2008). Figure 5-1 illustrates the normal anatomy of the lower digestive tract and depicts the points at which the stool transforms from fluid to solid feces as it travels through the colon on the journey to the rectum.

**Constipation**

**Constipation Case Study**

J.M. is a 59-year-old man with a history of hormone-refractory prostate cancer who has multiple bone metastases in his spine and pelvis. He has severe pain requiring the use of long-acting morphine 60 mg every 12 hours and uses another 15–30 mg of immediate-release morphine three to four times a day to be able to bathe and to walk a little around the house. He has been complaining of bloating and nausea and occasionally vomits. He has a decreased appetite and has been sleeping poorly. His primary care physician was con-
cerned about J.M.’s depression and poor sleep and started him on amitriptyline 25 mg at bedtime several weeks ago, which helped with J.M.’s sleep. J.M. states that he has not had a bowel movement in five days. His wife has been trying to give him prune juice and to get him to drink more fluids, but he has not had much success.

Overview

Definition

Constipation is a common symptom in patients with cancer that is known to cause physical, emotional, and psychosocial distress and can significantly affect quality of life if not treated in a timely and effective manner that can rival the distress caused by pain (Dhingra et al., 2013; Sykes, 2006). Because oncology nurses are on the front lines of cancer care and are advocates for cancer symptom management, they are in an ideal position to be proactive and to anticipate and manage constipation.

No universally agreed upon definition of constipation exists, and the incidence and characteristics of constipation in the oncology population vary considerably from the functional or idiopathic constipation that occurs in the general population (Clark & Currow, 2013). The perception of what a normal bowel movement is varies from one person to another (Haylock et al., 2014). For example, one patient may go for two days without a bowel movement and perceive this to be constipation, whereas many consider it to be a normal pattern, particularly if no discomfort is associated with the passage of stool. Many factors enter into establishing a useful working definition, and the definition may vary between clinicians and patients (McCrea et al., 2008). Most patients focus on the frequency, degree of straining, and a sense of incomplete evacuation or how much time they have to spend on the toilet. An international panel of experts organized by the Rome Foundation formulated a set of criteria to describe functional constipation that has been refined over the past 20 years; these criteria are currently known as the Rome III Criteria (Longstreth et al., 2006; Shih & Kwan, 2007) as shown in Figure 5-2. These diagnostic criteria have been used primarily to guide the diagnosis and treatment of irritable bowel syndrome. Typically, in current clinical practice settings, a normal bowel pattern is defined as at least three stools per week and no more than three stools per day (National Cancer Institute [NCI], 2013).

**FIGURE 5-2** Rome III Diagnostic Criteria* for Functional Constipation

<table>
<thead>
<tr>
<th>1. Must include 2 or more of the following:</th>
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<tbody>
<tr>
<td>a. Straining during at least 25% of defecations</td>
</tr>
<tr>
<td>b. Lumpy or hard stools in at least 25% of defecations</td>
</tr>
<tr>
<td>c. Sensation of incomplete evacuation for at least 25% of defecations</td>
</tr>
<tr>
<td>d. Sensation of anorectal obstruction/blockage for at least 25% of defecations</td>
</tr>
<tr>
<td>e. Manual maneuvers to facilitate at least 25% of defecations (e.g., digital, evacuation, support of the pelvic floor)</td>
</tr>
<tr>
<td>f. Fewer than 3 defecations per week</td>
</tr>
<tr>
<td>2. Loose stools are rarely present without the use of laxatives</td>
</tr>
<tr>
<td>3. There are insufficient criteria for irritable bowel syndrome</td>
</tr>
</tbody>
</table>

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

In patients with cancer, the picture of constipation becomes more complicated as one must build on the patient’s prior history of bowel function and take into account factors related to the cancer and its treatment. An estimated 15% of patients are likely to present with a prior history of functional constipation (Clark & Currow, 2013). The key characteristics of constipation from a clinical standpoint can be defined as difficult, infrequent passage of hard stool that is usually associated with abdominal cramping and rectal pain or discomfort and is usually accompanied by a feeling of incomplete evacuation (Haylock et al., 2014). One must also consider diarrhea in the context of a history of constipation as a primary indicator for fecal impaction. Leakage of stool around an impaction is often misinterpreted as diarrhea because the impacted stool induces secretions proximal to the obstruction, resulting in an overflow of liquid stool that passes around the impaction (Sweetser, 2012).

Incidence

The incidence of constipation in patients with cancer is difficult to quantify because of the subjective nature of the symptom and the number of factors that apply. While the use of opioids is certainly a common culprit, other factors such as disease and treatment, as well as the individual’s prior history of bowel habits, are also important factors (Mercadante, 2013). In one study, 40% (n = 151) of adult patients with cancer (N = 376) from 15 community oncology clinics participating in the AIM (Assessment Information Management) Higher Initiative reported experiencing constipation during their most recent chemotherapy cycle (Johnson, Moore, & Fortner, 2007). The AIM Higher Initiative was a quality improvement program intended to improve symptom assessment, information distribution, and management of five chemotherapy-related symptom areas: anemia, neutropenia, nausea and vomiting, diarrhea and constipation, and anxiety and depression (Johnson et al., 2007). In palliative care settings, studies have reported constipation incidence at 30%–90% (Clark & Currow, 2013). It is a contributing factor to many emergency department visits and may be the principal reason for presentation for emergent care in as many as 3.3% of visits (Gu, Gonzalez, & Todd, 2011).

Risk Factors and Etiology

Because of the prevalence of constipation in patients with cancer and its anticipated occurrence with specific treatments, one of the best approaches to management is to anticipate and prevent it before it occurs. This requires that oncology nurses have a thorough understanding of the risk factors for constipation and routinely take steps to identify patients who are at not only at risk but who also may be underreporting their symptoms. Patient and caregiver education is an essential component of this process.

An assessment of risk or predisposing factors should be performed prior to initiating treatment. Documenting patients’ risk factors will likely increase the oncology team’s awareness of the problem and provide a rationale for interventions (Johnson et al., 2007). Common factors that contribute to constipation in the general population include altered bowel habits, inadequate fluid intake, inadequate fiber in the diet, lack of exercise, lack of privacy, older age, and comorbidities that cause debilitation (Mercadante, 2013; NCI, 2013). Many of these factors also are likely to cause constipation in patients with cancer. Contributing risk factors in patients with cancer are inadequate fluid intake and opioid analgesics (Mercadante, 2013). The decreased stool transit time and increased time for water reabsorption caused by the bowel-slowing effect of opioids make constipation an inherent risk for patients receiving opioids. Other specific risks for constipation in patients with cancer are discussed in the rest of this section.

Constipation can occur as a symptom of the cancer itself. Tumor or malignant ascites fluid can press on and partially or totally occlude the bowel from either inside or out-
side the bowel lumen (NCI, 2013; Ripamonti, Gerdes, & Easson, 2013). For example, this is common in patients with ovarian cancer who develop peritoneal metastasis. In patients with small cell lung cancer, altered nervous system function, such as paraneoplastic autonomic neuropathy, can occur. Patients with advanced breast or prostate cancer may develop spinal cord compression, and if spinal cord injury is present, it leads to bowel atony. Constipation can occur as a result of this oncologic emergency (Mercadante, 2013; NCI, 2013).

Cancer-related immobility, dehydration, and paralysis could decrease peristalsis, which leads to constipation (Mercadante, 2013; NCI, 2013).

Constipation also can occur as a side effect or complication of cancer therapy. Being treated for cancer with surgery, chemotherapy, or radiation is a risk factor for developing constipation (Mercadante, 2013; NCI, 2013). For example, radiation to the anorectal area can lead to fibrosis, change innervation to the rectum or anal sphincter, and result in constipation (Haylock et al., 2014). Depression and anxiety from the cancer treatment can lead to immobility, which can cause constipation because of decreased peristalsis (Polovich, Olsen, & LeFevre, 2014).

Medications used to manage cancer-related symptoms, such as opioid analgesics, antiemetics, antihistamines, tricyclic antidepressants, and aluminum-containing antacids, can lead to constipation (Mercadante, 2013; NCI, 2013; Polovich et al., 2014).

Preexisting issues, including a history of altered bowel habits such as ignoring the urge to defecate, excessive use of laxatives or enemas, or the presence of anal fissures and other bowel disorders such as irritable bowel or diverticulitis, contribute to constipation risk as well. Neuromuscular disorders interrupting bowel innervation leading to bowel atony can be the result of spinal cord injury or compression and stroke. Weak abdominal muscles also can lead to bowel atony (NCI, 2013).

Metabolic disorders leading to constipation include hypothyroidism, lead poisoning, uremia, dehydration, hypercalcemia, hypokalemia, and hyponatremia (Mercadante, 2013; NCI, 2013). Depression and anxiety are contributing factors in constipation, as are other forms of distress, because they can lead to inactivity, which decreases peristalsis and leads to constipation (NCI, 2013; Polovich et al., 2014). Environmental factors that contribute to constipation include the proximity of the patient to the bathroom, the patient’s need for assistance in getting to the bathroom, an unfamiliar environment, inadequate lighting, change in bathroom habits such as use of the commode or bedpan, lack of privacy in the bathroom, and excessive temperatures leading to dehydration (NCI, 2013).

**Pathophysiology**

Decreased motility of the large intestine chiefly contributes to constipation. For example, as innervation to the colon decreases, the motility in the colon decreases, slowing the movement of stool through the colon and increasing the absorption of fluid. Physical factors related to aging include altered strength of contractions within the intestines, poor muscle tone within the colon, and sensory changes within the rectum and anus (McCrea et al., 2008).

Many causes of constipation exist in patients with cancer. Having adequate fluid and fiber in the diet is essential to normal bowel function. Numerous reasons can account for decreased fluid or fiber intake, ranging from side effects of treatments such as chemotherapy and radiation (e.g., nausea and vomiting, taste changes, anorexia, fatigue, mucositis) to baseline inadequate diet (Mercadante, 2013). These factors frequently are interrelated in patients with cancer. When oral intake is decreased, peristalsis is slowed because there is less fluid absorbed by
the bulk and decreased distention of the bowel (NCI, 2013). With decreased overall intake, fewer stools occur, the transit time increases, and the stool becomes hard and difficult to eliminate (Mercadante, 2013).

Decreased physical activity adversely affects normal bowel function and increases the likelihood of constipation. Patients with cancer experience many reasons for decreased activity, including those associated with the disease or to treatment-related effects such as fatigue. Other comorbidities, such as diabetes, are common and may contribute to fatigue as well as cause peripheral neuropathy, which may also affect bowel function. Patients also may have spinal cord injuries, compression fractures, and other metabolic disorders such as hypercalcemia that may significantly contribute to constipation (Mercadante, 2013).

Various classes of medications cause constipation, including chemotherapy. For example, vinca alkaloids such as vincristine, vinblastine, and vinorelbine cause autonomic nerve dysfunction (Mercadante, 2013). Rectal emptying is affected because afferent and efferent pathways from the sacral cord are involved. Vincristine and vinblastine cause neurotoxicity to the gastrointestinal tract, resulting in decreased colonic transit time that leads to decreased peristalsis or paralytic ileus (Mercadante, 2013; Polovich et al., 2014). The next most common chemotherapy agents that cause constipation are the taxanes, including paclitaxel and docetaxel, as well as oxaliplatin and thalidomide (Polovich et al., 2014). McMillan, Tofthagen, Small, Karver, and Craig (2013) studied patients on opioids and/or vinca alkaloids (N = 400) and reported that the constipation intensity was strongly related to constipation distress measured by the Memorial Symptom Assessment Scale (p = 0.000).

Opioids are commonly taken by patients with cancer. Opioid analgesics act directly on mu receptor sites in the intestine and the central nervous system to delay gastric emptying and decrease peristalsis. The severity of constipation is dose dependent. The higher the opioid dose, the greater the severity of constipation will be if it is not adequately prevented or managed (Haylock et al., 2014). General anesthesia and pudendal blocks contribute to constipation (NCI, 2013). Figure 5-3 provides an overview of medications that can cause constipation.

**FIGURE 5-3** Classes of Medications That Cause Constipation

- Aluminum-containing antacids
- Antiemetics
- Antihistamines
- Antiparkinsonian drugs
- Biologic response modifiers (e.g., thalidomide, lenalidomide)
- Calcium supplements
- Chemotherapeutic agents
  - Vinca alkaloids (e.g., vincristine, vinblastine, vinorelbine)
  - Taxanes (e.g., paclitaxel, docetaxel)
  - Platinum-based (e.g., oxaliplatin)
- Diuretics
- Iron supplements
- Monoclonal antibodies (e.g., bortezomib, ado-trastuzumab emtansine)
- Opioids
- Phenothiazines
- Sedatives
- Small molecule inhibitors (e.g., cabozantinib, crizotinib, nilotinib, sunitinib, vismodegib)
- Tricyclic antidepressants

Note. Based on information from Mercadante, 2013; Polovich et al., 2014; Wilkes & Barton-Burke, 2014.
Assessment

Although constipation is a common problem for patients with cancer, the symptom is underassessed and underreported by the healthcare team (McMillan et al., 2013). Underassessment of constipation can lead to the development of or increase the severity of a largely preventable symptom. Oncology nurses need to be skilled in the assessment of constipation to effectively manage this troublesome symptom.

Assessment of constipation is achieved through a thorough history and physical examination. A thorough history includes determining if risk factors are present such as medications, immobility, or treatment-related factors as described previously. If the patient is constipated, it is important to determine what has changed from the usual bowel pattern (Mercadante, 2013). Has the frequency of stool changed? Is the stool hard or soft? Is abdominal cramping present? Is there an increased use of laxatives? Does the patient have rectal fissures, abscesses, or hemorrhoids? If any of these are present, are they painful?

The assessment should include any factors that might contribute to constipation, such as fluid and fiber intake and activity level, because these are amenable to nursing interventions. The clinician should address the patient’s perception of the impact of constipation on quality of life and activities of daily living and what other factors may influence his or her response, such as anxiety or depression. Does the patient perceive incomplete evacuation specifically of stool following a bowel movement? Is rectal pain present? What other symptoms are present, such as anorexia or nausea and vomiting?

Pain assessment can serve as a template for constipation assessment. Just as with pain assessment, clinicians must note the characteristics of constipation, such as onset, frequency, and severity and precipitating, aggravating, and relieving factors. What interventions worked in the past when the patient was constipated? If diarrhea is present, the patient should be assessed for fecal impaction or bowel obstruction (Mercadante, 2013). A three-day dietary history is helpful in assessing the patient’s current diet. Consultation with a dietitian can be a helpful addition to the assessment process of a patient with constipation (Woolery et al., 2008).

A thorough history should be followed by a physical examination including inspection, auscultation, palpation, percussion, and examination. Inspection of the abdomen includes checking for symmetry, contour, distention, bulges, and peristaltic waves. Auscultation of bowel sounds includes noting the character, frequency, and presence or absence of bowel sounds in all four quadrants of the abdomen. Hypoactive bowel sounds include a reduction in the loudness, tone, or regularity of the sounds and can indicate a slowing of intestinal activity. Hypoactive bowel sounds are normal during sleep and also occur normally for a short time after abdominal surgery. Decreased bowel sounds often indicate constipation. Absent bowel sounds can indicate paralytic ileus, which is a potentially life-threatening problem for patients (Dains, Baumann, & Scheibel, 2012). Conversely, hyperactive bowel sounds reflect an increase in intestinal activity (Dains et al., 2012). This sometimes can occur with diarrhea and after the patient has eaten.

Palpation of the abdomen includes noting any masses or stool in the colon or any areas of increased tenderness or resistance. If resistance is present, the abdomen would feel firm instead of pliable. Abdominal tenderness and muscular resistance can be associated with chronic constipation. Deep palpation can be used to detect abdominal masses, including sausage-shaped fecal material in the left colon. A feces-filled colon can indicate the presence of constipation. Percussion involves checking for dullness in an otherwise tympanic area of the abdomen, as dullness is heard over areas with abdominal fluid or stool present. Rectal examination can be performed with caution to check for fecal impaction, hemorrhoids, or fissures in patients with adequate neutrophil counts of at least 1,500/mm$^3$ and platelet counts of at
least 150,000/mm³. Report changes such as abdominal distention, fecal impaction, rectal bleeding, and absent bowel sounds (Fortenbaugh & Rummel, 2007). The *Common Terminology Criteria for Adverse Events* (CTCAE) scale in Table 5-1 provides clinicians with assessment criteria to grade constipation severity and a common language for describing symptoms (NCI Cancer Therapy Evaluation Program [CTEP], 2010). This tool can help nurses to determine types of interventions that are needed based on the severity of the toxicity.

**Management and Evidence-Based Interventions**

The Oncology Nursing Society (ONS) publishes an evidence-based guideline for constipation in its Putting Evidence Into Practice (PEP) series (Bisanz et al., 2009; Thorpe, Byar, Conley, et al., 2014; Woolery et al., 2008) and updates are added regularly on the ONS PEP website (see www.ons.org/practice-resources/pep/constipation). Interventions for PEP topics are grouped into the following categories: Recommended for Practice, Likely to Be Effective, Benefits Balanced With Harms, Effectiveness Not Established, Not Recommended for Practice, and Expert Opinion. Figure 5-4 summarizes the interventions listed in the PEP resource on constipation.

More work needs to be done to further the evidence base for the management of constipation, particularly in the oncology population. Much of the research supporting the interventions listed as being effective or likely to be effective was not done specifically in the oncology patient population and therefore may have limitations.

**Prevention**

A preventive approach to constipation should be taken whenever possible. If the patient shows one or more risk factors upon assessment, the nurse should begin a prevention program immediately. This program should consist of increased dietary fiber consumption, including whole grains and vegetables; fluid intake to include eight 8-ounce servings a day; and consumption of warm or hot liquids to stimulate the bowel (NCI, 2013). The use of constipating medications, such as chemotherapy agents, opioid analgesics, sedatives, and antiemetics, should be avoided when possible. A program of active and passive exercise should be initiated based on the patient’s tolerance level. The patient will need a comfortable, quiet, private environment to have a bowel movement. Avoid the use of a bedpan when possible, and

<table>
<thead>
<tr>
<th>TABLE 5-1</th>
<th>Common Terminology Criteria for Adverse Events Grading for Constipation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>Description</td>
</tr>
<tr>
<td>1</td>
<td>Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema</td>
</tr>
<tr>
<td>2</td>
<td>Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL</td>
</tr>
<tr>
<td>3</td>
<td>Obstipation with manual evacuation indicated; limiting self-care ADL</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>

ADL—activities of daily living

### FIGURE 5-4  Management of Constipation

#### Recommended for Practice

*Interventions for which effectiveness has been demonstrated by strong evidence from rigorously designed studies, meta-analyses, or systematic reviews, and for which expectation of harms is small compared to the benefits.*

**Opioid Antagonist: Methylnaltrexone**

Subcutaneous methylnaltrexone 0.15 mg/kg appears effective in relieving opioid-induced constipation in a timely and predictable manner without reducing pain control or producing symptoms of opioid withdrawal.

**Oxycodone and Naloxone**

Combined oxycodone/naloxone relieved constipation in patients taking opioids for pain management.

**Transdermal Fentanyl**

Multiple studies showed evidence for decreased use of laxatives and lower incidence of constipation in patients on transdermal fentanyl.

#### Likely to Be Effective

*Interventions for which effectiveness has been demonstrated by supportive evidence from a single rigorously conducted controlled trial, consistent supportive evidence from well-designed controlled trials using small samples, or guidelines developed from evidence and supported by expert opinion*

**Amidotrizoate**

One study examined its effect as a potential osmotic laxative.

**Polyethylene Glycol**

Multiple studies in various cancer and noncancer populations showed efficacy and good tolerance of polyethylene glycol for managing constipation.

**Senna (Stimulant) and Docusate (Stool Softener) Regimen**

One study showed that sennosides (senna) alone produced more bowel movements than in combination with docusate, but the dosage was higher.

**Opioid Antagonist: Alvimopan**

Oral alvimopan may be effective for the treatment of opioid-induced constipation in patients taking opioids for chronic pain and may improve opioid-induced bowel dysfunction symptoms. Use of alvimopan does not appear to compromise analgesia or induce opioid abstinence. Further study is necessary (1) to look at efficacy with an oncology population, (2) to determine long-term efficacy, and (3) to determine an optimal dosing regimen.

### Opioid-Induced Constipation: Prophylactic Regimen

A proactive approach, including initiation of a prophylactic regimen, is needed to prevent constipation when taking opioids. However, not enough evidence exists to identify the most effective regimen (see Expert Opinion section).

#### Effectiveness Not Established

**Opioid-Induced Constipation: Opioid Rotation/Switching**

Research has demonstrated that some opioids have less constipating effect than others, and rotating opioids would decrease the associated side effects.

- Switching opioids from sustained-release oral morphine to transdermal fentanyl patches may decrease constipation.
- Switching opioids to methadone may result in a reduction in laxative use.

(Continued on next page)
Expert Opinion

Low-risk interventions that are (1) consistent with sound clinical practice, (2) suggested by an expert in a peer-reviewed publication (journal or book chapter), and (3) for which limited evidence exists. An expert is an individual who has authored articles published in a peer-reviewed journal in the domain of interest.

Special Note: Myelosuppressed Patients

Avoid rectal agents and/or manipulation (i.e., rectal examinations, suppositories, enemas) in myelosuppressed patients. These actions can lead to development of bleeding, anal fissures, or abscesses. In addition, avoid manipulation of the stoma of neutropenic patients.

General Constipation (Both Adult and Pediatric)

**Prevention**
- Take preventive measures in anticipation for patients receiving medications such as vincristine, vinblastine, vinorelbine, or other chemotherapies that slow colonic transit times.

**Interventions**
- Teach the patient about bowel function.
- Provide a comfortable, quiet, private environment for defecating.
- Provide a toilet, bedside commode, and any necessary assistive devices. Avoid the use of a bedpan when possible.
- Minimize use of constipating medications whenever possible.
- Involve the patient in development of a bowel regimen.
- Encourage the intake of warm or hot fluids.

Opioid-Induced Constipation

**Stimulant Laxatives Plus Stool Softener**

This combination is recommended when initiating opioid therapy. A useful bowel regimen includes docusate sodium (100–300 mg/day) along with senna (2–6 tablets twice a day). Bulk laxatives are not recommended for opioid-induced constipation because of the risk of bowel impaction in poorly hydrated patients.

- The laxative dose should be individually titrated for effectiveness according to bowel function, not opioid dosing.

Constipation in Adults

**Pharmacologic Interventions**
- Prokinetic medication (i.e., metoclopramide) should be reserved for use in individuals with severe constipation and those resistant to bowel programs. Caution: Avoid in patients with large abdominal tumors or bowel obstruction.
- Oral mineral oil is effective for hard stool but should not be used for routine prevention of constipation because it may interfere with absorption of some nutrients.
- Expert opinion supports the use of a stimulant laxative plus a stool softener in preventing and managing constipation in patients at the end of life.

**Nonpharmacologic Interventions**
- Recommended fluid intake per day is eight 8-oz servings in adults.
- Treat high and low impactions differently.
  - High impactions: These are comfortably relieved with low-volume (< 300 ml) milk and molasses enemas up to four times per day along with an oral laxative.
  - Low impactions: Oil-retention enemas soften hard stool. In nonmyelosuppressed patients, stool can be manually disimpacted followed by enemas of choice.

**Individualized Bowel Management Program**
- After the patient has gone three days without a bowel movement, initiate a bowel management program.
- A good program includes fluids, fiber, and a decrease in constipating medications or provision of medications to offset constipating side effects of medications.

(Continued on next page)
encourage the patient to use any assistive devices necessary, such as a raised toilet seat (Haylock et al., 2014; Woolery et al., 2008). If constipation occurs despite a preventive approach or if the patient risk factors include opioid analgesics or chemotherapy agents such as vinca alkaloids, oxaliplatin, or thalidomide, which are known to cause constipation, a more aggressive approach is necessary. A stool softener plus a stimulating laxative is recommended when initiating opioid therapy. One recommended regimen is docusate sodium 100–300 mg/day along with senna two to six tablets a day (Woolery et al., 2008). The laxative dose should be titrated to achieve results, not based on the opioid dose. Bulk-forming laxatives are not recommended for opioid-induced constipation. Research has shown that some opioids are less constipating than others. For example, switching from long-acting oral morphine to transdermal fentanyl may decrease constipation, and switching to methadone may result in decreased laxative use (Radbruch et al., 2000; Woolery et al., 2008). The goal is to anticipate the potential for constipation and prevent it wherever possible by choosing appropriate regimens and adapting them when needed recognizing that there is a lot of individual variation in response to treatment (Mercadante, 2013).

**Laxatives**

The goal of laxative therapy is to promote regular bowel elimination function without side effects such as abdominal cramping or diarrhea. Laxative therapy is not indicated in patients with suspected bowel obstruction caused by fecal obstipation (also known as impaction), tumor, or other factors because of the risk of bowel perforation. The categories of laxatives include bulk-forming agents, lubricants, salines, osmotics, detergents (also known as emollients or surfactants), and stimulant laxatives. These drugs are available as oral agents, suppositories, and enemas, depending on the agent selected (Haylock et al., 2014; Mercadante, 2013).

Bulk-forming laxatives include fiber, bran, psyllium, methylcellulose, muciloids, malt soup extracts, and carboxymethylcellulose. Bulk-forming laxatives increase peristalsis by absorbing water and allowing the stool to retain water, which in turn increases both the bulk and weight of the stool and distends the bowel. Fluid intake must be increased to 3 L/day with bulk-forming laxatives (Woolery et al., 2008). Bulk-forming laxatives are not indicated for patients who require fluid restrictions or who cannot tolerate drinking an increased volume of fluid, nor are they recommended for opioid-induced constipation or patients who are unable to drink adequate amounts of fluids because of the risk of bowel impaction (Haylock et al., 2014; Mercadante, 2013; Woolery et al., 2008).
Lubricants are used to coat and soften the stool, which allows it to move through the intestine without difficulty. Examples include mineral oil or liquid petrolatum. The onset of their action is 24–48 hours. Long-term use of lubricants can lead to malabsorption of fat-soluble vitamins, making them not useful as a prophylactic bowel regimen. Of particular significance is the potential for decreased absorption of vitamin K, which could interfere with coagulation. In addition, excessive doses of lubricants can lead to rectal seepage and perianal irritation (Haylock et al., 2014).

Saline or osmotic laxatives increase peristalsis by pulling water into the intestine and the stool to add to the volume of the stool (Mercadante, 2013). Saline laxatives include magnesium citrate, sodium biphosphate, and magnesium hydroxide. They are not indicated for the prevention of constipation but instead are used for acute constipation management. High doses produce watery stool within one to two hours. Lower doses work within 6–12 hours. Patients should be instructed not to take aluminum-containing antacids with magnesium-containing laxatives. Sodium salts should be avoided in patients with cardiac or renal disease, hypertension, and edema because sodium restrictions are usually indicated (Haylock et al., 2014).

Osmotic laxatives are not absorbed by the gut but increase peristalsis by causing an increased osmotic pressure gradient, which pulls water into the intestines and then into the stool. They may cause bloating and flatulence by bacterial metabolization that occurs in the colon (Mercadante, 2013). Examples of osmotic laxatives include glycerin, lactulose, polyethylene glycol, and sorbitol. Glycerin is available in suppository form. Both lactulose and sorbitol have a very sweet taste and may be difficult for some patients to tolerate. Amidotrizoate is a hyperosmolar contrast medium that has been studied for its effect as a potential osmotic laxative (Mercadante, Ferrera, & Casuccio, 2011). Increased doses of osmotic laxatives can result in watery diarrhea (Haylock et al., 2014).

Detergent or surfactant laxatives are also known as emollient laxatives or stool softeners and include docusate, docusate sodium, and docusate potassium. They act on the colon to reduce surface tension, which pulls water into the intestines and then into the stool. They may cause bloating and flatulence by bacterial metabolization that occurs in the colon (Mercadante, 2013). Onset of action is 12–24 hours for oral preparations and 2–15 minutes with rectal preparations. Surfactant laxatives are best used for short periods of time when straining with stool is to be avoided. They are not appropriate when used alone in a prophylactic bowel management program for long-term constipation. Enteric-coated detergent laxatives must be taken whole and not altered in any way in order to be effective (Haylock et al., 2014).

The two classes of stimulant laxatives are diphenylmethanes and anthraquinones. The diphenylmethanes include phenolphthalein and bisacodyl, which act directly on the colon by local irritation and stimulation of the intramural nerve plexus, which stimulates intestinal motility (Mercadante, 2013). The diphenylmethanes take 6–10 hours to work when taken orally and 15–60 minutes when taken rectally. The anthraquinones include senna products, casanthranol, and cascara and work by activating bacterial degradation in the intestine. Onset of action usually is 6–12 hours but can take as long as 24 hours for oral preparations and 15–60 minutes rectally. Both classes of stimulant laxatives can cause dependence, and normal bowel function may be lost with chronic use (Haylock et al., 2014).

The National Comprehensive Cancer Network® (2014) recommends the use of polyethylene glycol as a treatment alternative for patients with cancer who have persistent constipation. Polyethylene glycol is available as a standard dose with electrolytes and as a low dose without electrolytes. Polyethylene glycol should not be administered to patients with compromised kidney function (Woolery et al., 2008). Other reviews of the
evidence indicate that outcomes for polyethylene glycol, senna, and lactulose are similar enough that the agent of choice may depend on patient preference and cost (Ahmedzai & Boland, 2010).

Suppositories come from several different laxative classes and include glycerin, bisacodyl, and senna. Their onset of action occurs within 15–60 minutes. They are useful as a second step after oral laxatives have not been effective. Suppositories should not be placed within the stool; they should be placed between the rectal mucosa and the stool in order to be absorbed. Tolerance can develop, and suppositories are not recommended for long-term use. Rectal irritation can occur with repeated use of suppositories. Furthermore, no type of rectal manipulation, including administering a suppository, should be attempted in the presence of rectal fissures or when the patient’s neutrophil count is below 1,500/mm³ or the platelet count is below 150,000/mm³ (Haylock et al., 2014).

**Enemas**

Enemas are used to cleanse the distal colon after removal of impaction and are not recommended for long-term constipation management because of significant risks, including the potential for perforation (Niv, Grinberg, Dickman, Wasserberg, & Niv, 2013), particularly in patients with cancer who may have increased risk factors such as suppressed immune systems or who have undergone treatments affecting the bowel. The type of enema fluid used determines the mechanism of action. Vegetable oil and lubricants soften and lubricate the stool and are useful for relieving low impactions. Tap water and normal saline work by increasing the fluid volume in the colon. Soap used in enemas works as an irritant to stimulate peristalsis (Haylock et al., 2014). Milk and molasses enemas are useful for removing high impactions because the high sugar content in the molasses brings water into the bowel and helps to soften the stool (Bisanz, 2005; Woolery et al., 2008).

**Nonpharmacologic Interventions**

The effectiveness of nonpharmacologic interventions in adult patients has not been established. Dietary fiber often is recommended for the prevention and management of constipation, but the research evidence is inconclusive (Woolery et al., 2008). Fiber should not be used in patients with advanced disease or those with inadequate fluid intake (Mercadante, 2013; Woolery et al., 2008). Increased activity and exercise increase blood flow to the digestive organs, thereby improving motility, and are thought to be useful in preventing and managing constipation. However, few research studies exist, and they are conflicting (Woolery et al., 2008). Other nonpharmacologic interventions, such as aromatherapy, massage therapy, and biofeedback, have been examined but lack conclusive research evidence on their effectiveness (Woolery et al., 2008).

**Obstipation**

Fecal obstipation is known as impaction, which occurs when constipation has not been adequately managed. Large amounts of dry, hard stool sit in the rectum and cannot be properly eliminated. The patient may experience leakage of liquid stool around the obstipated area, which can be perceived as diarrhea (Sweetser, 2012). Other symptoms of obstipation include rectal discomfort, tenesmus, lower abdominal pain, lower back pain, urinary retention, and urinary incontinence due to extrinsic pressure on the bladder.

Rectal examination may reveal large amounts of dry, hard stool in the rectum, unless the obstipation is located higher than the rectum in the sigmoid colon. Other obstipation assessment criteria are similar to the assessment of constipation. An abdominal x-ray may be per-
formed, which would help to differentiate between the presence of excessive stool or provide
evidence of obstruction that may be contributing to the patient’s symptoms. Once obstipation
has been identified, the goal of treatment is to lubricate the bowel and soften the stool
so that the stool can be successfully removed. A nonstimulant laxative, glycerin suppository,
oil retention enema, or hypertonic phosphate enema may be used (Haylock et al., 2014).
The goal is to prevent damage, such as fissures or hemorrhoids, to rectal tissues. If manual
removal of obstipation is necessary, the patient could receive premedication with an anti-anxiety
agent or short-acting opioid to reduce the physical and psychological discomfort related
to the procedure. A topical anesthetic and a water-soluble lubricant are applied to the rec-
tal area below the obstipation.

Treatment of obstipation includes a rectal examination performed using a gloved finger
liberally lubricated with lidocaine ointment. Once the anal sphincter has relaxed, a second
finger can be inserted, and the two fingers break apart the stool. When most of the stool has
been removed, a cleansing enema and an aggressive bowel program should be undertaken.
This procedure should be avoided in neutropenic and/or thrombocytopenic patients (Hay-
lock et al., 2014).

Expected Patient Outcomes

Appropriate goals or expected outcomes of management of constipation in patients with
cancer include

• Preventing or minimizing the impact of constipation
• Establishing a regular bowel regimen including appropriate prophylactic and/or thera-
peutic medications to restore normal bowel function
• Maintaining normal fluid intake and encouraging adequate fiber intake
• Minimizing complications associated with constipation
• Improving quality of life.

Patient and Family Teaching Points

Patients often overlook the importance of regular bowel movements when faced with all of
the other concerns regarding their cancer and treatment stressors, and it may not be a subject
they want to talk about freely. It therefore is essential to emphasize the importance of maintain-
ing normal bowel function and to include a family member or significant other in the discussion,
particularly if the patient is not able to focus or is too fatigued to be in an optimal state for learn-
ing. Key points in patient and family education include

• Emphasize the importance of prevention.
• Explain the need for close monitoring of bowel function with attention to consistency, fre-
quency, and character of the stool.
• Encourage the patient or family member to keep a diary recording the number and fre-
cuency of stools and medications taken on a daily basis.
• Emphasize the importance of maintaining a regular regimen, particularly if the patient is
on medications likely to cause constipation.
• Emphasize the importance of maintaining fluid and nutritional intake, including ade-
quate fiber.
• Emphasize the need to report any change in bowel pattern, especially inability to have a
bowel movement for more than three days if accompanied by an increase in symptoms
such as nausea, vomiting, or abdominal pain.
• Encourage reporting of all medications, including over-the-counter and alternative medicines.
• Provide written instructions in clear language that is adapted to the level of understanding of the patient/family member and culturally appropriate.

Implications for Practice

Despite it being a much-overlooked symptom in terms of research, constipation remains an important focus for nursing care and is one that can make a significant difference in the patient’s quality of life. It can contribute to the development or worsening of other symptoms such as nausea and vomiting and therefore add to the patient’s overall symptom burden. For most patients, it can be prevented with expert nursing assessment and prompt intervention, but to be successful, nurses must be vigilant in maintaining surveillance of the efficacy of the plan and alert to new factors that may require an adjustment as patients go through the experience of cancer treatment.

Conclusion of Constipation Case Study

The nurse observes that J.M.’s abdomen is soft but distended. His bowel sounds are hypoactive in all quadrants. On palpation, the nurse can identify several sausage-like masses in the abdomen in the area of the transverse colon. Some tenderness is present with palpation but no rebound, and he is passing flatus. On further assessment, the nurse determines that J.M. has been taking occasional doses of milk of magnesia but has not been on a regular bowel regimen. The nurse recognizes that the patient has been on an opioid medication as well as a tricyclic antidepressant, and both are contributing to his constipation. Other factors include the patient’s decreased activity due to pain. He has always been a very active person who regularly ran and exercised daily, but with bone metastases he has become much more sedentary. His normal fluid intake has decreased significantly because he is feeling constantly nauseated, which is likely a symptom of the constipation. He is currently on a break from chemotherapy and his white blood cells and platelets are within normal limits. The nurse consults with the oncologist and recommends performing a bowel cleanout with a milk and molasses enema and starting the patient on a regular bowel regimen with instructions to take senna 8.6 mg and docusate 100 mg twice a day, increasing as needed to maintain a normal, comfortable bowel movement. J.M. reports significant relief of his bloating and abdominal discomfort following the enema, and two weeks later on reassessment the nurse learns that J.M. is now having a regular bowel movement every other day. His nausea has resolved, which has allowed him to increase his food and fluid intake as well.

Diarrhea

Case Study

M.L. is a 64-year-old man with metastatic adenocarcinoma of the colon. He opts to receive treatment with FOLFIRI (infusional plus bolus 5-fluorouracil [5-FU], leucovorin, and irinotecan). He comes to the clinic complaining of frequent watery diarrhea over the past 48 hours. He completed his chemotherapy about 10 days ago. He is having some nausea but no vomiting or fevers. He eliminates small amounts of liquid stool, but the urge to go to the bathroom comes on quickly and strong. He denies having pain but does experience cramping sometimes before defecation.
Overview

Although diarrhea is less prevalent than constipation, it is still one of the most common symptoms that complicates the treatment of patients with cancer (NCI, 2013). Any condition that causes increased intestinal secretions, decreased mucosal absorption, or altered motility can produce diarrhea. Diarrhea can occur anytime throughout the trajectory of cancer treatment, causing devastating physical and emotional effects (NCI, 2013).

Although formal definitions vary, diarrhea is usually defined as an abnormal increase in stool liquidity (greater than 300 ml stool), a stool weight of 200 g/day, and frequency (the passage of more than three unformed stools) during a 24-hour period that is beyond the patient’s baseline (Camilleri & Murray, 2012; NCI, 2013). Diarrhea often occurs when the fecal contents move so rapidly through the small intestine and colon that there is not enough time for the gastrointestinal secretions and oral contents to be absorbed (Camilleri & Murray, 2012).

Small bowel diarrhea is often associated with large volumes of stool. The stool tends to be light in color, watery, and generally non-bloody. Foul-smelling, greasy stools that are difficult to flush suggest steatorrhea (foul-smelling, oily, or frothy stools). When pain accompanies large-volume diarrhea, it is likely to be periumbilical or in the right lower quadrant, often intermittent, and cramping (Coleman, 2010). Diarrhea from large bowel disease may be smaller in volume and is usually dark in color and rarely foul smelling. The stools are soft, jelly-like, and often mixed with mucus or blood. Abdominal pain associated with large bowel ailments is usually hypogastric, left or right lower quadrant, or sacral. The pain is often continuous and may be associated with tenesmus (a feeling of incomplete defecation) if anorectal disease is present (Coleman, 2010).

Diarrhea can range from mild and self-limiting to severe and life threatening. Uncontrolled diarrhea can lead to volume depletion (dehydration), electrolyte imbalance, renal insufficiency, skin impairment, and cardiovascular compromise. Diarrhea can increase caregiver burden, especially in older adults or patients with advanced cancers (NCI, 2013).

Diarrhea sometimes is characterized as acute or chronic depending on its onset and duration. Diarrhea is considered acute if there is an abnormal increase in stool liquid that lasts more than four days but less than two weeks and chronic if it lasts for more than four weeks (Camilleri & Murray, 2012). More than 90% of acute diarrhea is associated with an infectious agent and is usually self-limiting (Camilleri & Murray, 2012). Other causes include food poisoning, medications, inflammatory or ischemic bowel disease, fecal impaction, enteral feedings, and recent ingestion of poorly absorbable sugars such as alcohol (Camilleri & Murray, 2012; NCI, 2013).

Chronic diarrhea may have a very late onset depending on the cause. It may persist longer than two months and often results from an unidentified causative agent, disease, disease process, or response from treatment-related tissue damage that interferes with normal physiologic functioning, such as surgical procedures (NCI, 2013).

Etiologies of diarrhea may arise from more than one causative agent or condition, including a single or combination of cancer treatments, which presents a challenge in the assessment and treatment of patients receiving cancer therapy. To prevent complications and develop an appropriate treatment plan, a careful assessment and identification of the causative agent is needed. Dose reductions, treatment delays, and lack of communication about treatment responses and adverse events, particularly in a curative adjuvant setting, can have direct adverse effects on patient outcomes (Stein, Voigt, & Jordan, 2010).
Incidence and Etiology

Diarrhea related to cancer and its treatment is now recognized as a cause of symptom distress and may have severe consequences in a variety of patient populations (Andreyev et al., 2012; Mercadante, 2013). The reported prevalence and severity of diarrhea vary greatly. Diarrhea can be observed in patients diagnosed with certain cancers such as carcinoid tumors, neuroendocrine hormone-producing tumors (e.g., vasoactive intestinal peptide tumor [VIPoma], gastrinoma, insulinoma, glucagonoma), and medullary thyroid tumors (Bisanz et al., 2010).

Diarrhea is commonly associated with cancer therapy (NCI, 2013). Conventional methods of diarrhea-causing treatment include surgery, chemotherapy or molecular targeted therapies, radiation therapy, and hematopoietic stem cell transplantation. Surgery, a primary treatment modality for many cancers, can affect the body by mechanical, functional, and physiologic alterations. Postsurgical complications of gastrointestinal surgery affecting normal bowel function that may contribute to diarrhea include increased transit time, gastroparesis, fat malabsorption, lactose intolerance, fluid and electrolyte imbalance, and dumping syndrome (NCI, 2013).

Diarrhea as a result of chemotherapy is a frequent problem seen in patients with cancer. Chemotherapy damages the intestinal mucosa lining, causing necrosis of the cells that line the intestines. These necrotic cells cause inflammation within the intestinal mucosa, causing decreased intestinal absorption, which results in diarrhea (Tortorice, 2011). Some chemotherapy agents are associated with diarrhea rates as high as 50%–80%, particularly with regimens containing fluoropyrimidines or irinotecan (NCI, 2013; Stein et al., 2010). Radiation therapy to the pelvis, abdomen, or lower thoracic and lumbar spine can lead to destruction of the cells in the lumen in the bowel, which can create severe and life-threatening diarrhea (NCI, 2013).

Diarrhea also occurs as a side effect of molecular targeted therapies such as some of the tyrosine kinase inhibitors and antibodies that are administered alone or in combination with chemotherapy. As more aggressive cancer therapy regimens and new therapies are developed and integrated into clinical practice, the scope of the problem of diarrhea in patients with cancer is likely to expand (Coleman, 2010).

Graft-versus-host disease (GVHD) is one of the most significant complications seen following allogeneic hematopoietic stem cell transplantation. The gastrointestinal tract is one of the more common sites for this manifestation. Common symptoms seen in gastrointestinal GVHD include nausea and vomiting, severe abdominal pain and cramping, and green, watery stool (Ezzone, 2011; NCI, 2013). The volume of GVHD-associated diarrhea may reach up to 10 L per day and indicates the degree and extensiveness of the mucosal damage (Ezzone, 2011; NCI, 2013).

One must also be alert to other causes of diarrhea including medication changes, particularly addition of antibiotic therapy, as well as psychosocial factors such as the stress and anxiety patients may experience associated with the demands of their diagnosis and treatment (NCI, 2013). Infections may also contribute to diarrhea and may be of viral, bacterial, protozoan, parasitic, or fungal etiology. Pseudomembranous colitis, which is often caused by 

Clostridium difficile,

is also a cause of diarrhea and may be resistant to treatment. Patients may develop diarrhea in response factors related to the underlying cancer, as well as to changes in diet, or other concomitant diseases. Difficulty adjusting the laxative regimen and impaction leading to leakage of stool around the fecal obstruction are common causes of diarrhea in patients receiving palliative care (NCI, 2013). A list of common causes of diarrhea in cancer can be found in Table 5-2.
TABLE 5-2  Common Causes of Diarrhea in Cancer

<table>
<thead>
<tr>
<th>Modality</th>
<th>Associated Condition or Treatments</th>
</tr>
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<tbody>
<tr>
<td>Cancer-related</td>
<td>Carcinoid syndrome</td>
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<tr>
<td>Colon cancer</td>
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<tr>
<td>Lymphoma</td>
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<tr>
<td>Medullary carcinoma of the thyroid</td>
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<tr>
<td>Pancreatic cancer, particularly islet cell tumors (Zollinger-Ellison syndrome)</td>
<td></td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td></td>
</tr>
<tr>
<td>Surgery- or procedure-related</td>
<td>Celiac plexus block</td>
</tr>
<tr>
<td>Cholecystectomy, esophagogastrectomy</td>
<td></td>
</tr>
<tr>
<td>Gastrectomy, pancreaticoduodenectomy (Whipple procedure)</td>
<td></td>
</tr>
<tr>
<td>Intestinal resection (malabsorption due to short bowel syndrome)</td>
<td></td>
</tr>
<tr>
<td>Vagotomy</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy-related</td>
<td>Capecitabine, cisplatin, cytosine arabinoside, cyclophosphamide, dacarbazine, daunorubicin, docetaxel, doxorubicin, 5-fluorouracil, interferon, irinotecan, leucovorin, methotrexate, oxaliplatin, paclitaxel, topotecan</td>
</tr>
<tr>
<td>Radiation therapy-related</td>
<td>Irradiation to the abdomen, para-aortics, lumbar, and pelvis</td>
</tr>
<tr>
<td>Bone marrow transplantation-related</td>
<td>Conditioning chemotherapy, total body irradiation, graft-versus-host disease after allogeneic bone marrow or peripheral blood stem cell transplants</td>
</tr>
<tr>
<td>Biologic therapy-related</td>
<td>Interleukin-2, interferons</td>
</tr>
<tr>
<td>Monoclonal antibodies: Bevacizumab, trastuzumab, cetuximab, panitumumab</td>
<td></td>
</tr>
<tr>
<td>Targeted molecules: Bortezomib, erlotinib, everolimus, gefitinib, gemtuzumab, imatinib, lapatinib, sorafenib, sunitinib, temsirolimus, vandetanib</td>
<td></td>
</tr>
<tr>
<td>Drug adverse effects</td>
<td>Antibiotics, magnesium-containing antacids, antihypertensives, colchicine, digoxin, iron, lactulose, laxatives, methylidopa, metoclopramide, misoprostol, potassium supplements, propranolol, theophylline</td>
</tr>
<tr>
<td>Concurrent disease</td>
<td>Diabetes, hyperthyroidism, inflammatory bowel disease (Crohn disease, diverticulitis, gastroenteritis, HIV/AIDS, ulcerative colitis), obstruction (tumor-related)</td>
</tr>
<tr>
<td>Infection</td>
<td>Clostridium difficile, Clostridium perfringens, Bacillus cereus, Giardia lamblia, Cryptosporidium, Salmonella, Shigella, Campylobacter, Rotavirus</td>
</tr>
<tr>
<td>Fecal impaction</td>
<td>Constipation leading to obstruction</td>
</tr>
<tr>
<td>Diet</td>
<td>Alcohol, milk and dairy products (particularly in patients with lactose intolerance) Caffeine-containing products (coffee, tea, chocolate); specific fruit juices (prune juice, unfiltered apple juice, sauerkraut juice)</td>
</tr>
<tr>
<td>High-fiber foods (raw fruits and vegetables, nuts, seeds, whole-grain products, dried legumes); high-fat foods (deep-fried foods, high fat–containing foods)</td>
<td></td>
</tr>
<tr>
<td>Lactulose intolerance or food allergies</td>
<td></td>
</tr>
<tr>
<td>Sorbitol-containing foods (candy and chewing gum); hot and spicy foods; gas-forming foods and beverages (cruciferous vegetables, dried legumes, melons, carbonated beverages)</td>
<td></td>
</tr>
<tr>
<td>Psychological factors</td>
<td>Stress</td>
</tr>
</tbody>
</table>

Note. Adapted from “Gastrointestinal Complications (PDQ®)” [Health Professional Version], by the National Cancer Institute, September 2013. Retrieved from http://cancer.gov/cancertopics/pdq/supportivecare/gastrointestinalcomplications.
Identifying the etiology of the diarrhea aids in the appropriate selection of interventions. Mechanisms of diarrhea that may be seen in patients with cancer are categorized as (a) osmotic, (b) malabsorptive, (c) secretory, (d) infectious/exudative, (e) dysmotility-associated, and (f) cancer treatment–related diarrhea from chemotherapy, radiation therapy, and/or molecular targeted therapies (Bisanz et al., 2010).

**Osmotic Diarrhea**

Osmotic diarrhea is related to the ingestion of poorly absorbable and osmotic active substances, such as mannitol, sorbitol, lactulose, and magnesium salts contained in antacids and laxatives (Bisanz et al., 2010; Camilleri & Murray, 2012). Water is pulled into the bowel lumen by the osmotic pressure of unabsorbed particles, increasing the water content of the gastrointestinal tract. The treatment of osmotic diarrhea is usually elimination of the causative agent (Bisanz et al., 2010).

**Malabsorptive Diarrhea**

Malabsorptive diarrhea is a combination of mechanical and biochemical mechanisms preventing effective absorptive processes. Malabsorption of fluid occurs when the lumen or mucosal integrity or other gut wall characteristics are altered. After a gastrostomy or pancreatectomy, enzyme deficiencies can occur that can inhibit complete digestion, such as those found in lactose intolerance and pancreatic insufficiency. Surgical resection also can reduce the absorptive ability of mucosal surfaces. The degree of malabsorption depends on the amount of colon resected, which can result in decreased fluid reabsorption by reducing the intestinal mucosal contact and transit time, resulting in decreased absorption of electrolytes or bile salts. This is called short bowel or short gut syndrome and occurs when more than 200 cm of bowel is resected. A primary feature of malabsorptive diarrhea is large-volume steatorrhea (foul-smelling, oily or frothy stools) (Coleman, 2010).

Celiac disease is the most common cause of malabsorptive diarrhea (Camilleri & Murray, 2012). This is a gluten-sensitive intestinal disorder characterized by villous atrophy and hyperplasia in the proximal small bowel that can present as fatty diarrhea (Camilleri & Murray, 2012). Another type of malabsorptive diarrhea that can be greasy, foul-smelling, and difficult to flush is fat malabsorption diarrhea. This type of malabsorption often is associated with weight loss and nutritional deficiencies with concomitant malabsorption of amino acids and vitamins (Camilleri & Murray, 2012).

Patients with hypoalbuminemia (serum albumin less than 2.5 g/dl) also may exhibit malabsorptive diarrhea. The low albumin leads to a decrease in oncotic pressure and results in edema of the intestinal mucosa. The fluid in the intestines cannot be reabsorbed and ultimately is eliminated as liquid stool (Camilleri & Murray, 2012).

**Secretory Diarrhea**

Secretory diarrhea results from overstimulation of the intestinal tract’s secretory capacity. The small intestines and large bowel mucosa secrete more fluids and electrolytes than can be absorbed by the bowel. Secretory diarrhea is characterized by large stool volume, which can exceed 1 L/hr of stool in a well-hydrated person. There is usually an absence of red or white blood cells in the stool, as well as absence of fever and other systemic symptoms (Bisanz et al., 2010). Secretory diarrhea persists when a patient fasts because the secretory process is independent of ingested substances. A classic example of acute secretory diarrhea is cholera. *Vibrio cholerae* causes an uncontrollable secretion of water. Similar symptoms are seen with other enterotoxins (e.g., *Escherichia coli* [*E. coli*], *Clostridium difficile* [*C. difficile*]) (Bisanz et al., 2010).
Antibiotic-associated diarrhea is defined as unexplained temporary diarrhea associated with use of antibiotics (Bartlett & Gerding, 2008; Bisanz et al., 2010). The most common cause of this diarrhea is an overgrowth and colonization of pathogenic bacteria from alteration of the normal gut (Bisanz et al., 2010). It occurs in approximately 29% of patients with diarrhea, with 25% of those cases attributed to *C. difficile* (Bisanz et al., 2010). Ninety percent of *C. difficile*-associated diarrhea is related to antibiotic use, especially penicillin (ampicillin), clindamycin, cephalosporin, and quinolones (Bartlett & Gerding, 2008; Bisanz et al., 2010). If left untreated, *C. difficile* infection can lead to severe diarrhea, hypovolemia, toxic megacolon with dilation and possible perforation of the colon, hemorrhage, and even death (Coleman, 2010). The onset of antibiotic-associated diarrhea or *C. difficile*-associated diarrhea usually occurs within four to nine days after stopping the antibiotic, but it can occur as late as eight weeks after discontinuation of treatment (Bartlett & Gerding, 2008; Bisanz et al., 2010).

Common causes of chronic secretory diarrhea are attributed to various hormones. Carcinoid tumors secrete serotonin, bradykinin, substance P, and prostaglandins that stimulate the intestines (Bisanz et al., 2010). Neuroendocrine tumors, such as VIPomas, cause secretion of vasoactive intestinal polypeptide hormones, which in turn stimulates intestinal activity. Patients with medullary thyroid cancer often experience diarrhea due to the release of calcitonin in the intestines (Bisanz et al., 2010).

Secretory diarrhea is a major feature of acute intestinal GVHD and occurs in nearly half of patients undergoing high-dose chemotherapy and radiation as a conditioning regimen (Tuncer, Rana, Milani, Darko, & Al-Homsi, 2012). Patients undergoing allogeneic hematopoietic stem cell transplantation have an autoimmune response to donor T lymphocytes in specific target tissues, including the epithelial lining of the intestinal wall (Coleman, 2010). Diarrhea usually occurs 15 days or later following engraftment but may occur as early as 7 days and as late as 100 days after receiving the donor cell infusion. A cascade of events causes the proliferation of inflammatory cells that ultimately produce mucosal tissue damage and may even completely denude the entire gastrointestinal tract (Coleman, 2010). Damage to the intestinal tract tissue is manifested by large-volume, greenish-colored liquid diarrhea in amounts that correlate with the extent of tissue damage. Patients may produce as much as 8–10 L within 24 hours (NCI, 2013; Ross & Couriel, 2005). Acute GVHD-related diarrhea may resolve with treatment or may continue on a chronic basis requiring long-term management (NCI, 2013). Acute GVHD may also be accompanied by selective damage to the liver, skin (rash), and mucosa of the entire gastrointestinal tract. Acute GVHD of the gastrointestinal tract can result in severe intestinal inflammation, sloughing of mucosal membranes, severe diarrhea, abdominal pain, nausea, and vomiting. This is typically diagnosed via biopsy and graded from I–IV based on the severity of diarrhea. Stage IV includes severe abdominal cramping with or without ileus formation (Anderson-Reitz, 2011).

### Infectious/Exudative Diarrhea

Infectious diarrhea is characterized by a systemic fever, pus, blood, or mucus in the stool. The diarrhea is caused by an infectious agent invading the intestinal mucosa. Within the intestinal wall, the hydrostatic pressure in the blood vessels and lymphatics causes water and electrolytes, mucus, protein, and cells to accumulate in the lumen of the bowel. The destruction of enzymes essential to carbohydrate and protein digestion can produce moderate to severe amounts of diarrhea. Fecal leukocytes are often found in fecal smears. The sudden onset of loose or watery stools in a previously healthy individual is usually of infectious origin (bacterial, viral, or parasitic). Examples of infectious diarrhea are Crohn disease, ulcerative colitis, and infections caused by *Salmonella* and *Shigella* (Bisanz et al., 2010).
Dysmotility-Associated Diarrhea

Dysmotility-associated diarrhea occurs when intestinal motility becomes altered in response to changes in mechanical stretch receptors and neural stimuli that determine peristaltic activity. This results in the rapid transit of stool through the colon, limiting adequate time for absorption of chyme into the epithelial cells. Small semi-liquid to liquid high-weight stools in variable volume and frequency occur (Mercadante, 2013).

Many causative factors may be responsible for dysmotility-associated diarrhea, including (a) fecal impaction from drug therapy (e.g., narcotics) that results in overflow diarrhea around the impaction, (b) obstructive processes that distend the bowel beyond its normal size (e.g., tumor, adhesions from surgery, radiation therapy), (c) the overingestion of peristaltic stimulants (e.g., laxatives), (d) opioid withdrawal syndrome, and (e) anxiety or stress (Bisanz et al., 2010; Camilleri & Murray, 2012).

Cancer Treatment–Related Diarrhea

Chemotherapy-induced diarrhea: In chemotherapy-induced diarrhea (CID), an imbalance between absorption and secretion leads to the production of a large volume of fluid and electrolytes in the small bowel. The fluid overwhelms the absorptive capacity of the colon, leading to large volumes of diarrhea. This type of diarrhea does not usually resolve with fasting. CID is a common problem, especially in patients with advanced cancer. CID depends upon the particular agent or combination of agents, dosage schedule, route of administration, and multimodality regimens including both chemotherapy and radiation (Gibson & Stringer, 2009). It may also occur as a result of treatment-related side effects such as when the neutropenic patient develops enterocolitis. Some chemotherapeutic regimens are associated with diarrhea rates as high as 50%–80%, particularly those containing fluoropyrimidines (e.g., 5-FU, flouxuridine) and topoisomerase inhibitors (e.g., irinotecan) (Eaton & Tipton, 2009; Stein et al., 2010).

The pathophysiology of CID is not well understood and is probably the result of a combination of mechanisms. Cytotoxic agents damage the intestine’s mucosal lining, altering water absorption. Within the colon, water follows chloride, and, in normal tissue, both are absorbed readily from the lumen of the bowel (Coleman, 2010). When the crypts of the colon are damaged from chemotherapy, chloride absorption is reduced and water is released into the lumen, resulting in diarrhea. Alteration in gut motility also occurs, with reduced transit time for bowel contents, again resulting in decreased water absorption.

Many antineoplastic agents cause mucosal damage characterized by sloughing of surface epithelial cells without basement membrane replacement, resulting in superficial ulceration and extensive bowel wall inflammation (Coleman, 2010). The resulting epithelial cell necrosis and inflammatory response trigger a cascade of events that stimulate secretion of large quantities of fluid and electrolytes from the intestinal wall, producing diarrhea. Reaction of the mucosa contributes to destruction of brush border enzymes, which are needed for carbohydrate and protein digestion, which, in turn, interferes with absorption (Camp-Sorrell, 2011). In neutropenic patients, endotoxins released by opportunistic pathogens exaggerate the inflammatory response and intensify the severity of the diarrhea. As a consequence, the patient may suffer from moderate to severe diarrhea immediately following and up to 14 days after chemotherapy (Muehlbauer & Lopez, 2014).

Although the occurrence of CID is unpredictable, several patient-related factors are associated with an increased incidence. These include age older than 65, female gender, poor performance status, associated bowel disease such as inflammatory or malabsorption process, bowel tumor, genetic polymorphisms affecting drug metabolism, and biliary obstruction (Stein et al., 2010). Diarrhea is a dose-limiting toxicity for certain chemother-
apy agents, particularly 5-FU, irinotecan, and capecitabine, although the mechanisms and manifestations differ.

The pathophysiology of 5-FU–associated diarrhea begins with the mitotic arrest of intestinal epithelial crypt cells. This then causes an increase in the ratio of immature secretory crypt cells to mature villous enterocytes, which thereby causes abnormal absorption and secretion of fluids and electrolytes (Teva Pharmaceuticals, 2012). Diarrhea associated with 5-FU can be watery or bloody (Cherny, 2008). Any disruption of the gut lining may increase the risk of enteric organisms entering into the bloodstream, causing the potential for overwhelming sepsis, particularly if the neutropenia coincides with diarrhea (Cherny, 2008). Severity is variable, and pathologic changes range in severity from a mild colitis to severe life-threatening necrotizing enterocolitis with pneumocystic colitis. Diarrhea is most commonly observed when 5-FU is coadministered with leucovorin. It is slightly more common with bolus rather than infusional administration of 5-FU and leucovorin (Cherny, 2008). There are no published data on the benefits of pharmacokinetically based dosing in patients receiving 5-FU-containing combination regimens, such as those containing oxaliplatin or irinotecan (Gamelin et al., 2008).

Dihydropyrimidine dehydrogenase (DPD) plays a central role in the metabolism of 5-FU. Patients with a DPD deficiency can be at risk for severe life-threatening toxicity such as diarrhea, mucositis, and pancytopenia (Cherny, 2008). Although the diagnosis can be made by radioimmunometric assay for the DPD enzyme, this test is not readily available, and consequently, most cases are diagnosed retroactively after severe complications have occurred. More recently, efforts have been undertaken to identify genetic markers, and several genotypes, including \textit{DPYD} and \textit{TYMS}, have been shown to predict clinical toxicity. Genetic testing is available, but validity has yet to be established (Jennings et al., 2013; Loganayagam et al., 2013). Nurses should incorporate information about DPD deficiency and its risk into patient education for individuals receiving 5-FU and consider consultation regarding DPD deficiency testing before initiation of treatment in patients with risk factors. The manufacturers of 5-FU and capecitabine recommend that patients with DPD deficiency should not receive these drugs because of the risk of severe and potentially fatal reactions. Another option is close monitoring of 5-FU levels and pharmacokinetically guided dosing. Unfortunately, most cases of DPD deficiency are diagnosed after a patient has experienced a severe reaction to 5-FU. Management of these patients should include aggressive hemodynamic support, parenteral nutrition, antibiotics, and hematopoietic colony-stimulating factors.

Irinotecan can cause acute diarrhea (occurring during or immediately following drug administration) or delayed diarrhea. Immediate-onset diarrhea is caused by acute cholinergic properties and often is accompanied by other symptoms of cholinergic excess, including abdominal cramping, rhinitis, lacrimation, and salivation. The mean duration of symptoms is 30 minutes, and they usually respond rapidly to atropine (Grenon & Chan, 2009; Stein et al., 2010). Delayed-onset diarrhea usually occurs at least 24 hours after drug administration and can be life threatening, especially when irinotecan is used in combination chemotherapy regimens with bolus IV 5-FU and leucovorin (Wilkes & Barton-Burke, 2014). The late diarrhea associated with irinotecan is unpredictable and noncumulative and occurs at all dose levels; however, it is more common with higher doses every three weeks than with lower weekly dosing (Cherny, 2008). The median time to onset is 6–14 days. The mechanism of irinotecan-induced delayed diarrhea is not known, but it is thought to be related to increased cholinergic activity and the formation of an active metabolite called SN-38. This enables a direct effect of the active agent on the colonic epithelium that binds to topoisomerase I and induces apoptosis, leading to the disturbance in the absorptive and secretory functions of mucosa. This
in turn stimulates the production of proinflammatory cytokines and prostaglandins, thereby contributing to secretory diarrhea (Camp-Sorrell, 2011; Grenon & Chan, 2009).

Capecitabine, a precursor of 5-FU, is an oral fluoropyrimidine carbamate cytotoxic agent. The fluoropyrimidine carbamate molecule is metabolized to 5-FU at the tumor site (Wilkes & Barton-Burke, 2014). About 50% of patients who receive capecitabine will develop diarrhea, with patients older than age 80 experiencing increased effects (Wilkes & Barton-Burke, 2014). CTCAE (NCI CTEP, 2010) grade 2 diarrhea is cause to interrupt treatment (Wilkes & Barton-Burke, 2014). The dose should be reduced for the second and third occurrences of diarrhea, and treatment should be discontinued if there is a fourth occurrence (Wilkes & Barton-Burke, 2014).

**Neutropenic enterocolitis:** Neutropenic enterocolitis (also called *necrotizing enterocolitis* or *typhlitis*) is an acute life-threatening complication of chemotherapy that is most commonly observed with high-dose treatments, such as those used with hematopoietic stem cell transplantation, but can be seen with other myeloblastic therapies as well (Cherny, 2008).

Neutropenic enterocolitis usually occurs when the absolute neutrophil count is less than 500/mm$^3$. Patients often present with fever, abdominal pain, nausea, vomiting, diarrhea, and commonly, sepsis (Cherny, 2008). Abdominal pain is often diffuse or localized to the right lower quadrant. In some circumstances pain may be absent, particularly in patients who have received steroid therapy (Cherny, 2008).

The pathogenesis of neutropenic enterocolitis is multifactorial (Cherny, 2008). It often results from mucosal injury by cytotoxic drugs, neutropenia, and impaired host defense to invasion by microorganisms (Cherny, 2008). The microbial infection leads to necrosis of various layers of the bowel wall. Anatomically, the cecum is almost always affected, and the process often extends into the ascending colon and terminal ileum. The predilection for the cecum is possibly related to its distensibility and its relatively diminished vascularization. Polymicrobial infection is frequent, and various bacterial and fungal organisms, including gram-negative rods, gram-positive cocci, anaerobes (e.g., *C. difficile*), and *Candida*, are often seen infiltrating the bowel wall (Cherny, 2008).

The diagnosis is based on signs and symptoms and imaging studies (Cherny, 2008). Plain abdominal radiographs may demonstrate dilated loops of bowel, thickening of the bowel wall that takes on a “thumbprint” appearance resulting from bowel wall edema, or indications of a right lower quadrant mass from phlegmon or purulent material accumulation (Cherny, 2008). Pneumatosis intestinalis (presence of gas within the wall of the gastrointestinal tract) may be seen on radiographs. Free intraperitoneal air is an indication of bowel wall perforation (Cherny, 2008; Wang et al., 2011).

Computed tomography (CT) scanning is the preferred imaging modality. CT scanning techniques can evaluate the entire abdomen for pathology, especially in patients with distended loops of bowel and ileus, for whom ultrasound would not be possible. Scans commonly demonstrate concentric thickening of the bowel wall, a fluid-filled cecum, pericolic fluid collections or abscesses, pneumatosis intestinalis, and free air if an underlying perforation exists (Cherny, 2008).

Abdominal ultrasonography can identify thickening of the bowel wall that produces a target or halo sign. In addition, ultrasound is useful as a follow-up tool to assess the gradual decrease in bowel wall thickness during resolution (Cherny, 2008).

**Targeted therapy-associated diarrhea:** Diarrhea is common in patients receiving the small-molecule epidermal growth factor receptor (EGFR)–related tyrosine kinase inhibitors, such as erlotinib, gefitinib, or lapatinib, with a reported incidence of 60% in all patients (Stein et al., 2010). However, dose reduction is seldom required, and the rate of severe diarrhea (grade 3 or 4) with EGFR therapies is less than 10% (NCI CTEP, 2010; Stein et al., 2010). However, co-
administration of these agents with 5-FU, irinotecan, or capecitabine may exacerbate the toxicity (Grenon & Chan, 2009). Multitargeted tyrosine kinase inhibitors (e.g., sorafenib, sunitinib) cause all grades of diarrhea in 30%–50% of patients (Stein et al., 2010). Mammalian target of rapamycin inhibitors (e.g., everolimus, temsirolimus) cause diarrhea in up to 40% of patients, with severe diarrhea occurring in only 5% (Cherny, 2008). For patients who are on bortezomib, a proteasome inhibitor used in the treatment of multiple myeloma and mantle cell lymphoma, diarrhea occurs in 51%, with 8% experiencing grade 3 or 4 diarrhea (Cherny, 2008). Monoclonal antibodies as single agents (such as cetuximab, a chimeric antibody, and panitumumab, a humanized antibody) have been reported to cause grade 2 and 3 (21% and 1%–2%, respectively) diarrhea (Stein et al., 2010). Table 5-2 lists cancer treatment agents causing diarrhea.

Radiation-induced diarrhea: Radiation-induced diarrhea (RID) usually occurs one to two weeks after the start of treatment and continues until one to two weeks after the completion of treatment (Bisanz et al., 2010). It is often caused by damage of the mucosa as a result of decreased absorption in water and electrolytes. Factors contributing to the occurrence and severity of the diarrhea include the total dose of radiation, fractionation, volume of bowel irradiated in the field, and concomitant chemotherapy (Coleman, 2010).

Acute and chronic diarrhea can result from radiation therapy directed to the abdominal, pelvic, para-aortic, and lumbosacral fields. Radiation enteritis is a complication of abdominal and pelvic radiation. Radiation therapy interacts with cells to cause cellular death, which leads to diarrhea, especially when the cells are most vulnerable to the killing effect of radiation therapy during the G2 and M phases. Rapidly proliferating tissues, such as small intestine crypt cells, are particularly sensitive to radiation. They undergo apoptosis (programmed cell death), and the crypt cells are shed from the intestinal villi. Acute diarrhea from radiation enteritis is seen during this phase. Concurrent administration of chemotherapy may enhance apoptosis and exacerbate the diarrhea (Tortorice, 2011).

Acute radiation enteritis side effects occur at approximately 10 Gy and can last up to 8–12 weeks after therapy (NCI, 2013). Common side effects of acute radiation enteritis include diarrhea, rectal urgency (referred to as tenesmus), gas, bloating, and cramping. These symptoms usually resolve without specific therapy within two to six months (Cherny, 2008). Late-onset effects of abdominal radiation may occur months to years after completion of radiation therapy and are manifested as chronic radiation enteritis (NCI, 2013). Chronic radiation enteritis is secondary to mucosal atrophy with vasculitis and fibrosis progressing over time, resulting in narrowing of the intestinal lumen with dilation of the bowel proximal to the stricture. The affected segments of intestine are thickened. Functional changes include malabsorption, narrowing of the bowel lumen (thus predisposing to obstruction), and changes that may result in intestinal fibrosis and ischemia (Cherny, 2008). Ischemic changes may lead to fistula formation, ulceration, obstruction, abscess formation, stricture, perforation, and chronic bleeding.

Chronic radiation enteritis is less common than acute radiation enteritis and is usually associated with radiation doses greater than 45 Gy (Cherny, 2008). Chronic radiation enteritis may present months to years after completion of therapy (NCI, 2013). As a result, these late effects may necessitate dietary modifications, pharmacologic management, and, in some instances, surgical intervention for supportive care and treatment (NCI, 2013).

**Assessment**

Assessment of patients with possible treatment-induced diarrhea should include a detailed medical and dietary history, medication review, and description of stools. The history about
the diarrhea should include detailed questions regarding the frequency of stools during the past 24 hours, consistency of the stool, and associated symptoms, which can help to identify the etiology and intervention that may be most effective (Cherny, 2008; NCI, 2013). Physical examination should focus on the identification of dehydration and abnormalities of the abdominal and rectal areas. When appropriate, abdominal radiographs can be ordered to evaluate for abdominal obstruction or fecal impaction. A chemistry panel should be checked for evidence of dehydration, hypokalemia, or renal impairment (Cherny, 2008). If enteric infections are suspected, stool samples should be checked for fecal leukocytes, *C. difficile* toxins A and B, and other organisms including *Salmonella*, *E. coli*, *Campylobacter*, and infectious colitis (Cherny, 2008). If neutropenic enterocolitis is suspected, abdominal CT should be considered.

The most commonly used scale for rating cancer-related diarrhea is the current version of the CTCAE (NCI CTEP, 2010) (see Table 5-3). The CTCAE evaluates and grades diarrhea by number of stools per day, incontinence, and increase in ostomy output compared to baseline. It is a Likert-type scale for rating the severity of diarrhea with grades 1–5 (NCI CTEP, 2010). Although the CTCAE provides a standard objective foundation for evaluating treatment-induced diarrhea, additional evaluation is warranted. A comparison of the CTCAE and the Eastern Cooperative Oncology Group (2007) Common Toxicity Criteria is presented in Table 5-3.

Additional clues to the etiology of diarrhea include a detailed assessment of medication, dietary intake, and recent travel. The patient’s use of complementary and alternative therapies needs to be elicited, as herbal supplements and teas may be self-administered without

<table>
<thead>
<tr>
<th>Grade</th>
<th>NCI CTCAE</th>
<th>ECOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Increase of &lt; 4 stools/day over baseline; mild increase in ostomy output compared to baseline</td>
<td>Increase of 2–3 stools/day over baseline</td>
</tr>
<tr>
<td>2</td>
<td>Increase of 4–6 stools/day over baseline; moderate increase in ostomy output compared to baseline</td>
<td>Increase of 4–6 stools/day, or nocturnal stools, or moderate cramping</td>
</tr>
<tr>
<td>3</td>
<td>Increase of ≥ 7 stools/day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL</td>
<td>Increase of 7–9 stools/day or incontinence, or severe cramping</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Increase of ≥ 10 stools/day or grossly bloody diarrhea, or need for parenteral support</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
<td>—</td>
</tr>
</tbody>
</table>

* Definition: A disorder characterized by frequent and watery bowel movements.

* Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.

ADL—activities of daily living; ECOG—Eastern Cooperative Oncology Group; NCI CTCAE—National Cancer Institute Common Terminology Criteria for Adverse Events

Note. Based on information from Eastern Cooperative Oncology Group, 2007; National Cancer Institute Cancer Therapy Evaluation Program, 2010.
the knowledge of healthcare providers. Figure 5-5 lists a number of supplements that may cause diarrhea.

Patients should be questioned regarding related symptoms that might indicate hemodynamic compromise or the underlying etiology. Assessment of weight loss and reduced urine output can assist in delineating the amount of fluid depletion and hydration status. Specifically, questions should include information about dizziness, orthostatic symptoms, lethargy, cramping, abdominal pain, nausea, vomiting, fever, and rectal bleeding. These symptoms should be classified as complicated or uncomplicated, with therapy based on this classification (NCI, 2013).

Uncomplicated symptoms include grade 1 or 2 diarrhea with no other signs or symptoms, and management is conservative. Complicated symptoms include grade 1 or 2 diarrhea with any one of the following risk factors: moderate to severe cramping, grade 2 or higher nausea or vomiting, decreased performance status, fever, sepsis, neutropenia, bleeding, or dehydration. Grade 3 or 4 diarrhea is also classified as complicated (Cherny, 2008; NCI, 2013; NCI CTEP, 2010). A telephone triage algorithm that incorporates subjective and objective assessment findings and employs CTCAE severity grading of diarrhea may direct treatment recommendations.

Patient assessment is of the utmost importance to determine if the clinical manifestations are severe in a patient receiving treatment for cancer, as ongoing treatment may be affected. Antineoplastic agents administration may need to be held or modified, or a radiation treatment may need to be held (Coleman, 2010).

Patients may be reluctant to tell their nurse about any toxicity because they may believe that it may lead to dose reduction, which will cause treatment to be less effective. It is important to inform patients that side effects and adjustments in chemotherapy or radiation doses are common. Stress to patients the importance of relaying any symptoms accurately and in a timely manner, as failure to adjust doses early may lead to severe, life-threatening toxicities, treatment delay, and possibly even greater dose reduction.

**Physical Findings**

Physical examination includes vital signs; auscultation of lungs; auscultation of the abdomen for the presence or absence of bowel sounds and palpation to assess for masses, ascites, hepatosplenomegaly, rebound tenderness, and guarding; and inspection for perianal irritation or fistulas. Findings may help identify the location in the bowel where the

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**FIGURE 5-5  Herbs and Supplements That Can Cause Diarrhea**

<table>
<thead>
<tr>
<th>Herbs and Supplements That Can Cause Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High-dose vitamin C</td>
</tr>
<tr>
<td>• Magnesium</td>
</tr>
<tr>
<td>• Potassium</td>
</tr>
<tr>
<td>• Aloe</td>
</tr>
<tr>
<td>• Bromelain</td>
</tr>
<tr>
<td>• Buckhorn</td>
</tr>
<tr>
<td>• Cascara</td>
</tr>
<tr>
<td>• Cat's claw</td>
</tr>
<tr>
<td>• Creatine</td>
</tr>
<tr>
<td>• “Dieter’s” teas</td>
</tr>
<tr>
<td>• Eucalyptus oil</td>
</tr>
<tr>
<td>• Fish oil</td>
</tr>
<tr>
<td>• Flaxseed and flaxseed oil</td>
</tr>
<tr>
<td>• Garlic</td>
</tr>
<tr>
<td>• Guggulipid</td>
</tr>
<tr>
<td>• Lecithin</td>
</tr>
<tr>
<td>• Milk thistle</td>
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<tr>
<td>• Rhubarb</td>
</tr>
<tr>
<td>• Rose hips</td>
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<tr>
<td>• Sarsaparilla</td>
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<tr>
<td>• Senna</td>
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</tbody>
</table>

Chapter 5  Bowel Dysfunction  103

problem originated. Absent or hyperactive bowel sounds may indicate an obstructive process. Fecal impaction may be determined from a rectal examination. Examination of the perianal or peristomal area for impaired skin integrity from repetitive cleansing or wiping is required, as well as assessment of skin turgor and oral mucosa to evaluate hydration status.

The presence of fever, blood in the stool, abdominal pain, weakness, or dizziness warrants immediate medical attention to rule out infection, bowel obstruction, or dehydration. The order of abdominal assessment is important to minimize patient discomfort. Begin with inspection, followed by auscultation for bowel sounds, proceeding to percussion, and leaving palpation for last.

The presence of fecal impaction must be considered, as diarrhea may occur as absorption at the site of obstruction is impaired and only fluid is allowed to pass around the obstructed area. This may be suspected if a patient complains of acute and severe cramping that occurs before small amounts of diarrhea or occurs in the absence of any other risk factors. Risks must be considered before performing any digital rectal examination or disimpaction in patients with thrombocytopenia and/or neutropenia (Coleman, 2010). Figure 5-6 illustrates the critical clinical manifestations of diarrhea that may be seen with a thorough assessment and physical examination.

Laboratory Results

No specific diagnostic tests validate diarrhea, but several tests can help clarify the etiology. Laboratory tests may include stool cultures for bacterial, fungal, and viral pathogens. A complete chemistry panel and complete blood count can provide information regarding the effect of diarrhea on electrolytes and white blood cell count in response to an infection. Urinalysis with specific gravity can provide information regarding hydration status. Patients suspected of having an endocrine hormone–producing tumor may need a 24-hour urine collection for 5-hydroxyindoleacetic acid (known as 5-HIAA) or serum analysis for chromogranin A, C-peptide, gastrin, glucagon, insulin growth factor, pancreatic polypeptide, vasactive intestinal peptide binding protein, and calcitonin (Warner, 2005). Investigations for chronic diarrhea of unknown origin can include breath tests to evaluate lactose, bile acid, and carbohydrate absorption; small intestine biopsy; intestinal angiograms; and vitamin $B_{12}$ level. In some cases, radiographic procedures are conducted to identify ileus, obstruction, or other abnormalities. Any invasive radiographic imaging with contrast or endoscopic evaluation with biopsy should be reserved for patients with persistent diarrhea refractory to antidiarrheal interventions, particularly in immunocompromised individuals.

<table>
<thead>
<tr>
<th>FIGURE 5-6</th>
<th>Critical Clinical Manifestations of Cancer Treatment–Related Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dehydration</td>
<td></td>
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<tr>
<td>• Life-Threatening hypokalemia, metabolic acidosis, hypercalcemia, or malnutrition</td>
<td></td>
</tr>
<tr>
<td>• Cardiovascular compromise</td>
<td></td>
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<tr>
<td>• Impaired immune function following frequent episodes of chemotherapy-induced diarrhea</td>
<td></td>
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<tr>
<td>• Reduced absorption of oral medications</td>
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<tr>
<td>• Pain</td>
<td></td>
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<tr>
<td>• Anxiety</td>
<td></td>
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<tr>
<td>• Exhaustion</td>
<td></td>
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<tr>
<td>• Decreased quality of life</td>
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</tbody>
</table>

Note. Based on information from Camp-Sorrell, 2011; Coleman, 2010; Stein et al., 2010; Tortorice, 2011.
Evidence-Based Interventions

The American Society of Clinical Oncology (ASCO), NCI, and ONS provide clinical guidelines for cancer treatment–related diarrhea. ASCO and NCI treatment guidelines classify diarrhea as complicated, uncomplicated, radiation induced, and chemotherapy induced (Benson et al., 2004; NCI, 2013). ONS outlines diarrhea management strategies in a PEP resource (see www.ons.org/practice-resources/pep/diarrhea). This resource provides evidence-based oncology nursing interventions for diarrhea that can be used in the clinical setting. It classifies the evidence as Recommended for Practice, Likely to Be Effective, Benefits Balanced With Harms, Effectiveness Not Established, Effectiveness Unlikely, and Not Recommended for Practice (Muehlbauer et al., 2009). Recommendations for the treatment of CID and RID are presented along with levels of evidence. See Table 5-4 for comparison of ASCO and ONS guidelines.

Treatment of diarrhea entails the use of targeted pharmacologic therapy and adjunctive supportive care such as dietary modification, bowel rest, fluid and electrolyte replacement, and skin care, as well as delaying, reducing the dose, or discontinuing the causative agent (Benson et al., 2004). Patients and caregivers need to be educated about which symptoms require immediate attention and how to monitor and document symptoms effectively. To accomplish these goals, the interventions must match the identified cause and the specific needs of the patient by incorporating both nonpharmacologic and pharmacologic strategies.

Nonpharmacologic Interventions

Anticipation and prompt management of diarrhea related to cancer and its treatment may be more realistic to minimize toxicity and associated side effects than any prevention strategy. Dietary modifications for patients receiving chemotherapy and radiation therapy are commonly implemented prophylactically before treatment to prevent or lessen the severity of cancer treatment–related diarrhea. This may include a low-fiber, low-residue diet. Each nutritional plan should be tailored with consideration of religious, cultural, and personal preferences and any allergies (Shaw & Taylor, 2012).

Patients with diarrhea should discontinue foods, beverages, and medications known to produce or aggravate diarrhea. In some cases, dietary modifications for diarrhea management include eating small, frequent meals and avoiding lactose-containing food (e.g., milk and dairy products), spicy foods, alcohol, caffeine-containing foods and beverages, certain fruit juices, gas-forming foods and beverages, high-fiber foods, and high-fat foods (Bisanz et al., 2010; Muehlbauer et al., 2009; NCI, 2013).

For mild cases of diarrhea, the BRAT (bananas, rice, applesauce, toast) diet may reduce the frequency of stools (NCI, 2013). When experiencing diarrhea, patients should be encouraged to increase clear liquid intake to at least 3 L/day (e.g., water, sports drinks, broth, weak decaffeinated teas, caffeine-free soft drinks, clear juices, gelatin) (NCI, 2013). If patients do not tolerate the BRAT diet, they can try a clear liquid diet. Once solid foods are reincorporated, small, frequent meals (up to six meals per day) may be suggested (Bisanz et al., 2010).

Oncology nurses need to encourage patients to stay hydrated and to adhere to recommended dietary modifications. Initiating a nutrition consult with a dietitian can be beneficial to assist patients in assessing and choosing foods and customizing a diet to maintain adequate nutrition and hydration. Dietary recommendations to alleviate or eliminate diarrhea are presented in Table 5-5.

Patients requiring tube feedings may have psyllium or pectin added to their formula to prevent diarrhea (Coleman, 2010). Using lactose-free and fiber-containing products, minimizing the risk of bacterial contamination of formulas during preparation, diluting med-
### TABLE 5-4 Comparison of ASCO and ONS Evidence-Based Guidelines for the Management of Cancer Treatment–Related Diarrhea

<table>
<thead>
<tr>
<th>Topic</th>
<th>ASCO</th>
<th>ONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line treatment</strong></td>
<td>Dietary modifications: Loperamide 4 mg followed by 2 mg every 4 hours</td>
<td>Recommended for CRID and RID: Loperamide 4 mg followed by 2 mg every 4 hours</td>
</tr>
<tr>
<td><strong>Diarrhea refractory to loperamide: mild to moderate diarrhea (ASCO) or grade 2 or 3 (ONS)</strong></td>
<td>OCTREOTIDE: Octreotide 100–500 mcg with dose escalation as needed or tincture of opium or budesonide</td>
<td>Likely to be effective for CRID: 150 mcg octreotide SC TID for 5 days</td>
</tr>
<tr>
<td></td>
<td>RID: Continuation of loperamide 2 mg every 2 hours; replacement of fluid and electrolytes</td>
<td>Likely to be effective for RID: Octreotide 100 mcg SC TID</td>
</tr>
<tr>
<td><strong>Complicated (ASCO) or severe (ONS) diarrhea</strong></td>
<td>Complicated CID: IV octreotide 100–150 mcg SC or IV TID with dose escalation until diarrhea is controlled, and an antibiotic (fluoroquinolone); hospitalization possibly necessary; stool workup; laboratory tests</td>
<td>Recommended for severe CID: Octreotide 100 mcg SC TID for 3 days, then 50 mcg SC TID for 3 days</td>
</tr>
<tr>
<td></td>
<td>Complicated RID: Hospitalization possibly not necessary; continuation of loperamide; may not need octreotide; avoidance of antibiotics, which may worsen diarrhea</td>
<td>Likely to be effective for severe CID: 30 mg long-acting repeatable octreotide intramuscularly 7–14 days prior to day 1 of chemotherapy, then every 28 days up to 6 doses</td>
</tr>
<tr>
<td><strong>Prevention</strong></td>
<td>ASCO states that no definitive data exist, but the future is promising.</td>
<td>Likely to be effective: Cholestyramine and levofloxacin for CID prevention; psyllium fiber for RID prevention</td>
</tr>
<tr>
<td></td>
<td><strong>Assessment recommendations:</strong> Increased monitoring (weekly assessment of gastrointestinal toxicity); blood tests no more than 48 hours prior to chemotherapy; increased management such as antibiotic treatment if diarrhea lasts more than 24 hours; discontinuation of chemotherapy if severe CID; death possible</td>
<td>Effectiveness not established: Budesonide, oral alkalization, charcoal, for prevention of irinotecan-induced diarrhea; probiotics and glutamine for CID prevention</td>
</tr>
<tr>
<td></td>
<td>Benefits balanced with risks: Amifostine infusion or neomycin for irinotecan-induced diarrhea</td>
<td>Effectiveness not established: Antioxidants (vitamins E and C) for treatment of RID</td>
</tr>
<tr>
<td></td>
<td>Effectiveness unlikely: Sulfasalazine and selenium supplementation for prevention of RID; pentosan polysulfate for treatment of RID</td>
<td>Not recommended for practice: Sucralfate for prevention of RID</td>
</tr>
</tbody>
</table>

ASCO—American Society of Clinical Oncology; CID—chemotherapy-induced diarrhea; CRID—chemotherapy- and radiation-induced diarrhea; ONS—Oncology Nursing Society; RID—radiation-induced diarrhea; SC—subcutaneously

Note. Based on information from Benson et al., 2004; Oncology Nursing Society, 2011.

A Guide to Oncology Symptom Management (Second Edition)

TABLE 5-5 Dietary Recommendations for Diarrhea Prevention

<table>
<thead>
<tr>
<th>Recommendation for Homeostasis</th>
<th>Consume</th>
<th>Avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydration</td>
<td>Lots of clear fluids (8–10 large glasses), which may include weak, tepid tea and gelatin</td>
<td>Alcohol</td>
</tr>
<tr>
<td></td>
<td>Sports drinks</td>
<td>Coffee and tea with caffeine</td>
</tr>
<tr>
<td></td>
<td>Juice*</td>
<td>Very hot or cold beverages</td>
</tr>
<tr>
<td></td>
<td>Fluids with glucose, as glucose absorption drives sodium and water back into the body</td>
<td>Milk</td>
</tr>
<tr>
<td></td>
<td>Clear broth/bouillon</td>
<td>Carbonated drinks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prune and orange juices</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Small amounts of soft, bland food</td>
<td>Spicy, greasy, or fried foods</td>
</tr>
<tr>
<td></td>
<td>Consider BRAT diet: bananas, rice, applesauce, toast</td>
<td>High-fiber foods (whole-grain products, beans, raw vegetables, seeds, popcorn, pickles, fruit)</td>
</tr>
<tr>
<td></td>
<td>Foods high in protein (beef, chicken, turkey, eggs)</td>
<td>Hyperosmotic supplements (Ensure®)</td>
</tr>
<tr>
<td></td>
<td>Potassium-rich food (bananas, fruit juices, potatoes without the skin, avocados, asparagus tips)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Foods containing pectin (beets, unspiced applesauce, peeled apples, ginger tea)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low-fiber foods (white bread, white rice)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Foods eaten at room temperature</td>
<td></td>
</tr>
</tbody>
</table>

* Do not eat or drink grapefruit products until cleared by your doctor.


ications with water, and altering the feeding infusion rate to infuse over time rather than bolus administration are other considerations to prevent diarrhea (Coleman, 2010). More research is needed on psyllium fiber supplementation to identify the type and dose to effectively treat and/or prevent diarrhea for any patient receiving chemotherapy or radiation therapy (Muehlbauer et al., 2009).

Careful monitoring of the use and frequency of laxatives and stool softeners may help to prevent diarrhea. A healthy bowel regimen with adequate exercise, fluid intake, and dietary fiber should be encouraged. Incorporation of a bowel regimen in patients who require narcotics for pain management needs to be assessed and monitored to see if it reduces the incidence of fecal impaction.

Perianal, perineal, and any peristomal skin must be assessed in patients experiencing diarrhea. Liquid stool contains acids and can be very caustic to bare skin, causing excoriation and skin breakdown depending on the length of exposure and recurring episodes of stooling (Coleman, 2010). The affected area should be cleansed after each episode to limit exposure time of stool on the skin. Mild soap and water or alcohol-free baby wipes are the cleansing products of choice. The skin should be patted dry, rather than rubbed, and, if possible, allowed to air dry. Sitz baths of tepid water several times a day may minimize discomfort. A skin barrier product such as petroleum jelly, Desitin® ointment, or other moisture barrier product may be used, but caution must be taken in their removal because skin damage from rubbing may cause additional damage (Coleman, 2010). Rectal pouches may be used in hospitalized patients with severe diarrhea or persistent fecal incontinence to promote skin integ-
Nurses must remind patients receiving radiation to be careful to not wash off treatment field markings and to check with the radiation therapy team before application of any skin products.

Diarrhea is usually high in sodium, potassium, and bicarbonate. The use of oral rehydration formulas (commercial products available include Pedialyte® and Gatorade®) is based on the principle that carbohydrate absorption, especially glucose, in the small bowel facilitates sodium and water reabsorption from the intestinal lumen into the intravascular compartment (Coleman, 2010). Sports drinks that claim to replenish fluid and electrolyte loss during exercise may be used for fluid replenishment but have little effect on increasing stool consistency and may actually increase diarrhea in some people because of the high osmolality of the drinks (Coleman, 2010).

Early nutritional intervention is crucial to avoid poor outcomes, including malnutrition, persistent diarrhea, and even death. Controversy exists as to what types of foods are best indicated during an acute episode of diarrhea, but they should provide sufficient calories, contain easily absorbable nutrients, and be palatable to the patient. Because of the significant water and electrolyte loss with diarrhea, any dietary plan should include effective oral forms of rehydration. Other foods recommended for diarrhea treatment include avocados, asparagus tips, beets, unspiced applesauce, and peeled apples, as well as ginger tea (Coleman, 2010).

Complications of diarrhea include the potential for cardiac dysrhythmias because of significant fluid and electrolyte loss, especially the loss of potassium to a level less than 3.5 mEq/L (Coleman, 2010). Urinary output of less than 30 ml/hr for two to three consecutive hours, muscle weakness, paresthesias, hypotension, anorexia, and drowsiness require prompt attention. If the patient is hospitalized, the nurse should consult the physician about fluid replacement. Patients and their family members should know to contact their provider for instructions. Proactive assessment and management of diarrhea by the nurse and the patient to effectively manage the symptom and its consequences are essential to have a positive effect on treatment outcome and the patient’s well-being. Oncology nurses are in a unique position to identify patients who are at high risk for potentially life-threatening symptoms.

Pharmacologic Interventions

Antidiarrheal agents can be classified as absorptive agents, intestinal transit inhibitors, intraluminal (or proabsorptive) agents, and antisecretory agents (NCI, 2013). The goals of pharmacologic therapy include inhibition of intestinal motility, reduction in intestinal secretions, and promotion of absorption.

Absorptive agents: Absorptive agents include substances that form a gelatin mass that gives density to the fecal material. Methylcellulose and pectin have been commonly used, but little data exist to support their efficacy. They may not be well tolerated in some patients because of the large volume required for therapeutic effect and the associated abdominal discomfort and bloating that can occur. Psyllium fiber, which is commonly recommended for laxative therapy, can be helpful because it absorbs water from the intestinal tract and adds bulk to the stool. There is historical preliminary evidence using psyllium fiber in the treatment of RID (Murphy, Stacey, Crook, Thompson, & Panetta, 2000), and it is classified as Likely to Be Effective in the ONS PEP resource (Thorpe, Byar, Davis, Held-Warmkessel, & Kiker, 2014).

Adsorbents such as kaolin, clays, and activated charcoals have been used extensively, but again, no data support their use (NCI, 2013). Furthermore, they may inhibit absorption of other oral antidiarrheals that may be coadministered.

Intestinal transit inhibitors: Intestinal transit inhibitors are the most commonly used agents in the treatment of all types of diarrhea (NCI, 2013). Opioids, such as loperamide, are the
preferred treatment for diarrhea because they bind to receptors within the gastrointestinal tract and reduce diarrhea by slowing intestinal motility, decreasing intestinal secretions, and increasing intestinal fluid absorption while having limited side effects (Bisanz et al., 2010; Stein et al., 2010). Compared to diphenoxylate, loperamide is two to three times more potent (Wilkes & Barton-Burke, 2014). Other opioid derivatives that are available include tincture of opium, morphine, and codeine (NCI, 2013).

Loperamide is started at an initial dose of 4 mg followed by 2 mg after every unformed stool (Wilkes & Barton-Burke, 2014). For CID, loperamide 4 mg followed by 2 mg PO every four hours is the standard first-line therapy. High-dose loperamide (2 mg PO every two hours; 4 mg every four hours at night) has shown moderate effectiveness in controlling diarrhea associated with irinotecan chemotherapy (Muehlbauer et al., 2009). That dose should not be given for more than 48 hours. Regardless of the dose, however, loperamide may be less effective in patients with grade 3 or 4 diarrhea (Cherny, 2008; NCI, 2013).

No recent interventions specifically addressing RID have reached the level of evidence needed to be recommended for practice; however, the use of loperamide continues to be recommended as the standard of practice for patients with mild symptoms (Muehlbauer et al., 2009).

**Intraluminal (or proabsorptive) agents:** Proabsorptive agents include diphenoxylate/atropine, which decreases transit time in the small intestine and increases bile absorption. Diphenoxylate is formulated with atropine in an effort to decrease opioid dependence with side effects that are associated with the atropine, which may include abdominal distention and cramping, dry mouth, and sedation (Wilkes & Barton-Burke, 2014).

**Antisecretory agents:** Mucosal prostaglandin inhibitors, also referred to as *antisecretory agents*, include aspirin, bismuth subsalicylate, corticosteroids, and octreotide. Aspirin may be useful for RID (Bisanz et al., 2010). Bismuth subsalicylate is believed to have direct antimicrobial effects on *E. coli*, hence its prophylactic use in traveler’s diarrhea. This agent is contraindicated in patients who should not be taking aspirin, and large doses can produce toxic salicylate levels (Bisanz et al., 2010). Corticosteroids reduce edema associated with obstruction and radiation colitis and can reduce hormonal influences of some endocrine tumors.

Octreotide, a somatostatin analog, is currently the most promising agent in the management of severe diarrhea caused by a variety of diseases and treatments. Octreotide acetate is an antisecretory agent given to patients who do not respond to loperamide therapy. It has multiple antidiarrheal actions, including inhibiting or suppressing release of growth hormone, insulin, glucagon, vasoactive intestinal peptide, luteinizing hormone, serotonin, secretin, motilin, and gastrin; reducing motility; and increasing absorption of water, electrolytes, and nutrients from the gastrointestinal tract (Wilkes & Barton-Burke, 2014). It also has been effective in relieving diarrhea associated with carcinoid syndrome and vasoactive intestinal peptide–secreting adenomas (Wilkes & Barton-Burke, 2014).

The drug is available either as a short-acting subcutaneous (SC) or IV preparation and a long-acting depot injectable. For CID, octreotide may be initiated at 100–150 mcg SC three times daily for five days then titrated upward to 500 mcg SC administered three times daily until symptoms are controlled (NCI, 2013; Shaw & Taylor, 2012). That dose may be more effective than standard doses in patients with CID who fail loperamide. Octreotide 30–40 mg intramuscularly 7–14 days prior to day 1 of chemotherapy, then every 28 days up to six doses, or octreotide long-acting release 20–30 mg monthly may be considered (Shaw & Taylor, 2012).

An option for the treatment of severe RID is 100 mcg SC three times daily until resolution of diarrhea. In a meta-analysis by Sun and Yang (2014), the use of octreotide was most effective as a therapeutic agent rather than as a prophylactic agent in patients receiving chemotherapy or radiation therapy (Zachariah et al., 2010).
**Other agents:** Diarrhea associated with select antineoplastic agents may not be preventable, but assisting patients to anticipate, recognize, and intervene early may decrease its severity. Early-onset (occurring during or shortly after infusion) or late-onset (occurring more than 24 hours after infusion) diarrhea seen in association with the administration of irinotecan can sometimes be prevented with IV or SC atropine (Coleman, 2010).

Another drug in which the benefit must be balanced with harms is neomycin, an antibiotic that prevents intestinal absorption of SN-38 (the active metabolite of irinotecan), often used in patients receiving irinotecan chemotherapy. Oral neomycin 660 mg three times daily administered for three consecutive days starting two days before irinotecan, or 1,000 mg three times a day continuously from two days prior to five days after the second cycle of treatment, may be effective in reducing irinotecan-related diarrhea (de Jong et al., 2006; Kehrer et al., 2001; Shaw & Taylor, 2012). The caution to using this is that patients receiving neomycin had a 4.5-fold higher risk of grade 2 nausea than those in the placebo group (39.9% vs. 8.8%, p < 0.01) (de Jong et al., 2006).

CID, especially from 5-FU and calcium folinate infusion for colorectal cancer, may be managed with high-dose amifostine (800 mg/m² weekly). Amifostine can cause a sharp drop in blood pressure, as well as nausea, vomiting, chills, and dizziness. However, as emphasized in the ONS PEP evidence-based guidelines (Muehlbauer et al., 2009; Thorpe, Byar, Davis, et al., 2014), use of amifostine should be carefully assessed to determine if the benefit outweighs the risks before it is used.

Many additional agents are being investigated for the management of diarrhea, but none have been shown to be effective at this time. Innovative strategies to minimize diarrhea secondary to radiation therapy are also being evaluated, such as pretreatment with cholestyramine to bind bile acids and glutathione to bind free radicals released by tissues being irradiated. Although some case reports suggest the efficacy of glutamine in relieving diarrhea and other gastrointestinal symptoms associated with cancer therapy, one randomized controlled trial that used oral glutamine to prevent pelvic radiation-induced diarrhea was unable to demonstrate any benefit (Kozelsky et al., 2003).

Psyllium fiber has been shown to be likely to be effective for prevention of RID (Thorpe, Byar, Davis, et al., 2014). Probiotic supplementation, including VSL#3®, *Lactobacillus acidophilus*, and *Lactobacillus rhamnosus*, which are currently the focus of ongoing research, were initially also listed under Likely to Be Effective in the ONS PEP guideline; however, they are currently listed as Effectiveness Not Established and require further research (Thorpe, Byar, Davis, et al., 2014). Probiotics, which are usually made from lactic acid–producing bacteria such as *Lactobacillus* species found in fermented foods and cultured milk products, are being evaluated as agents in preventing CID. The use of probiotics may be effective in preventing RID in high-risk patients undergoing radiation to the lower abdomen and pelvis. In particular, the administration of the VSL#3 strain, beginning on the first day of radiation and continuing until the conclusion of the radiation treatment, resulted in a significant difference in the number of bowel movements and toxicity in a study evaluating 409 patients undergoing pelvic radiation following surgery for sigmoid, rectal, or cervical cancers (Bowen et al., 2007). In another study, *Lactobacillus acidophilus* given to patients with locally advanced cervical cancer (N = 63, with 32 receiving *Lactobacillus acidophilus* plus *Bifidobacterium bifidum* and 31 receiving placebo) during pelvic irradiation significantly reduced grade 2–3 diarrhea (9% in the treatment group vs. 45% in the placebo group, p = 0.002) (Chitapanarux et al., 2010). Researchers using psyllium fiber during pelvic irradiation for prostate or gynecologic cancer found that 1–2 teaspoons daily was effective in reducing the incidence and severity of diarrhea. Additional research is needed to determine the optimal probiotic strain or strains, dosage, and timing of administration (Muehlbauer et al., 2009).
Other agents used to treat RID do not have enough research to establish adequate scientific evidence of effectiveness. Medications in this category include those for irinotecan-related diarrhea such as oral alkalization, budesonide, charcoal, and cholestyramine plus levofloxacin (Muehlbauer et al., 2009). Vitamins E and C may help to treat RID, but more research is needed (Kennedy et al., 2001). Glutamine’s effectiveness has not been established (Muehlbauer et al., 2009). Sulfasalazine, selenium, and pentosan polysulfate have no proven effectiveness in the prevention or treatment of RID. Sucralfate is not recommended for prevention or treatment of RID (Bisanz et al., 2010; Muehlbauer et al., 2009; Thorpe, Byar, Davis, et al., 2014).

Antimicrobials can be effective in treating infectious diarrhea, particularly diarrhea caused by enterotoxins (e.g., *C. difficile*) (Bisanz et al., 2010). Metronidazole is often recommended as the drug of choice for treating *C. difficile*-associated diarrhea. Patients who do not respond to metronidazole are then given oral vancomycin (Bisanz et al., 2010). The duration of treatment for either of these drugs should be at least 10–14 days. Nurses should stress to patients the importance of completing the antimicrobial treatment. They also should instruct patients not to use antidiarrheal medications because of the importance of preventing retention of the toxin, which could increase the likelihood of developing toxic megacolon (Bisanz et al., 2010).

Emergency management of diarrhea-associated complications such as hypotension or acidosis may be an initial priority (Coleman, 2010). Monitoring the number, amount, and consistency of bowel movements is important. Fluid and electrolyte replacement is critical. Administration of antidiarrheal medications is appropriate to reduce stool frequency, volume, and peristalsis. Nurses must reassess the severity of diarrhea at an appropriate interval after administration of antidiarrheal medication. They must also educate patients and family members on when to start antidiarrheal medication and on appropriate hydration and nutrition (Coleman, 2010).

**Uncomplicated Chemotherapy-Induced and Radiation-Induced Diarrhea**

NCI (2013) recommendations for the treatment of grade 1 or 2 diarrhea and no other complications or symptoms are oral hydration, dietary modifications, and loperamide. The initial dose of loperamide is 4 mg followed by 2 mg every four hours (not to exceed 16 mg per day) (Shaw & Taylor, 2012). If diarrhea resolves and the causative factor is determined to be related to chemotherapy, patients can continue with dietary modifications and discontinue the loperamide when diarrhea-free for 12 hours (Shaw & Taylor, 2012; Stein et al., 2010). If mild to moderate diarrhea persists for more than 24 hours, the loperamide dose should be increased to 2 mg every two hours, and oral antibiotics may be started as prophylaxis for infection (Shaw & Taylor, 2012).

Uncomplicated CID that persists and has not resolved after 24 hours on high-dose loperamide (48 hours total treatment with loperamide) should be managed by the healthcare team for further evaluation, including complete stool and blood workup (Shaw & Taylor, 2012; Stein et al., 2010). Stool workup should include evaluation for pathogens. Fluids and electrolytes should be replaced as needed. Loperamide should be discontinued, and the patient should be started on a second-line antidiarrheal agent, such as octreotide (100–500 mcg with dose escalation as needed), or other second-line agents (e.g., oral budesonide or tincture of opium) (Shaw & Taylor, 2012).

If the diarrhea resolves and the patient is receiving radiation, the patient should continue loperamide until radiation is complete. For persistent diarrhea caused by radiation, the patient should continue loperamide 2 mg every two hours. A second-line option to consider is tincture of opium. Two preparations of tincture of opium are available, and, because of the variation in the amount of morphine contained in each preparation, diligent dispens-
ing and administration are essential. Deodorized tincture of opium, the preferred preparation, contains the equivalent of 10 mg/ml morphine. The recommended dose is 10–15 drops in water every three to four hours (Shaw & Taylor, 2012). Paregoric (camphorated tincture of opium), which is less concentrated, is an alternative and may be given 5 ml every three to four hours (Benson et al., 2004).

### Complicated Chemotherapy-Induced Diarrhea

Aggressive management with hospital admission and IV fluids should be considered for patients with grade 2 diarrhea that does not resolve after 24 hours of high-dose loperamide. Hospitalization is recommended for all patients with severe diarrhea (grades 3 and 4) (Shaw & Taylor, 2012).

ASCO guidelines (Benson et al., 2004) for the treatment of complicated CID include IV fluids with octreotide 100–150 mg SC or IV three times daily with dose escalation until the diarrhea is controlled and an antibiotic treatment (fluoroquinolone) (Shaw & Taylor, 2012). Laboratory workup, including fecal occult blood, fecal leukocytes, C. difficile, E. coli, Salmonella, and Campylobacter, should be done, as well as a complete blood count and basic metabolic panel (Shaw & Taylor, 2012). ASCO guidelines suggest that hospitalization be considered.

For complicated RID, hospitalization may not be necessary. These patients often are continued on loperamide, but if the patient does not respond, octreotide may be indicated at a starting dose of 100 mg SC three times a day (Shaw & Taylor, 2012). For complicated or severe RID, antibiotics may worsen the diarrhea (Benson et al., 2004).

### Graft-Versus-Host Disease

Acute GVHD is treated primarily with glucocorticoids that are initiated promptly and tapered as tolerated depending on the patient’s response. Patients with grade IV GVHD usually have a poor prognosis. If the GVHD is severe, it requires more intense immunosuppression involving steroids and additional medications such as anti-diarrheal agents to control the disease (Anderson-Reitz, 2011).

In addition to pharmacologic agents to control GVHD, a specialized five-phase dietary regimen should be instituted to effectively manage the diarrhea associated with GVHD. Phase 1 consists of total bowel rest until the diarrhea subsides. Nitrogen losses associated with diarrhea can be severe and are compounded by the high-dose corticosteroids used to treat GVHD. Phase 2 reintroduces oral feedings consisting of isotonic, low-residue, lactose-free beverages to compensate for the loss of intestinal enzymes secondary to alterations in the intestinal villi and mucosa. If these beverages are well tolerated, phase 3 reintroduces solids containing minimal lactose, low fiber, low fat, low total acidity, and no gastric irritants. In phase 4, dietary restrictions are progressively reduced as foods are gradually reintroduced and tolerance is established. Phase 5 includes the resumption of the patient’s regular diet; however, most patients usually remain lactose intolerant (Anderson-Reitz, 2011).

### Chronic Radiation-Induced Diarrhea

Opioid anti-diarrheal agents are recommended for management of chronic RID but are contraindicated in patients with obstructive symptoms (Cherny, 2008). Evidence has shown that hyperbaric oxygen therapy may help relieve symptoms of chronic radiation enteritis (Shadad, Sullivan, Martin, & Egan, 2013).

### Management of Neutropenic Enterocolitis

Management of neutropenic enterocolitis is challenging, and the risk of mortality is high because of the complications, especially sepsis. The initial treatment for neutropenic coli-
tis is medical management, administration of broad-spectrum antibiotics, granulocyte–
colon-stimulating factors, nasogastric decompression, IV fluids, bowel rest, and serial abdomi-
nal examinations (Cherny, 2008). In most patients, these measures are sufficient, and symp-
toms resolve after neutropenia is resolved (Cherny, 2008). Blood transfusions may be neces-
sary because the diarrhea is often bloody and the patient may be pancytopenic. Anticholin-
ergic, antidiarrheal, and opioid agents should be avoided because they may aggravate ileus
(Cherny, 2008).

Surgical intervention for the treatment of enterocolitis is controversial because of the sig-
nificant risk of morbidity and mortality of patients, but those who fail to respond to medi-
cal interventions may be carefully considered (Cherny, 2008). Some indications for surgery
include (a) persistent gastrointestinal bleeding after correction of thrombocytopenia and
cogulopathy, (b) evidence of intraperitoneal perforation, (c) abscess formation, (d) clinical
deterioration despite aggressive supportive measures, and (e) high suspicion of other
intra-abdominal processes such as bowel obstruction or acute appendicitis (Cherny, 2008). If
exploratory surgery is required, it usually involves resection of the portion of the bowel that
is necrotic, most commonly resulting in a right hemicolectomy, an ileostomy, or a mucous
fistula. Failure to remove the necrotic focus in these severely immunocompromised patients
is potentially fatal (Cherny, 2008).

**Expected Patient Outcomes**

Appropriate goals or expected outcomes of managing diarrhea in patients with cancer include
• Prevent or minimize diarrhea whenever possible.
• Enhance recovery of intestinal mucosa from the effects of chemotherapy or radiation ther-
  apy.
• Restore normal bowel function.
• Eliminate causative factors.
• Maintain nutrition and fluid and electrolyte balance through hydration and supplemen-
tation.
• Minimize the risk of complications.
• Eliminate or reduce diarrhea-associated morbidity and mortality.
• Prevent cancer treatment delays or regimen modifications.
• Improve cancer treatment outcomes.
• Protect skin integrity.
• Optimize patients’ quality of life.

Measurable outcomes are needed to assess the effectiveness of the management of diar-
rhea, including quantitative measures as well as the patient’s self-report of quality of life.
Reductions in the number of daily stools and episodes with a concomitant decrease in stool
liquidity are objective parameters (Coleman, 2010). Tools need to be developed and tested
for use in a variety of settings to measure the effectiveness of interventions.

**Patient and Family Teaching Points**

Patients and families need to be active participants in patient care to effectively prevent and
manage diarrhea. Nurses can teach patients to control diarrhea through fluid intake, dietary
modification, medications, and increasing activity level. The teaching should take place at
a time when the patient is feeling rested and able to learn. Ideally, the patient should not
be actively experiencing diarrhea during the teaching session. If the patient is too fatigued
or ill, a family member or significant other may be the primary focus for teaching. Teaching begins as soon as a risk factor for diarrhea is identified and continues through the treatment trajectory.

- Instruct patients to report any signs of diarrhea.
- Educate patients at high risk for developing diarrhea about measures to prevent or ameliorate the severity of diarrhea.
- Assist patients in understanding when diarrhea can be self-managed and when to seek help.
- Educate patients on when to start antidiarrheal medications (e.g., with certain chemotherapeutic agents, antidiarrheal medication should be provided so that patients can self-administer at the onset of diarrhea).
- Educate patients about appropriate hydration and nutrition.
- Instruct patients to clean rectal area with mild soap and water after each bowel movement, rinse well, and pat dry with a soft towel. Additional protection may be provided by applying a moisture-barrier ointment.
- Recommend patients to take warm sitz baths to relieve pain related to perianal inflammation.
- Educate patients about symptoms that may be life threatening, including excessive thirst, fever, dizziness or light-headedness, palpitations, rectal spasms, excessive abdominal cramping, watery or bloody stools, and continued diarrhea while on antidiarrheal treatment. Stress that these symptoms require immediate contact with the healthcare provider.
- Provide written materials with specific healthcare provider contact numbers, and review information at each visit. Consider visual and cognitive impairments and adjust for them.
- Stress the importance of reporting the occurrence and character of diarrhea.
- Instruct patients and caregivers to report self-care measures employed at home, especially any home remedies taken or other alternative therapies employed.
- Customize patient self-care sheets to assist in the control of diarrhea.
- Provide a self-care behavior log for patients to record side effects of cancer treatment and rate the severity of the side effect and its resultant distress using a visual analog scale or some other measurement scale.
- Provide information that is culturally sensitive and understandable to patients whose first language is not English.

Implications for Practice

Diarrhea can be an ongoing challenge for patients receiving chemotherapy or radiation therapy and can be a life-threatening condition if left untreated. By obtaining a detailed history and physical assessment and communicating the results within the healthcare team, oncology nurses have the opportunity to optimize the prevention and management of cancer treatment–related diarrhea.

Bowel assessments should be performed at the start of treatment and continued throughout the trajectory of cancer treatment. Accurate assessment, including dietary intake, is the first step in choosing the appropriate management of diarrhea at various stages of treatment. Nutritional management in conjunction with bowel assessment and pharmacologic measures may decrease the rate and frequency of diarrhea episodes. Oncology nurses need to be aware of the evidence-based practice guidelines for the prevention and management of cancer treatment–related diarrhea and consistently incorporate these guidelines into their practice. With the appropriate evidence-based practice and multidisciplinary approach, the healthcare team can effectively manage diarrhea in patients with cancer. ONS PEP resources
provide evidence-based oncology nursing interventions for diarrhea that can be used in the clinical setting (Muehlbauer et al., 2009; Thorpe, Byar, Davis, et al., 2014).

**Conclusion of Diarrhea Case Study**

M.L. described his diarrhea as liquid stools occurring four to six times a day, which is different from his normal stool consistency and bowel routine. In consideration of the chemotherapy agents he received, particularly irinotecan, the nurse begins M.L. on the recommended initial pharmacologic intervention for diarrhea according to the ONS PEP guidelines, which is loperamide at an initial dose of 4 mg PO followed by 2 mg every four hours. The nurse also reviews general diet strategies with the patient, including consuming five to six small, frequent meals and consuming at least 8–10 servings (8 oz each) of room-temperature liquid per day. The nurse emphasizes the importance of close monitoring of the patient by a caregiver for continued or increasing frequency of diarrhea. The nurse encourages M.L. to report any of these changes immediately. Late occurrence of diarrhea may lead to dehydration and electrolyte imbalance, which, if not treated early and promptly, could lead to life-threatening consequences. The nurse will follow the patient closely to make sure that he is adhering to the recommended plan of care. If modification is needed, it can be addressed at each follow-up visit, telephone follow-up, or telephone triage call.

**Need for Future Research**

More research is needed in almost every aspect of bowel dysfunction. This includes better means of describing and assessing, preventing, and managing constipation and diarrhea. Both are well-established problems for patients with cancer, fall within the purview of nursing care, and provide a vital topic for ongoing nursing research. Constipation and diarrhea are multifaceted, and the incidence and contributing factors need to be better defined in order to develop more sensitive and timely interventions that can be tested, validated, and used to improve the quality of life of patients with cancer.

Oncology nurses have a responsibility to use the available evidence in their practice to assess and manage bowel dysfunction. Unfortunately, to date, limited research is available for interventions for constipation. While more progress has been made in determining effective interventions for treatment-related diarrhea, significant questions remain, and much still needs to be done to bring the evidence to a higher level for both constipation and diarrhea. There is a rich opportunity for oncology nurses to elevate their bedside observations and clinical experience by incorporating current practice guidelines and monitoring outcomes, as well as partnering with experienced researchers to develop new protocols that refine and test interventions. Most of what is currently done to treat constipation, for example, falls under the ONS PEP evidence level of Expert Opinion, which is one of the lowest levels. Efforts should be made to more systematically observe and test these interventions to validate them and establish a higher level of evidence for practice. Many nurses are involved in clinical trials of new chemotherapy and biotherapy agents and should be attuned to the development of side effects related to bowel dysfunction. This will enable them to be proactive in studying and responding to the rapidly changing landscape of symptoms experienced by patients with cancer.

When applicable, oncology nurses should recommend inclusion of documentation of bowel function in research protocols so that more data can be systematically collected.
and the evidence base expanded. Oncology nurses are on the front lines of cancer symptom management, and the challenge is to provide leadership in symptom management research.

**Conclusion**

Oncology nurses are at the forefront of patient care and play a vital role in the assessment and management of the myriad bowel dysfunctions that can complicate the care of patients with cancer. Both constipation and diarrhea can have a significant impact on patients’ quality of life and treatment outcomes if they are not adequately assessed and treated. Early intervention using evidence-based practice guidelines such as those provided by the ONS PEP resources (Thorpe, Byar, Conley, et al., 2014; Thorpe, Byar, Davis, et al., 2014) facilitates quality cancer care. The impact of the morbidity of diarrhea and constipation may be decreased by employing guidelines and stressing aggressive and timely management. Serious consequences such as bowel perforation from untreated constipation or malnutrition or even renal failure from untreated diarrhea are preventable when astute nurses implement the appropriate interventions. Education of healthcare providers and patients regarding the importance of assessing and managing bowel function is essential to improve or restore normal physiologic function and, in turn, positively influence the quality of life of patients and their families.

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Case Study

A.J. is a 49-year-old African American male carpenter with a 34 pack-year smoking history and an episodic alcohol drinker who presented with dysphagia and unintentional 20-pound weight loss over six months. Upon physical examination of the oropharynx, a mass was discovered on his tonsils. Biopsy results revealed squamous cell carcinoma, stage III, with involvement of the lymph nodes in his left neck. Further initial assessment planning included chest imaging, computed tomography (CT) scan with contrast of the primary site and neck, an examination under anesthesia with endoscopy, dental evaluation, human papillomavirus tumor testing, and positron emission tomography–CT. Treatment included four cycles of neoadjuvant chemotherapy with cisplatin, docetaxel, and 5-fluorouracil followed by concomitant chemotherapy with weekly paclitaxel and radiation therapy. Following chemotherapy and radiation therapy, he underwent a resection of the tumor and right lymph node dissection. The healthcare team is concerned that this patient is at high risk for cancer anorexia-cachexia syndrome (CACS).

Overview

CACS is a complex syndrome comprising two distinct symptoms (Adams, Shepard, et al., 2009) characterized by involuntary, severe, and chronic weight loss that is minimally responsive to standard interventions (Bozzetti, 2013; Fearon et al., 2011). CACS occurs over a spectrum in which patients may or may not progress through all stages over time (Fearon et al., 2011) as depicted in Figure 6-1. CACS occurs when protein or caloric requirements are not met, either because of decreased intake, increased requirements, or inappropriate utilization of nutrients (Adams, Shepard, et al., 2009). Wasting and malnutrition have long been recognized as predictive of poor outcomes in patients with cancer and are the direct cause of death in approximately 20% of patients with advanced cancer (Bozzetti, 2013). People with CACS have poor appetite and significant weight loss, leading to weakness and fatigue as well as potentially life-threatening metabolic disturbance. Impaired nutritional status and pro-
tein deficiency can affect response to chemotherapy and increase toxicity from therapy, thus leading to increased morbidity and mortality (Baracos, 2006; Mattox, 2005; Slaviero, Read, Clarke, & Rivory, 2003). Patients with CACS may have decreased quality of life (QOL), especially in physical, psychological, and social functioning (Lis, Gupta, Lammersfeld, Markman, & Vashi, 2012; Oberholzer et al., 2013).

Risk Factors and Associated Incidence

The term *cachexia* is derived from the Greek words *kakos* (“bad”) and *hexis* (“condition”). Cancer cachexia is common and occurs in 80% of patients with advanced cancer (del Ferraro, Grant, Koczywas, & Dorr-Uyemura, 2012). A multitude of factors drive the diagnosis of CACS, including percentage of weight loss, body mass index (BMI) changes, presence of systemic inflammation, decreased food intake, muscle wasting, and asthenia (Fearon et al., 2006, 2011; Strasser et al., 2006).

CACS represents a wasting syndrome involving loss of muscle and fat caused directly by tumor factors or indirectly by abnormal response to tumor presence (Dodson et al., 2011; Stewart, Skipworth, & Fearon, 2006). Cachexia may be best defined as a state of depletion, synonymous with emaciation (Baracos, 2006). Weight loss in patients with cancer usually is represented by loss of muscle mass, which leads to decrease in function as measured by performance status tools such as the Karnofsky scale (Karnofsky, Abelmann, Craver, & Burchenal, 1948). Involuntary weight loss at diagnosis or as a result of treatment varies widely by tumor type and treatment modality, with the greatest risk for nutritional deficits occurring with multimodality treatments. Anorexia and cachexia most commonly develop in patients with gastric (85%), pancreatic (83%), lung (61%), prostate (57%), and colon (54%) cancers (del Ferraro et al., 2012; DeWys et al., 1980).
Pathophysiology

The pathophysiology of this largely misunderstood clinical problem is multifaceted and complex. The interaction between cancer cells and the host produces immune alterations, which in turn trigger various overlapping syndromes of anorexia-cachexia. These syndromes can be divided into three categories—metabolic, neurohormonal, and anabolic alterations—all of which lead to loss of appetite, early satiety, asthenia, muscle wasting, and loss of fat (Strasser & Bruera, 2002).

Immune alterations between host and tumor include proinflammatory cytokines and tumor-derived catabolic glycoproteins that play a major role in all three syndromes of cancer cachexia (Tisdale, 1997). In response to a tumor, the body’s immune system produces several proinflammatory cytokines that include interleukin (IL)-1, IL-6, tumor necrosis factor-alpha, interferon alpha, and interferon gamma in patients with cancer (Argilés, Busquets, & López-Soriano, 2003; Tan, Gupta, Shum, & Polly, 2013). Increased levels of any of these cytokines alone or in combination over time are sufficient in reproducing many of the varied features in CACS (Gelin et al., 1991; Ohnnuma, 2010; Seruga, Zhang, Bernstein, & Tannock, 2008; Strassmann, Fong, Kenney, & Jacob, 1992). Through the use of experimental animal models, the use of specific cytokine antagonists was observed to alleviate cachexia symptoms, thus providing supplementary evidence of the involvement of proinflammatory cytokines in cachexia (Matthys & Billiau, 1997; Noguchi, Yoshikawa, Matsumoto, Svaninger, & Gelin, 1996; Sherry et al., 1989). These cytokines appear to be important in the metabolic processes involved in CACS and demonstrate closely interrelated activities and even synergistic effects (Argilés et al., 2003; Tan et al., 2013).

Circulating tumor-derived catabolic factors incite major metabolic changes that are characteristic in patients with CACS. These factors derived from cancer include lipolytic as well as proteolytic factors (Ohnnuma, 2010; Tisdale, 2003). The lipolytic catabolic factors work directly on breaking down adipose tissue, while the proteolytic factors work on skeletal muscle, neither of which affect actual food intake (Beck, Mulligan, & Tisdale, 1990; Ohnnuma, 2010; Taylor, Gercel-Taylor, Jenis, & Devereux, 1992; Tisdale, 2003; Todorov et al., 1996).

Metabolic alterations are present in CACS. Hypermetabolism and high rates of glucose usage are very prominent features in tumor-bearing cancers (Tisdale, 2003). The increased energy usage and glucose turnover through raised metabolism caused by cancer can cause weight loss and other characteristic symptoms of CACS (Lundholm, Edström, Karlberg, Ekman, & Scherstén, 1982; Tisdale, 2000). Other metabolic alterations include decreased lipogenesis, increased lipolysis, and increased lysis of muscle proteins (Argilés, Meijising, Pallarès-Trujillo, Guirao, & López-Soriano, 2001; Attaix, Combaret, Tilignac, & Taillandier, 1999).

Alteration of neurohormonal processes between the brain and gut plays an important role in the mechanism of CACS. Taste sensation and neurohormonal signals from the gastrointestinal tract and neurotransmitters in the hypothalamus and other brain regions regulate food intake (Schwartz, Woods, Porte, Seeley, & Baskin, 2000). The presence of serotonin contributes to the disorder of cachexia. Abnormal use of tryptophan, the progenitor of serotonin, by tumor cells leads to excess levels of plasma free tryptophan in patients with cancer (Krause, Humphrey, von Meyenfeldt, James, & Fischer, 1981). This leads to excess tryptophan in the cerebrospinal fluid, causing increased serotonin production and secretion in the ventromedial hypothalamic serotonergic system. This has a decreasing effect on appetite, and a close relationship between elevated free tryptophan levels in plasma and anorexia has been shown in patients with cancer (Cangiano et al., 1994; Ohnnuma, 2010).
Anabolic changes in CACS involve altered levels of anabolic hormones, including growth hormone, insulin-like growth factors, and anabolic steroids. Low levels of testosterone in patients with cancer cachexia are associated with weight loss, decreased lean body mass, and disease progression (Burney et al., 2012; Vigano et al., 2010).

Anorexia is the major and most prominent symptom in CACS. It is defined as an involuntary loss of appetite or desire to eat (Adams, Shepard, et al., 2009). Patients with cancer very often experience nausea, changes in taste, and early satiety, or the feeling that they are full before they have eaten adequately (Davis, Walsh, Lagman, & Yavuzsen, 2006; Walsh, Donnelly, & Rybicki, 2000). Abnormalities in taste and smell, causing patients to become nauseated or simply to not desire food that they may have otherwise craved, are common symptoms of cancer (Belqaid et al., 2014; Fried, 2012; Ohnuma, 2010). Oral mucositis (inflammation of the tissues of the mouth) as well as xerostomia (dry mouth) caused by damage to salivary glands often result from chemotherapy or radiation treatments to the area of the oral cavity and throat. Cancer also may affect primary or secondary organs of the alimentary tract. For example, a tumor of the esophagus or stomach that directly obstructs the passage of food prevents nutrient intake through the alimentary tract in patients with cancer. Thus, mechanical interference of the alimentary and gastrointestinal tracts exists, which leads to anorexia and malnutrition (Inui, 2002; Topkan, Yavuz, & Ozyilkan, 2007).

Catabolic states unrelated to cancer, such as infection, diabetes, chronic diseases (chronic heart failure, chronic renal failure), and hyperthyroidism, may contribute to the loss of skeletal muscle. Deconditioning caused by prolonged bed rest and inactivity is also associated with loss of muscle mass (Strasser & Bruera, 2002).

The biologic complexities of CACS are not fully understood. Many factors and mechanisms contributing to its occurrence are currently being studied, but no single factor can be attributed to the cause of CACS in patients with cancer. Rather, it is a series of many varied factors and mechanisms that, through close interaction and interrelation, formulate the intricate pathophysiology of cancer cachexia. CACS manifests itself through the interrelation of anorexia and early satiety, chemotherapy, radiation, and the cancer itself, mechanical obstruction, neurologic abnormalities or dysfunction, and various metabolic differentiations (Adams, Shepard, et al., 2009; Bozzetti, 2013; Fearon et al., 2006).

Assessment

Screening

A complete history, physical examination, and nutritional screening, which includes speech and swallowing assessment, is indicated in patients who present with signs of CACS or with a high risk for syndrome development (Mueller, Compher, Ellen, & American Society for Parenteral and Enteral Nutrition [A.S.P.E.N.] Board of Directors, 2011) (see Table 6-1). The history should include review of weight patterns, gain and loss cycles, and patterns of nutritional intake. A complete nutritional assessment is strongly recommended at diagnosis and periodically throughout treatment (Academy of Nutrition and Dietetics, 2007).

The patient’s history should include cancer diagnosis; course and treatment to date; current medications (both prescribed and over the counter); typical 24-hour diet, both current and prediagnosis; ability to perform activities of daily living; and any associated symptoms such as dysphagia, odynophagia, xerostomia, and altered taste. Functional status can be measured by using the Karnofsky performance status tool or a more detailed instru-
ment such as the Functional Assessment of Anorexia/Cachexia Therapy (Karnofsky et al., 1948; Ribaudo et al., 2000). The Edmonton Symptom Assessment Scale or the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) may be used for overall symptom and quality of life assessment (Chang, Hwang, & Feuerman, 2000).

The Patient-Generated Subjective Global Assessment (Bauer, Capra, & Ferguson, 2002; Detsky et al., 1987) can be useful in screening for cancer cachexia. This tool provides a patient- and clinician-generated score that grades nutritional and malnutrition risk in a wide range of hospital patients (Bauer et al., 2002; Brown, 2002). This subjective global assessment is a validated clinician tool that measures nutritional status based on the features of a medical history (e.g., weight changes, dietary intake changes, gastrointestinal symptoms that have persisted for more than two weeks, changes in functional capacity) and physical examination (e.g., loss of subcutaneous fat, muscle wasting, ankle or sacral edema, ascites) (Bauer et al., 2002; Brown, 2002). The Functional Assessment of Anorexia and Cachexia Therapy

<table>
<thead>
<tr>
<th>TABLE 6-1</th>
<th>Summary of Assessment for Cancer Anorexia-Cachexia Syndrome</th>
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<tbody>
<tr>
<td>Category</td>
<td>Description</td>
</tr>
</tbody>
</table>
| General information | Cancer diagnosis and stage  
Cancer treatment  
Current medications |
| Symptoms | Gastrointestinal symptoms associated with cancer and/or treatment  
Other symptoms: Pain, dyspnea, fatigue, delirium, anxiety  
Edmonton Symptom Assessment Scale (symptom assessment tool) |
| Nutrition | Weight pattern  
Weight changes  
Body mass index  
Dietary/caloric intake: 24-hour diet recall, food journaling  
Body composition:  
• Skinfold thickness  
• Mid-arm circumference  
• Bioelectrical impedance analysis  
• Muscle mass and strength  
Computed tomography scan, magnetic resonance imaging, or dual-energy x-ray absorptiometry  
Upper limb, hand grip strength  
Comprehensive assessment with a validated measure |
| Function | Performance status (Karnofsky, Eastern Cooperative Oncology Group)  
Functional Assessment of Anorexia/Cachexia Therapy (function and quality-of-life tool) |
| Laboratory tests | Complete blood count, renal function, liver function, electrolytes, albumin, prealbumin, transferrin, testosterone, C-reactive protein |
| Psychosocial | Coping with changes in self-image  
Emotional distress  
Attitudes of patient and family regarding nutrition  
Financial problems |

Note. Based on information from Academy of Nutrition and Dietetics, 2007; Baracos, 2006; Bauer et al., 2002; Brown, 2002; Chang et al., 2000; Davis et al., 2009; Del Fabbro et al., 2006; Detsky et al., 1987; Fearon et al., 2011; Karnofsky et al., 1948; Langer et al., 2001; Maltzman, 2004; Mueller et al., 2011; Ribaudo et al., 2000; Rosenzweig, 2014; Strasser & Bruera, 2002; Thoresen et al., 2012.
12-question subscale known as the A/CS-12 is a brief nutritional assessment that can be implemented within an outpatient clinic or practice setting (Davis et al., 2009). Referral to an oncology nutritionist or other professional who is qualified to provide a comprehensive nutritional assessment is recommended if nutritional screening identifies the presence of or risk for malnutrition.

CACS is associated with decreased QOL (Thoresen et al., 2012). Severe weight loss produces changes in body image that may generate anxiety and depression in patients and their families. Psychological interventions are recommended to address the severe emotional distress experienced by patients with CACS. Counseling should be directed to both patients and family members and should address concerns about QOL, body image, and starvation (Del Fabbro, Dalal, & Bruera, 2006; Strasser & Bruera, 2002).

**Physical Assessment**

A main component of CACS is weight loss. This includes loss of fatty tissue as well as muscle mass. Patients usually appear emaciated and report a profound loss of appetite and early satiety and possibly nausea and vomiting. Other symptoms include dry mouth, changes in smell and taste, constipation, bloating, and abdominal pain (Baracos, 2006). Patients also may report amenorrhea, polyuria, and cold intolerance (Langer, Hoffman, & Ottery, 2001; Rosenzweig, 2014). Patients commonly report decreased mental skills, attention span, and concentration. When the cachexia is severe, alterations in metabolic functions, such as electrolyte imbalances, can occur. As a result, patients develop loss of strength, increased fatigue and weakness, and possibly numbness, tingling, twitching, involuntary movements, and pain (Langer et al., 2001; Maltzman, 2004). This in turn can lead to the inability to perform activities of daily living. Electrolyte imbalances can lead to cardiac arrhythmias, which can lead to death.

The patient may present with tachycardia or tachypnea and may have dysrhythmias. Poor muscle tone and temporal wasting can indicate loss of muscle mass or cachexia progression. A protuberant abdomen may indicate late-stage ascites. Skin will be dry with poor turgor and the hair and nails may be dry and brittle. An oral examination may reveal poor dentition, lesions, and dry mucous membranes.

The physical examination should include (a) measurement of weight loss as a percentage of the patient’s usual body weight, (b) current weight as it compares to ideal body weight, and (c) a history of decreased appetite or food intake. Laboratory tests such as folate, transferrin, albumin, prealbumin, retinol-binding protein, and C-reactive protein are useful in assessing malnutrition (Fearon et al., 2011). A quantitative measurement of the individual’s body composition should include BMI (i.e., weight and height measurement), lean body mass (i.e., fat-free mass), and anthropometric measures (Dodson et al., 2011). Edema or obesity can mask the detection of loss of muscle mass; therefore, direct anthropometric measurement of muscul arity is recommended. Anthropometric measurements may include skinfold thickness assessment, bioelectrical impedance analysis, and dual-energy x-ray absorptiometry scan (Dodson et al., 2011), as well as CT scan or magnetic resonance imaging of the lumbar spine (Fearon et al., 2011).

**Treatment Overview**

CACS originates from a combination of factors, including reduced dietary intake, deficiency in the anabolic endocrine setting, hyperexpression of catabolic elements, lack of phys-
ical activity, and presence of comorbid conditions (Suzuki, Asakawa, Amitani, Nakamura, & Inui, 2013). The general approach to the management of CACS should be tailored to each individual patient’s needs.

Unfortunately, no single agent has been found to be effective in treating CACS. Implementation of a combination of modalities by an experienced interdisciplinary team is recommended for best practice (Granda-Cameron et al., 2010; Suzuki et al., 2013). Patients with CACS should be enrolled in programs that address aspects of care, including (a) early detection of the problem, (b) correction of secondary causes (physical and emotional symptoms), (c) dietary counseling and other nutritional interventions, (d) exercise to maintain muscle mass, and (e) use of drug combinations that increase anabolism, reduce muscle proteolysis, and reverse the inflammatory state of cancer cachexia (Fearon, Arends, & Baracos, 2013; MacDonald, 2007).

Multiple organizations have developed supportive and nutritional care guidelines for the management of anorexia and/or cachexia associated with cancer. A summary of these organizations and links to these guidelines and other web-based resources is presented in Table 6-2.

The objectives of cancer cachexia therapy are to reverse or slow the progression of the cachexia syndrome, control CACS or other associated symptoms, improve physical and emotional function and body image, improve patients’ QOL, and prolong life expectancy (Blum et al., 2010). The National Cancer Institute (2014) suggested that patients with advanced cancer may benefit from nutritional support in the following ways: improved well-being, reduced risk of infection, reduced asthenia, and lessened side effects.

Current interventions to treat cancer cachexia include treatment of the underlying disease or cancer, nutritional counseling, education, and a combination of pharmacologic therapies directed to improve symptoms and reverse or delay progression of the syn-

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<tr>
<th>TABLE 6-2</th>
<th>Cancer Anorexia-Cachexia Syndrome Resources for Healthcare Professionals</th>
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<tr>
<td><strong>Organization</strong></td>
<td><strong>Resources</strong></td>
</tr>
<tr>
<td>European Palliative Care Research Collaborative</td>
<td>Clinical Practice Guidelines on Cancer Cachexia in Advanced Cancer Patients: <a href="http://www.epcrc.org/publication_listfiles.php?id=mWdBCMi5eXVtcNFk7Gnq">www.epcrc.org/publication_listfiles.php?id=mWdBCMi5eXVtcNFk7Gnq</a></td>
</tr>
<tr>
<td>National Comprehensive Cancer Network (NCCN)</td>
<td>NCCN Clinical Practice Guidelines in Oncology: Palliative Care, including anorexia/cachexia: <a href="http://www.nccn.org/professionals/physician_gls/pdf/palliative.pdf">www.nccn.org/professionals/physician_gls/pdf/palliative.pdf</a></td>
</tr>
<tr>
<td>National Cancer Institute</td>
<td>Nutrition in Cancer Care (PDQ®) [Health professional version]: <a href="http://www.cancer.gov/cancertopics/pdq/supportivecare/nutrition/HealthProfessional">www.cancer.gov/cancertopics/pdq/supportivecare/nutrition/HealthProfessional</a></td>
</tr>
<tr>
<td>Oncology Nursing Society (ONS)</td>
<td>ONS Putting Evidence Into Practice: <a href="http://www.ons.org/practice-resources/pep/anorexia">www.ons.org/practice-resources/pep/anorexia</a></td>
</tr>
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</table>
drome. One of the best approaches to treating CACS is to reverse or slow the progression of the syndrome by eliminating cancer completely (Coss, Bohl, & Dalton, 2011). Unfortunately, this is not an option for many patients with advanced disease. Although the use of systemic antineoplastic therapy or radiation therapy may cure some cancers, it may increase the treatment-related toxicities that can contribute to cancer cachexia (Couch et al., 2007). However, if cancer therapy is carefully chosen to meet patients’ individual needs, treatment may provide improvement in both symptoms and QOL (Bozzetti, 2013). Both early recognition of CACS and optimal symptom management are critical to improve patients’ nutritional status (MacDonald, 2007; Stewart et al., 2006) and subsequently their disease experience.

Evidence-Based Interventions

Interventions for CACS will be described in the following paragraphs based on the levels of evidence defined by the Oncology Nursing Society (Adams, Cunningham, Caruso, Norling, & Shepard, 2009). The recommendations are summarized in Table 6-3.

It is important to note that all recommendations should be interpreted within the patient context. The Oncology Nursing Society recommendations evaluate the quality of the research supporting an intervention. However, the risks and benefits of providing an inter-

<table>
<thead>
<tr>
<th>TABLE 6-3</th>
<th>Summary of Interventions for Cancer Anorexia-Cachexia Syndrome Based on Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of Evidence</td>
<td>Intervention</td>
</tr>
<tr>
<td>Recommended for practice</td>
<td>Progestational agents (megestrol acetate, medroxyprogesterone)</td>
</tr>
</tbody>
</table>

(Continued on next page)
### TABLE 6-3  Summary of Interventions for Cancer Anorexia-Cachexia Syndrome Based on Strength of Evidence (Continued)

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Intervention</th>
<th>Action (or Potential Action)</th>
<th>Nursing Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended for practice (cont.)</strong></td>
<td>Corticosteroids (dexamethasone, methylprednisolone, prednisolone)</td>
<td>Increase appetite</td>
<td>May be used short-term (&lt; 3 months) or sparingly (&lt; 1 month), with limited doses and frequency of use, and with close monitoring. Diabetic patients with cancer require close blood glucose monitoring with potential dose adjustments with insulin or diabetic medications. Side effects may include immunosuppression, hyperglycemia, generalized weakness, fat redistribution, decreased bone density, bruising, and skin fragility. Risk-benefit analysis of the medication should be considered prior to implementation.</td>
</tr>
<tr>
<td>Likely to be effective</td>
<td>Nutritional support with enteral nutrition</td>
<td>Improves nutritional parameters such as calorie and protein intake</td>
<td>Use in conjunction with dietary counseling. Consider metallic taste changes from chemotherapy. Dyspepsia and other symptoms or factors such as neurologic changes or dementia, depression, and/or anxiety may affect the degree of anorexia and/or cachexia. Interdisciplinary care for treating the primary illness or condition should help offset some of the nutritional demands on the patient. Automatic nutrition referrals should be considered for patients with head and neck, gastrointestinal, lung, prostate, and hematologic cancers. No clear dietary recommendations exist for advanced-stage or terminally ill patients with cancer.</td>
</tr>
<tr>
<td></td>
<td>Dietary counseling</td>
<td>Aids in sustaining nutritional intake and adhering to nutritional recommendations</td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>Increases muscle mass and endurance; improves quality of life</td>
<td>Appropriate for symptom management and quality-of-life improvement</td>
<td></td>
</tr>
<tr>
<td>Benefits balanced with harms</td>
<td>Nutritional support with parenteral nutrition</td>
<td>Improves nutritional parameters</td>
<td>Not recommended as routine intervention for cancer cachexia. Risk-benefit analysis should be considered prior to implementation.</td>
</tr>
</tbody>
</table>

(Continued on next page)
A Guide to Oncology Symptom Management (Second Edition)

Orexigenic drugs are used for the treatment of CACS. These medications are appetite stimulants indicated for patients experiencing anorexia. Progestational agents (such as megestrol acetate [MA] and medroxyprogesterone acetate [MPA]) and corticosteroids (such as dexamethasone, methylprednisolone, and prednisolone) are the only two drug types recommended for practice to improve anorexia (Adams, Shepard, et al., 2009). The nursing implications and risk-benefit analysis of each medication should be taken into account for each patient before implementing.

**Recommended for Practice**

TABLE 6-3

Summary of Interventions for Cancer Anorexia-Cachexia Syndrome Based on Strength of Evidence (Continued)

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Intervention</th>
<th>Action (or Potential Action)</th>
<th>Nursing Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness not established</td>
<td>Omega-3 fatty acid supplementation</td>
<td>Improves appetite</td>
<td>Risk-benefit analysis should be considered prior to implementation of all interventions listed in this evidence category.</td>
</tr>
<tr>
<td></td>
<td>Ghrelin</td>
<td>Improves appetite</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anabolic agents</td>
<td>Maintain or improve lean body mass and weight gain; improve body composition and strength</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Growth hormone</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Insulin-like growth factor</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• Testosterone</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Testosterone analogs (oxandrolone, nandrolone)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Prokinetic agents (metoclopramide)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thalidomide</td>
<td>Lessens weight loss; improves functioning; improves appetite</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other medications: mirtazapine, OHR118 (peptide), Radix Astragalii, rikkunshito, nonsteroidal anti-inflammatory drugs, cyclooxygenase (COX)-1 and COX-2 inhibitors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. Based on information from Academy of Nutrition and Dietetics, 2007; Adams, Shepard, et al., 2009; Ardies, 2002; Argilés et al., 2001, 2013; Argilés & Stemmler, 2013; August & Huhmann, 2009; Bauer et al., 2005; Bozetti, 2013; Brown, 2002; Chasen et al., 2011; Colomer et al., 2007; Davis et al., 2009; Del Fabbro et al., 2006; DeWys et al., 1980; Fearon et al., 2006; Garcia, J.M., et al., 2013; Garcia, V.R., et al., 2013; Hiura et al., 2012; Kauh et al., 2011; Kurebayashi et al., 1999; Langer et al., 2001; Lee & Lee, 2010; Leśniak et al., 2008; Lundholm et al., 2007; Macciò et al., 2012; Madeddu et al., 2012; Mantovani et al., 1997; Mantovani, Macciò, Madeddu, Serpe, Anthoni, et al., 2010; Mantovani, Macciò, Madeddu, Serpe, Massa, et al., 2010; Mazzotta & Jeney, 2009; Mercadante, 1998; Mulligan et al., 1999; Naoi et al., 2006; National Comprehensive Cancer Network, 2014; Ohno et al., 2011; Ojo & Bowden, 2012; Orr & Singh, 2004; Ottery, 1996; Penna et al., 2011; Reid, Hughes, et al., 2012; Reid, Mills, et al., 2012; Riechelmann et al., 2010; Solheim et al., 2013; Stroud, 2005; van der Meij et al., 2010; Wilkes et al., 2011; Yamashita & Ogawa, 2000; Yavuzsen et al., 2005; Yennurajalingam et al., 2012; Zinna & Yarasheski, 2003.
Progestational Agents

A recent Cochrane systematic review of the literature demonstrated a benefit of MA over placebo for improved appetite and weight gain (Garcia, López-Briz, Sanchis, Perales, & Bort-Martí, 2013). These authors analyzed 23 randomized clinical trials in 3,428 patients with cancer evaluating the efficacy of MA compared to placebo or other medications. Patients taking MA had mild weight gain and statistically significant appetite improvement. This effect was not seen when compared to other medications. Leśniak, Bała, Jaeschke, and Krzakowski (2008) systematically reviewed 30 trials including 4,429 people with advanced cancer. This review and meta-analysis found that MA was associated with appetite improvement greater than 5% that led to weight gain, although no difference was found in these outcomes compared to glucocorticosteroids. These reviews suggest that MA can help improve appetite in patients with late- or advanced-stage cancer.

Three additional randomized controlled trials were completed looking at the effect of MA plus other potential appetite and weight improvement medications (Macciò et al., 2012; Madeddu et al., 2012; Mantovani, Macciò, Madeddu, Serpe, Massa, et al., 2010). In all studies when MA was administered in combination with another medication (such as an antidepressant), outcomes such as appetite, lean body mass, and inflammatory markers had a more pronounced improvement compared to the administration of MA alone, demonstrating the multifactorial nature of CACS.

Yavuzsen, Davis, Walsh, LeGrand, and Lagman (2005) completed a systematic review of the treatment of anorexia and weight loss in cancer cachexia and concluded that progestational agents (MA, MPA) were effective appetite stimulants in patients with cancer. The dose range of MA described in this review was 160–1,600 mg/day, and the dose range for MPA was 300–1,200 mg/day. The results showed that both MA and MPA improved appetite and weight, were safe with acceptable side effects, and had minimal effect on QOL. A final conclusion on the optimal dose, time to start, or duration of treatment was not reached within this systematic review. However, a recent review by Argilés, Anguera, and Stemmler (2013) recommended that dosing should start at 160 mg/day and be increased until 800 mg/day is reached. The most widely reported dose in this review was 320–800 mg/day. MA has only been tested for clinical use for up to three months; therefore, long-term use is not recommended (Argilés et al., 2013). More research is needed to determine the optimal dose and duration of MA, as well as the safety profile of the drug at different dosing levels.

Two studies showed a relationship between the effect of MPA on IL-6 in breast cancer cells both in vitro and in vivo (Kurebayashi, Yamamoto, Otsuki, & Sonoo, 1999; Yamashita & Ogawa, 2000). More studies are necessary to confirm the impact of the inflammatory process of cancer cachexia.

It is important to be aware of the potential side effects of MA and to evaluate these side effects within diverse cancer populations and larger participant sample sizes. Side effects of MA and MPA are listed in Table 6-3. MA may or may not be indicated in patients with hormone-dependent tumors, such as breast and prostate cancers, and therefore caution is necessary when prescribing or administering this medication.

Corticosteroids

A systematic review of the treatment of anorexia in patients with cancer noted that corticosteroids are effective in improving appetite (Yavuzsen et al., 2005) and lean body mass (Mantovani, Macciò, Madeddu, Serpe, Antoni, et al., 2010) but not weight gain (Adams, Shepard, et al., 2009). Methylprednisolone sodium and methylprednisolone improved appetite and QOL. Doses of methylprednisolone and methylprednisolone sodium were
32–125 mg/day. Doses were 10 mg/day for prednisolone and 3–8 mg/day for dexamethasone.

Standard indications for withholding corticosteroids apply to patients with CACS, including contraindications or drug interactions. For patients with diabetes and cancer, a risk-benefit analysis should be completed prior to prescribing (Kauh et al., 2011). Side effects are listed in Table 6-3. Use of these drugs should be limited to patients seeking short-term supportive care for anorexia (Adams, Shepard, et al., 2009).

Likely to Be Effective

Nutritional Support With Enteral Nutrition

Methods of nutrition administration include enteral and parenteral. Enteral nutrition (EN) can be administered either by oral intake or via a catheter or tube, with later absorption of nutrients by the gastrointestinal tract. The oral route is best for patients who are able to eat. EN through a catheter or tube is indicated if the gastrointestinal tract is intact but swallowing or mastication is compromised by disease, or if it is needed to pass an obstructed area. EN is used mainly in patients with cancer of the head and neck or esophagus. Parenteral nutrition (PN) refers to the administration of nutrients through a large IV catheter (Bozzetti, 2013).

Nutritional support is provided by a combination of dietary counseling and interventions for both EN and PN and is an important component of caring for patients with cancer and altered nutritional status (August & Huhmann, 2009). Nutritional support and dietary counseling may be effective for patients with cancer cachexia who are experiencing starvation caused by gastrointestinal tumors or treatment toxicity (Del Fabbro et al., 2006), in combination with pharmacologic treatments. More research is needed to determine the actual independent effect of dietary counseling and support.

EN is the most common and least invasive nutritional support choice for patients with a functioning gastrointestinal tract because it maintains the gut-mucosal barrier and immunologic function (Bozzetti, 2013). Both EN and PN improve some nutritional indicators, including body weight, fat mass, and nitrogen balance (Academy of Nutrition and Dietetics, 2007). Although EN can be administered orally in most cases, the enteral regimen requirements needed to improve lean body mass and visceral proteins are very high, which makes it impossible to achieve in patients who are unable to eat (Bozzetti, 2013).

The nutritional regimen recommended to improve lean body mass and visceral protein requirements is 35 kcal/kg and 1.3 g of amino acid/kg, and the recommended regimen to improve immune response is at least 42 kcal/kg and 2.3 g of amino acid/kg. Overall, clinical benefits are reported to occur when intake is 250–600 kcal/day (Bozzetti, 2013).

The use of tube feeding is indicated when disease or treatment compromises swallowing or mastication (e.g., cancer of the head and neck or esophagus) (Bozzetti, 2013). The different types of tube feeding include nasogastric, gastrostomy, and jejunostomy. Gastrostomy and jejunostomy are efficient methods of providing long-term EN and are better tolerated than the nasogastric tube. However, large volumes infused continuously may not be tolerated, causing nausea, vomiting, and diarrhea. All tube feeding requires strict hygiene and infection control practices (Ojo & Bowden, 2012). A recent systematic literature review demonstrated that rates of infection or complications are not significantly different between a percutaneous endoscopic gastrostomy tube and nasogastric tube (Bozzetti, 2013), and there is no evidence to support choosing one over the other when providing nutritional support. Therefore, clinicians should select the best option for the particular patient when providing EN.
Dietary Counseling

Preliminary evidence supports the benefit of dietary counseling in patients with CACS in conjunction with other interventions, especially for sustaining nutritional intake and following nutritional support recommendations. However, the independent effects of dietary counseling have not been established. Ravasco, Monteiro-Grillo, and Camilo (2003) studied the impact of individualized nutritional counseling on nutritional status and QOL in 125 patients with cancer who were referred to radiation therapy. In this prospective non-controlled study, patients reported increased nutritional intake and overall improvement in QOL after implementation of nutritional counseling.

Dietary counseling was evaluated in two randomized controlled trials, one in 75 patients with head and neck cancer undergoing radiation therapy (Ravasco, Monteiro-Grillo, Vidal, & Camilo, 2005b) and the other in 111 patients with colorectal cancer undergoing radiation therapy (Ravasco, Monteiro-Grillo, Vidal, & Camilo, 2005a). Both studies found that at three months, individuals receiving counseling (n = 25 and n = 37, respectively) were able to sustain nutritional intake compared to those receiving only nutritional supplementation.

A prospective study using an interdisciplinary team approach demonstrated benefits from nutritional counseling and symptom management. In this study, 186 patients received individualized nutritional education and aggressive symptom management. Patients were able to stop weight loss and stabilize or improve albumin or transferrin levels (Ottery, Slju-ka, & Hagan, 1995). One multicenter randomized clinical trial by the Cancer Cachexia Study Group in Australia reported that oral nutritional supplements improved caloric intake and body composition in 200 patients with pancreatic cancer undergoing radiation therapy (Bauer, Capra, Battistutta, Davidson, & Ash, 2005).

On the contrary, a systematic review on symptom management of cancer-related anorexia and cachexia found no major benefit from dietary counseling (Brown, 2002). This review identified seven studies of nonpharmacologic food-intake interventions. All seven studies were randomized clinical trials that investigated the effects of nutritional counseling and commercial oral liquid supplements. All studies reported improved caloric intake as a result of the nutritional counseling; however, none reported improvement in survival, tumor response, or nutritional status (Brown, 2002). Similar findings were reported in a prospective randomized clinical trial that examined the effect of frequent nutritional counseling on oral intake, body weight, response rate, survival, and QOL in patients with lung, ovarian, and breast cancers who were undergoing chemotherapy (Ovesen, Allingstrup, Hannibal, Mortensen, & Hansen, 1993). This study reported that dietary counseling increased daily energy intake of calories and protein with minimal gain weight, but results showed no difference in QOL between the control and experimental groups (Ovesen et al., 1993). Overall, nutritional counseling increases caloric intake and may improve nutritional parameters and QOL. Based on current evidence, nutritional counseling may work best in conjunction with other forms of nutritional support. Further research is needed to definitively recommend this intervention for practice.

Exercise

Regular physical activity may decrease the side effects of cancer therapy and prevent or reverse cachexia through suppression of inflammatory processes and enhancement of insulin sensitivity, protein synthesis, and antioxidant activities (Ardies, 2002). Patients with cachexia who comply with a proper exercise program gain muscle protein mass, increase their endurance, and improve their physical function (Zinna & Yarasheski, 2003). Limited evidence is available about the impact of exercise on CACS; however, some literature
is beginning to measure the impact of exercise in combination with pharmacologic interventions, and results are promising in animal models (Penna et al., 2011). More research is needed to evaluate the potential effectiveness of this promising intervention and its effect on CACS.

**Effectiveness Not Established**

**Omega-3 Fatty Acid Supplements**

Omega-3 fatty acids provided in fish oils have been investigated in patients with cancer who have anorexia and weight loss and show promise as an intervention to improve symptoms of CACS (Bozzetti, 2013). Eicosapentaenoic acid (EPA) is the most widely investigated omega-3 fatty acid. Omega-3 fatty acids have a role in the treatment of anorexia by triggering the production of orexigenic neurotransmitters in food-intake regulatory nuclei in the hypothalamus (Goncalves et al., 2006).

A Cochrane review (Dewey, Baughan, Dean, Higgins, & Johnson, 2007) and a systematic review (Mazzotta & Jeney, 2009) provided inconclusive evidence of EPA's effect on weight gain. However, results from five trials in the Cochrane review found that EPA may be effective over time to help decrease weight loss and promote weight gain (Dewey et al., 2007), but it may not be effective alone (Mazzotta & Jeney, 2009) and may be best if used as part of a supplement (Colomer et al., 2007).

In 40 patients with advanced lung cancer, those taking omega-3 fatty acids had superior weight maintenance, QOL, and performance status compared to the control group (van der Meij et al., 2010). However, details about the intervention were not described, such as the type of oral nutrition supplementation, and the sample size was small. Mantovani, Macciò, Madeddu, Serpe, Massa, et al. (2010) completed a five-arm randomized controlled trial with 322 adult patients with advanced cancer and found that the arm that included MPA or MA, EPA, L-carnitine, and thalidomide was most effective in improving the CACS-related outcomes. However, it was challenging to determine which part of the intervention actually made the difference, and therefore results are impossible to interpret. Ryan et al. (2009) examined the effect of EPA-enriched EN on body composition following surgery in 53 patients with esophageal cancer. The small sample size made results difficult to interpret, but findings did show that participants receiving EPA maintained body composition and had no more significant complications. A large randomized controlled trial in 518 weight-losing patients with advanced gastrointestinal or lung cancer did not show a benefit of EPA in treating CACS over an 8-week treatment period, although the results did trend to favor those receiving EPA (Fearon et al., 2006). Therefore, overall, large-scale randomized controlled trials are needed to define the benefits of omega-3 fatty acids for use in CACS treatment.

**Ghrelin**

Ghrelin is a gastric hormone that is thought to be mediated through growth hormone and whose mechanism of action is not fully understood (Argilés & Stemmler, 2013). In a recent randomized controlled trial evaluating the effects of 50 mg of anamorelin, a ghrelin receptor agonist, orally daily for three weeks in 16 participants with cancer, no effect was found on caloric intake, although participants did report improved appetite (Garcia, Friend, & Allen, 2013). In a randomized controlled trial with 42 patients with esophageal cancer randomized to take 3 mcg/kg of ghrelin orally twice daily for seven days, patients in the intervention group (n = 21) had less decline in intake and lower incidence of anorexia; however, minimal differences were found in caloric intake (Hiura et al., 2012). A large-scale random-
ized controlled trial is needed to determine the effectiveness of ghrelin on CACS, in addition to establishing an effective dose and treatment period.

Thalidomide

Thalidomide has a number of actions, including inhibition of angiogenesis, immunomodulation, and anti-inflammatory effects (Stroud, 2005). Thalidomide has been found to attenuate weight loss, improve physical functioning, and improve appetite and nausea in patients with advanced cancer (Davis et al., 2012; Mantovani, Macciò, Madeddu, Serpe, Massa, et al., 2010; Reid, Mills, et al., 2012).

In a study of 21 patients with advanced cancer, researchers found no difference in patients who took 100 mg of thalidomide daily for 14 days compared to patients who received the placebo (Yennurajalingam et al., 2012). This study was limited by a small sample size and high attrition. Wilkes et al. (2011) completed a small randomized controlled trial in 22 patients with advanced cancer and found no group differences and a high attrition rate. One systematic review found that there was insufficient evidence to either support or refute the use of thalidomide for the management of cancer cachexia (Reid, Mills, et al., 2012). Insufficient evidence exists to suggest the use of thalidomide for treatment of cancer cachexia as a result of small sample sizes or adverse side effects of thalidomide (Davis et al., 2012; Mantovani, Macciò, Madeddu, Serpe, Massa, et al., 2010). Thalidomide has been shown to cause birth defects in pregnancy. However, the use of thalidomide in patients with cancer was investigated only in the late-, advanced-, or terminal-stage cancer populations who were not seeking pregnancy.

Anabolic Agents

Anabolic agents help to promote body composition by maintaining or enhancing lean body mass. These agents include growth hormone, insulin-like growth factor-1, testosterone, dihydrotestosterone, and the testosterone analogs oxandrolone and nandrolone decanoate (Langer et al., 2001). Anabolic steroids promote protein nitrogen accumulation; therefore, they could be used to counteract the progressive nitrogen loss associated with cancer cachexia (Argilés et al., 2001). Testosterone replacement in patients with decreased testosterone levels improved weight gain and physical activity (Langer et al., 2001). A review on the use of anabolic agents in the treatment of cancer cachexia concluded that oxandrolone was safe and effective for the treatment of AIDS-related cachexia and suggested potential benefits in patients with cancer (Langer et al., 2001). Oxandrolone improves body composition and muscle strength (Orr & Singh, 2004). More research is needed to determine if this pharmacologic approach is effective.

Other Medications

A number of pharmacologic agents are being tested as potential interventions for patients experiencing CACS. These agents include insulin (Lundholm et al., 2007), mirtazapine (Riechelmann, Burman, Tannock, Rodin, & Zimmermann, 2010), OHR118 (peptide) (Chasen, Hirschman, & Bhargava, 2011), and complementary or alternative therapies such as Astragali Radix (also known as Radix Astragali) (Lee & Lee, 2010) and rikkunshito (Ohno et al., 2011). Nonsteroidal anti-inflammatory drugs (NSAIDs) are being considered as a potential agent to improve body weight and mass in patients with cancer (Lee & Lee, 2010; Solheim, Fearon, Blum, & Kaasa, 2013) in addition to cyclooxygenase (COX)-1 and COX-2 inhibitors (Naoi, Kogure, Saito, Hamazaki, & Watanabe, 2006). One systematic review addressed the use of NSAIDs for the management of cachexia in patients with advanced-stage or terminal cancer (Reid, Hughes, Murray, Parsons, & Cantwell, 2012). Inconclusive evi-
ence exists to suggest the use of NSAIDs (celecoxib) for the treatment of cancer cachexia in this patient population because of inadequately powered results based on smaller sample sizes. Research is needed to further elucidate the impact these pharmacologic interventions could have on CACS.

**Benefits Balanced With Harms**

PN is not routinely recommended for nutritional support unless a patient encounters prolonged starvation and is not a candidate for EN. EN is the first choice over PN when appropriate for the patient (Bozzetti, 2013). For patients with advanced-stage disease or those who are severely malnourished, PN may be an option for care to help stabilize weight loss and nutritional status. However, according to the National Comprehensive Cancer Network® (NCCN®, 2014) palliative care guidelines, PN is not the focus of CACS care, and the focus should remain on treating the symptoms of CACS and providing patient and family support.

**Patient Teaching Points**

Early supportive nutritional care and interdisciplinary or healthcare team management is recommended for the successful management of CACS (Adams, Shepard, et al., 2009). A multidisciplinary approach should be used and is based on the resources available within each practice setting. Nursing care of patients with CACS centers on the management of the symptoms related to the cancer and its treatment that may adversely affect appetite and nutritional status, such as nausea, vomiting, diarrhea, pain, fatigue, and taste changes. This is especially important in those diagnoses that place patients at high risk for poor nutritional outcomes, such as head and neck, gastrointestinal, or thoracic cancers (Bozzetti, 2013). It is important to consider automatic nutrition referral for these high-risk patients, who may be classified as precachectic (Fearon et al., 2011). Frequent, small meals are helpful, but empty-calorie foods should be avoided, and each meal or snack should provide the maximum calories and protein possible (McClement, 2005).

Enlisting the help of the patient and family in symptom management is important. By using food and calorie diaries as well as reporting symptoms, the patient and family can partner with the healthcare team. Eliminating the symptoms will improve nutritional intake and prevent cachexia. Early or precachectic patients with cancer receiving EN or PN support will require additional education and support to ensure understanding and compliance with nutritional treatments (Academy of Nutrition and Dietetics, 2007; Fearon et al., 2011).

Incorporating the recommended validated measures into clinical practice to assess and then manage the impact of CACS on patients’ QOL is an important way to deliver supportive patient care. Promoting patient and family interaction and providing emotional and educational support to the family can be helpful. Encouraging family meals can help with food intake as well as family bonds. Decreasing stress and pressure at meal times is important. Patients often tolerate small, frequent meals better than large meals. Patients should participate in meal planning, but allowing others to cook may conserve energy and decrease the negative impact of odors on appetite. Engaging in light exercise may stimulate appetite as well, and using small amounts of seasonings can enhance taste (Academy of Nutrition and Dietetics, 2007; NCCN, 2014).

The opportunity for improving outcomes in CACS exists through a standardized and proactive approach in identifying patients who are at risk for nutritional deficiencies and muscle loss. Early intervention is imperative, as deterioration caused by muscle loss frequently
is irreversible.Clinicians should assess patients’ nutritional status at each visit, just as with functional status. All patients should be screened at cancer diagnosis and reevaluated at regular intervals for nutritional problems. Screenings should include weight changes, dietary intake, functional status, symptoms affecting nutrition, physical examination, and projected nutritional problems (Mueller et al., 2011).

Need for Future Research

Randomized trials are needed to evaluate the impact of patient education, counseling, support, and follow-up on CACS. Additionally, more data are required related to omega-3 fatty acids and dosing parameters. Future research should also focus on specific interventions to tease out which components of multifactorial interventions tested in randomized trials actually made the difference (e.g., MA, L-carnitine, celecoxib). Use of appetite stimulants in patients with hormone-sensitive cancers needs to be addressed further. Currently, the research evidence shows that neither progestins nor corticosteroids are superior to the other in stimulating appetite or enhancing weight gain in the management of anorexia-cachexia. In general, no adequate treatment intervention for managing CACS appears to exist (Davis et al., 2012; Reid, Hughes, et al., 2012; Reid, Mills, et al., 2012).

Larger, multimodality treatment intervention studies involving dietary education, nutritional protein intake, and physical activity for the purposes of enhancing lean body mass and muscle strength should be considered. Because of the paucity of long-term nutrition intervention studies, research should be designed to evaluate the early cancer cachexia staging of precachexia. The majority of randomized controlled trials were performed in patients with late-stage or advanced cancer who had refractory cachexia. Clear language to differentiate “advanced,” “terminal,” or “palliative care” patients from advanced but nonprogressive stage III and IV patients with cancer who do not necessarily require palliative care should be used. Therefore, staging of cancer cachexia is paramount in describing whether a patient is potentially refractory to treatment or is treatable. Based on the current evaluation of systematic reviews and randomized controlled trials addressing palliative care in patients with cancer, no nutritional or dietary recommendations can be made for refractory cachexia. Finally, given that cancer cachexia is a syndrome with multiple causes, a multimodal treatment approach should be the focus of future studies (Fearon et al., 2013).

Conclusion of Case Study

Assessment, dietary counseling, and nutritional support services and referral, in conjunction with pharmacologic intervention, such as MA or corticosteroids, would be effective in helping A.J. manage his CACS. Therefore, the nurse completes a full nutritional assessment using the A/CS-12 measure, in addition to regular symptom and QOL assessment, and identifies that the patient is at risk for CACS. In collaboration with the patient’s physician, the nurse refers the patient to a dietitian for nutritional counseling to provide support before CACS develops and to discuss the potential for future nutritional support interventions. The nurse educates the patient and his family about the importance of monitoring dietary intake and reporting any change in appetite or weight to the clinical team immediately. The nurse talks with the patient and his family about the potential benefits of light exercise or activity to stimulate his appetite and combat a multitude of
other symptoms, such as fatigue. The physician prescribes the patient MA to combat anorexia, which typically occurs in head and neck cancers. The patient agrees with the plan and will be reevaluated at each clinical visit for changes in weight or BMI and any reported decrease in appetite.

Conclusion

CACS is a wasting syndrome characterized by changes in appetite, poor caloric intake, weight loss, and loss of muscle and fat leading to a patient’s diminished function and performance status. The pathophysiology of CACS is multifactorial; therefore, its treatment should include a combination of modalities provided by an interdisciplinary team. As key members of this team, oncology nurses need to understand the complexity of cancer cachexia in order to conduct a comprehensive assessment and provide appropriate treatment and care.

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References


CHAPTER 7

Caregiver Burden

Norissa J. Honea, PhD, RN, AOCN®, CNRN

Case Study

R.M. is a 54-year-old woman and primary caregiver for her husband, a self-employed truck driver diagnosed with stage IVA squamous cell carcinoma of the oropharynx. She works nights at a nearby large department store as an inventory stocker and carries medical insurance benefits for herself and her husband through her job. Also living in the home with the couple are their 30-year-old daughter, who is a part-time student while working two jobs as a waitress, and their 12-year-old grandson.

Since her husband’s diagnosis, R.M. says she has not slept well, is always tired, and has lost weight. She smokes two packs of cigarettes per day and has hypertension and diabetes. She admits she has not eaten as well as she used to and has occasionally missed doses of her medications. She has been taking her husband to and from appointments for his radiation, chemotherapy, and checkups with various providers. In addition to caring for her husband, she also looks after her 73-year-old mother who has heart disease and lives nearby, visiting her nearly every day and trying to attend her doctor visits as well. She relies on her daughter to help with meal preparation and housework but does not want to rely very heavily on her because she does not want her to quit school.

Overview

Cancer affects not only the patient with the disease but also his or her family. Life as the family previously knew it suddenly changes. People assuming the caregiver role need a crash course in medical terminology; new information, skills, and resources; strategies for coping; and communicating with providers as they navigate the complexities of dealing with cancer and its treatment. Fear and uncertainty overshadow the lives of both the caregiver and the care recipient. Caregivers are often overwhelmed by their own emotional response at hearing the loved one has been diagnosed with cancer. As a result of the interdependent relationship between caregiver and patient, reacting as one emotional system, one individual’s distress and reactions influence the other’s (Hagedoorn, Sanderman, Bolks, Tuinstra, & Coyne, 2008; Northouse, 2012).

In 2014, an estimated 1.7 million people in the United States received a diagnosis of cancer (American Cancer Society, 2014). Many of those will need some kind of help during
their illness trajectory (Given, Given, & Sherwood, 2012). Caregiving usually comes from someone like a spouse or partner, an adult child, a sibling, a parent, or another person with a family-type bond who assumes the role of caregiver because it is delegated to them, often by default. Caregiving as defined by Hermanns and Mastel-Smith (2012) is “the process of helping another person who is unable to do for themselves in a ‘holistic’ (physically, mentally, emotionally, and socially) manner” (p. 15).

Caregiving activities can be performed by a primary and maybe a secondary caregiver. A primary caregiver is usually the one who performs the bulk of the caregiving tasks on a consistent basis, whereas a secondary caregiver is one who is available either as back-up or to perform a specialized function when needed or requested (Reinhard, Levine, & Samis, 2012). Some secondary caregivers provide sporadic help (i.e., when convenient) while others may not be reliable in their assistance. Increasingly, some family caregivers function in the role from a distance, such as when caring for a loved one living in another city or state (Mazanec, Daly, Ferrell, & Prince-Paul, 2011). In 2006, Wolff and Kasper noted that more than half of primary caregivers were the sole care provider without any secondary involvement. This fact is important because it indicates that as a society, we are seeing increased numbers and percentages of caregivers with greater burdens because more are sole caregivers (Reinhard et al., 2012). (See definitions in Table 7-1.)

### Caregiving Activities

Caregiving for patients with cancer comprises both tangible assistance and intangible assistance, such as providing emotional, social, and spiritual support. Time spent in caregiving tasks and behaviors that form the caregiving role is referred to as caregiving demand (Schumacher et al., 2008). Many factors contribute to this demand, including care recipient and caregiver characteristics, abilities, and resources. Care recipient functional status, disease site and stage, prognosis, and treatment modalities are several examples of factors that dictate the type and amount of care required from a caregiver. Those in a later stage of disease are usually more debilitated and require more care. Consider the care recipient’s physical, cognitive, behavioral, and affective abilities and whether the person can independently perform activities of daily living (ADLs) like walking or personal care (Katz & Akpom, 1976) to determine care requirements. It is also important to consider how independently he or she can perform instrumental ADLs such as paying bills and being able to protect oneself from unsafe situations (Lawton & Brody, 1969).

Tangible help from family caregivers includes assistance with ADLs, instrumental ADLs, and healthcare advocacy. Helping with ADLs involves personal care activities such as bathing, toileting, grooming, and feeding. Instrumental ADLs include meal preparation, laundry, shopping, transportation, medication administration, treatment monitoring, treatment-related symptom management, and paying bills. Healthcare advocacy involves communication with healthcare providers and insurers on behalf of the care recipient. Thus, a considerable amount of caregivers’ time is spent providing emotional, instrumental, social, spiritual, medical, financial, and other support to their loved one with cancer (National Alliance for Caregiving & AARP, 2009). Caregivers must carefully consider whether they have the willingness, abilities, time, and resources to perform their role. Notably, the caregiving role and activities are in addition to current family roles, so family members must juggle the conflicting responsibilities of caregiver, spouse, parent, and employee, thereby challenging one’s priorities and perceptions.
TABLE 7-1 Definitions of Caregiver Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Caregiver burden</td>
<td>Disruptions in routines, relationships, privacy, and career and leisure time resulting from caregiving (Savundranayagam et al., 2011)</td>
</tr>
<tr>
<td></td>
<td>Types of burden (Savundranayagam et al., 2011)</td>
</tr>
<tr>
<td></td>
<td>• Stress burden: Tension and anxiety</td>
</tr>
<tr>
<td></td>
<td>• Relationship burden: Changes in caregiver–care recipient relationship</td>
</tr>
<tr>
<td></td>
<td>• Objective burden: Time infringements</td>
</tr>
<tr>
<td>Caregiver burnout</td>
<td>A state of physical, mental, and emotional exhaustion in which the caregiver feels overwhelmed and unable to perform the caregiving role (Kasuya et al., 2000)</td>
</tr>
<tr>
<td>Caregiving demand</td>
<td>Time spent in caregiving tasks and behaviors that form the caregiving role (Schumacher et al., 2008)</td>
</tr>
<tr>
<td>Caregiver self-efficacy</td>
<td>Confidence or belief in one’s ability to fulfill the physical and emotional needs of the care recipient (Steffen et al., 2002)</td>
</tr>
<tr>
<td>Caregiver strain</td>
<td>Feeling difficulty, either in task-specific or global performance of their caregiving role (Schumacher et al., 2008)</td>
</tr>
<tr>
<td>Mutuality</td>
<td>The quality of the relationship between the caregiver and care recipient as partners (Schumacher et al., 2008)</td>
</tr>
<tr>
<td>Preparedness</td>
<td>Perceived readiness to undertake the multiple aspects of the caregiving role (Schumacher et al., 2008)</td>
</tr>
<tr>
<td>Quality of life</td>
<td>The subjective well-being of the caregiver, which includes health and functioning, socioeconomic status, and psychological, emotional, spiritual, and family domains (Ferrans, 1990; Lim &amp; Zebrack, 2004)</td>
</tr>
<tr>
<td>Symptom experience</td>
<td>The presence of preexisting symptoms in caregivers may interfere with their ability to assume and fulfill the caregiving role. In addition, caregivers may develop new symptoms or have existing symptoms worsen during the course of their caregiving activities (Fletcher et al., 2008).</td>
</tr>
</tbody>
</table>

Caregiver Perceptions

Relationship Between Caregiver and Care Recipient

Each caregiver and caregiving situation is unique. However, commonalities exist across situations, such as motivation for caregiving and the tasks performed. Pearlin, Mullan, Semple, and Skaff (1990) asserted that “caring is the affective component of one’s commitment to the welfare of another, caregiving is the behavioral expression of this commitment,” and that both “are intrinsic to any close relationship where people attempt to protect or enhance each other’s well-being” (p. 583). Mutuality concerns the quality of the relationship between caregiver and care recipient as partners (Schumacher et al., 2008). A closely related term is marital satisfaction, which has been identified as a predictor of role adjustment among spouses (Northouse, Mood, Templin, Mellon, & George, 2000). When the abilities of one individual change because of illness, care needs, and disability, the other person in the relationship takes on more. The relationship becomes unbalanced and can develop into a source of stress, conflict, and communication problems (Pearlin et al., 1990).
**Caregiver Quality of Life**

Caregiver quality of life (QOL) is a multidimensional construct that concerns the subjective well-being of the caregiver. It includes health and functioning, socioeconomic status, and psychological, emotional, spiritual, and family domains (Ferrans, 1990; Lim & Zebrack, 2004). Perceptions of QOL may be viewed through lenses of both undesirable aspects and gratifying aspects of family caregiving (Hunt, 2003; Lim & Zebrack, 2004). Undesirable aspects are most often labeled as burdens, hassles, strain, and stress, whereas gratifying aspects are regarded as benefits and rewards, such as caregiver esteem, uplifts of caregiving, satisfaction, finding meaning, and enhancement of the experience (Hunt, 2003). Much of the caregiving literature focuses on the negative aspects of caregiving, yet exploration of the rewards in caregiving activities and role performance should not be neglected. Caregivers who feel that their contribution and care make a difference to their care recipient may find that their own QOL improves through their acceptance of their caregiving role/situation, empathy, appreciation for the relationship with family and others, and reprioritization, which can enhance their self-view (Kim, Schulz, & Carver, 2007).

**Preparedness and Self-Efficacy**

Perceived readiness to undertake the multiple aspects of the caregiving role is known as preparedness (Archbold, Stewart, Greenlick, & Harvath, 1990). A sense of greater preparedness has been associated with lower levels of reported caregiver strain (Archbold et al., 1990) and less tension, anxiety, confusion, anger, and fatigue (Schumacher et al., 2008). Much attention is devoted to the person with cancer; however, many family caregivers are left feeling unprepared for caregiving. Van Ryn et al. (2011) observed that half of the caregivers in their study reported not receiving the training that they felt was necessary to care for their loved one. The need to learn new skills often requires great attention and time for caregivers to perform those skills well, adding to their distress. Self-efficacy denotes a confidence or belief in one’s ability to fulfill his or her own physical and emotional needs (Marks & Allegrante, 2005) and those of the care recipient (Steffen, McKibbin, Zeiss, Gallagher-Thompson, & Bandura, 2002). When caregivers lack such confidence and perceive their resources or abilities as being insufficient, caregiver distress and burden, poorer relationship quality, and poorer QOL follow.

**Risk Factors and Associated Incidence**

A study by the National Alliance for Caregiving and AARP (2009) examined the role of caregivers in the United States. Caregivers who reported poorer health and strain were those who had been providing care for five years or more or for at least 21 hours of care per week with little consistent help from other family members. Researchers examining caregivers of patients with lung cancer found that they experienced worsening QOL over time (Grant et al., 2013). Mosher, Bakas, and Champion (2013) noted other changes, sometimes reported in more than half of the caregivers, as including worsening of coping abilities, energy, and emotional well-being, as well as lack of time for social activities with friends. Such intense caregiving can place caregivers at great risk for depression (National Alliance for Caregiving & AARP, 2009).

Reportedly, caregivers providing care to a loved one with functional disabilities, cognitive impairment, or behavioral disorders experience greater burden (Pinquart & Sörensen,
2003, 2007; Sherwood et al., 2006), as do caregivers who themselves have more physical problems (Jepson, McCorkle, Adler, Nuamah, & Lusk, 1999). According to Cannuscio et al. (2002), spousal caregivers experienced a six times higher rate of symptoms for depression and anxiety than noncaregivers. Those caring for a parent experienced twice as much depression and anxiety as did noncaregivers.

As caregiver burden and burnout ensue, there is potential for caregivers to act in an abusive manner in their caregiving relationship (Beach et al., 2005). Some caregivers are in their situations not by choice or are in situations involving neuropsychiatric or behavioral problems. Such caregivers may feel even greater burdens yet have no other options, leaving them vulnerable to neglect or abuse (verbally and/or physically) from their care recipient (Erosa, Elliott, Berry, & Grant, 2010; Yan & Kwok, 2011).

Consequences of Caregiving

**Caregiver Stress, Strain, and Burden**

Theories about role acquisition (Schumacher, 1995, 1996; Schumacher, Stewart, Archbold, Dodd, & Dibble, 2000); stress, health, coping, and adaptation (Lazarus & Folkman, 1984; Selye, 1976); and the study of mind-body connection (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002) have formed the basis of the research and understanding of caregiver response and adaptation to caregiving demands (Kiecolt-Glaser, Gouin, & Hantsoo, 2010; Pearlin et al., 1990; Sherwood et al., 2008). Acquiring the caregiver role is a distinctly subjective process. Time is needed to acquire and achieve mastery of skills and knowledge and is influenced by the relationship between the care recipient and the caregiver (Schumacher, 1995). An apt analogy for caregiver role acquisition is like learning dance steps with a partner. In this case, the care recipient leads (by his or her needs), and the caregiver follows in response.

Caregiver stress (or distress), triggered in response to a cancer diagnosis in a loved one (stimulus event), occurs when the demands of caregiving outweigh the personal and social resources of an individual. The Cancer Family Caregiving Experience Model proposed by Fletcher, Miaskowski, Given, and Schumacher (2012) takes into account concurrent components of the stress process, the cancer trajectory, and contextual factors, as illustrated in Figure 7-1. The stimulus in this stress process model is the loved one’s cancer diagnosis, stage (point along disease trajectory), and resultant treatment and disease sequelae. Caregivers’ primary appraisal takes place as they size up their situation. The care recipient’s illness factors dictate the type, amount, and duration of supervision and care required of the caregiver. The secondary appraisal occurs as caregivers consider their own willingness, capacity, and resources to carry out the needed care for their loved one.

The way a caregiver perceives and appraises the stressfulness of his or her caregiving situation (e.g., the care recipient’s needs for care) and the personal and social resources available (Gaugler et al., 2005) lead to psychobehavioral and biophysical responses (Sherwood et al., 2008) (see Table 7-2). The effects of both behavioral and physiologic responses affect one’s overall health and well-being. Contextual factors such as whether the caregiver lives with the care recipient, other family or employment obligations, and income level, must also be considered. Disease trajectory is important in this model because as the illness progresses, the increased requirement for caregiving is likely to lead to greater caregiver burden.

Caregiver strain and caregiver burden, two closely related terms, are both used to describe the consequences of caregiving activities that affect the caregiver’s emotional and physical
health. Caregiver strain is said to occur when caregivers feel difficulty, either in task-specific or more global performance of their caregiving role (Schumacher et al., 2008). Similarly, caregiver burden is a multidimensional construct focusing on (a) tension and anxiety (stress burden), (b) changes in caregiver–care recipient relationship (relationship burden), and (c) time infringements (objective burden) or disruptions (in routines, relationships, privacy, and career and leisure time) due to caregiving (Savundranayagam, Montgomery, & Kosloski, 2011). Tamayo et al. (2010) found that caregivers identified burden as their most important concern for QOL. For example, when not able to keep up with competing demands, one is faced with whether to remain in or leave the workforce (Yabroff & Kim, 2009), where employment has offered financial security and insurance benefits. According to a report by Reinhard, Levine, and Samis (2013), employed caregivers felt significantly greater stress over providing care along with completing their other responsibilities compared to nonemployed caregivers. Increased feelings of being stressed about responsibilities was especially noted by caregivers who provided three or more complex medical care tasks and/or had more than five chronic conditions with which to deal (Reinhard et al., 2013). When caregivers perceive their resources being insufficient, caregiver distress, burden, and poorer QOL occur, often manifesting as emotional, behavioral, or physical symptoms.
The Mind-Body Connection Model is an extension of the stress process model used to examine changes in caregiver physical and mental health. For example, Goode, Haley, Roth, and Ford (1998) found that as caregivers’ perceptions of stressfulness increased, physical health and depression worsened. Similarly, Wu et al. (1999) noted a correlation between stress from spousal caregiving and immune suppression in caregivers, contributing to the caregivers’ poor response to influenza virus vaccination. Stress hormones are also affected. For example, the stress hormones that elevate insulin levels thereby alter glucose metabolism and, in turn, lead to increased blood lipid levels, high blood pressure, and obesity (Vitaliano, Scanlan, Krenz, Schwartz, & Marcovina, 1996). Immune suppression and the associations of insulin dysregulation leave individuals at greater risk for illness. More recently, researchers have demonstrated that compared to noncaretakers, changes in neurohormonal and inflammatory processes over time have been found in caregivers (Rohleder, Marin, Ma, & Miller, 2009). Furthermore, chronic lack of sleep associated with these physiologic changes places people at increased risk for metabolic, cardiovascular, and stroke morbidity and mortality (Faraut, Boudjeltia, Vanhamme, & Kerkhofs, 2012). This clinical information can help nurses identify who may be at greater risk with regard to gender and the care recipient’s disease trajectory. As an example, results from the Caregiver Health Effects Study, in examining stressors and health in spousal caregivers, indicated that men appeared to experience more physiologic stress responses such as hypertension, and men also had a higher risk of mortality during their bereavement period compared to women (Bookwala & Schulz, 2000; Schulz & Beach, 1999).

The symptoms of depression, anxiety, sleep disturbance, fatigue, and pain in family caregivers in the cancer, dementia, and Parkinson disease populations were reviewed by Fletcher, Dodd, Schumacher, and Miaskowski (2008). They looked at the symptoms in the context of the Symptom Management Model, which consists of the symptom experience, management strategies, and caregiver outcomes (e.g., functional status, QOL). The most frequently studied symptom was depression, and little was found about the frequency, severity, and effects of the symptoms of anxiety, sleep disturbance, fatigue, and pain on family caregivers.

### Table 7-2: Psychobehavioral and Physiologic Responses to Stress of Caregiving

<table>
<thead>
<tr>
<th>Type</th>
<th>Stress Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychobehavioral</td>
<td>Tension, anxiety, panic, depression, anger</td>
</tr>
<tr>
<td></td>
<td>Sleep disturbance</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Changes in appetite/diet</td>
</tr>
<tr>
<td></td>
<td>Reliance on substances (i.e., food, tobacco, alcohol, drugs)</td>
</tr>
<tr>
<td></td>
<td>Lack of exercise and leisure activity</td>
</tr>
<tr>
<td></td>
<td>Inattention to self-care and preventive health practices</td>
</tr>
<tr>
<td>Physiologic</td>
<td>Increased blood pressure and heart rate</td>
</tr>
<tr>
<td></td>
<td>Impaired glucose metabolism</td>
</tr>
<tr>
<td></td>
<td>Inflammatory response</td>
</tr>
<tr>
<td></td>
<td>Acute onset of illness</td>
</tr>
<tr>
<td></td>
<td>Exacerbation of a chronic illness</td>
</tr>
<tr>
<td></td>
<td>Weight change</td>
</tr>
</tbody>
</table>

Note. Based on information from Schulz & Sherwood, 2008.
However, sleep disturbances have been correlated with fatigue, anxiety, and depression (Pawl, Lee, Clark, & Sherwood, 2013) and can manifest from prolonged exposure to intense caregiving demands, where high levels of life disruption place caregivers at risk for burnout. Burnout is a state of physical, mental, and emotional exhaustion in which caregivers feel overwhelmed and unable to perform the caregiving role (Kasuya, Polgar-Bailey, & Takeuchi, 2000). Strain, burden, and burnout all affect caregivers’ QOL and well-being.

The psychological burden of caring for a loved one with cancer is widely described in the caregiving literature as depression, tension, anxiety, or panic. However, in one study of 200 family caregivers of someone with advanced cancer, 13% of the caregivers reportedly met diagnostic criteria for a psychiatric disorder, with one-fourth of the caregivers having sought mental health treatment after their loved one was diagnosed with cancer (Vanderwerker, Laff, Kadan-Lottick, McColl, & Prigerson, 2005). When comparing caregiver populations (cancer, schizophrenia, and Alzheimer disease), all caregivers reported significant levels of burden, yet caregivers of someone with cancer reported greater levels of depression (Papastavrou, Charalambous, Tsangari, & Karayiannis, 2012). The importance of assessing and recognizing psychological burden and making necessary referrals may help ameliorate such burden.

**Health Behaviors**

Responsibility for performing caregiving tasks in addition to usual activities can deprive caregivers of needed sleep, nutrition, exercise, or time for self. Neglect of one’s own health can result from abandoning preventive health behaviors or participating in risky behaviors that could jeopardize health. In fact, results from the Caregiver Health Effects Study pointed to caregiving as a health hazard, increasing the risk of mortality compared to non-caregiving controls (Beach, Schulz, Yee, & Jackson, 2000; Schulz & Beach, 1999; Vitaliano, Zhang, & Scanlan, 2003). Two factors that appear to moderate changes in health are exercise (King, Baumann, O’Sullivan, Wilcox, & Castro, 2002; Tung & Gillett, 2005) and social support (Brummet et al., 2006; Goode et al., 1998; Pinquart & Sörensen, 2006, 2007; Stetz & Brown, 2004).

The concept of social support comprises several dimensions (Sherbourne & Stewart, 1991). First, functional support is the degree to which relationships serve express functions. Second, emotional support comprises love, caring, and empathy. Third, the instrumental type is the tangible support provided, whereas information support brings guidance and feedback for problem solving. Lastly, the existence and quantity of companionships for leisure or recreational time and connectedness to others are found within a structural support network.

Burton, Newsom, Schulz, Hirsch, and German (1997) examined preventive health behaviors among spousal caregivers (n = 819) comparing levels of caregiving (high, moderate, and non caregiving). Their results indicated that those in high-level caregiving situations who also felt a weak sense of control over their situation were significantly (p < 0.0001) more likely to not get enough rest (29%), not have enough time to exercise (32.2%), not have enough time to rest or recuperate when ill (18.3%), and miss doses of prescription drugs (20.3%) when compared to non caregivers. Matthews, Dunbar-Jacob, Sereika, Schulz, and McDowell (2004) described adherence to a number of preventive health behaviors such as routine medical care, blood pressure checks, and screening for heart disease, cancer, arthritis, or diabetes in caregivers age 50 and older. Although those caregivers performed most of the age- and gender-appropriate preventive practices, they were less likely to adhere to the guidelines (Matthews et al., 2004). Still, caregivers with a stronger sense of control over
their situation reportedly are more likely to practice good preventive health behaviors (Burton et al., 1997).

Health promotion includes self-care behavior, a concept where one makes decisions and takes actions to prevent or cope with a problem, such as to restore or improve health (e.g., when one has uncontrolled diabetes or hypertension) (Acton, 2002; Denyes, Orem, & Bekel, 2001). Such behaviors or practices include maintenance of good dietary and sleeping habits, avoidance of smoking and inactivity, promotion of environmental and home safety, and maintenance of good personal hygiene habits. Richard and Shea (2011) defined self-care as any activity that one undertakes to achieve, maintain, or promote optimal health, even those specific to acute or chronic conditions. Health-seeking behaviors are those that include recognition of symptoms and seeking help to reduce discomfort and restore health. These actions can be performed either by the individual or by someone else. Family members or spouses/partners can advocate and remind each other about the importance of health maintenance, fostering preventive health behaviors (Bowman, Rose, & Deimling, 2005). Caregiving activities can distract people from these self-care activities and thus result in risky behaviors that lead to poorer health (Acton, 2002; Beach et al., 2000; Vitaliano et al., 2003).

Lifestyle and the use of alcohol in response to caregiving demands have received little attention. However, Rospenda, Minich, Milner, and Richman (2010) explored the relationship between caregiver burden and alcohol consumption in a community sample of working caregivers in Chicago. Their findings indicated that social isolation and emotional burden predicted greater consumption of alcohol. They found greater consumption of alcohol in those who were younger, were male, and had higher education and income levels (Rospenda et al., 2010).

In a meta-analysis of 176 studies, Pinquart and Sörensen (2007) examined correlates of caregivers’ physical health. Depressive symptoms in caregivers, behavior problems in care recipients, older age, and being male had strong associations with the physical health of caregivers. These results support the small but significant gender differences in an earlier publication reporting that women had greater caregiver burden and depression with lower levels of subjective well-being and physical health than men (Pinquart & Sörensen, 2006).

**Assessment**

In addition to usual health assessment that includes vital signs and weight, caregiver symptom and burden assessment is also essential in clinical practice. Domains in the assessment of family caregivers should include (a) the caregiving situation (what are the care recipient’s needs for care), (b) a caregiver’s willingness to be in the caregiver role, (c) a caregiver’s ability, capacity, and health in order to perform in the role, and (d) what skills and knowledge the caregiver possesses to undertake the challenges of caregiving (Northouse, Williams, Givven, & McCorkle, 2012). A number of caregivers may feel they are in the role by default, so assessing their willingness, available help, and living situation gives context to the possible distress they may have from caregiving activities. Mounting intensity of caregiving across the trajectory, especially nearing the end of life, brings greater challenges in supporting caregivers to ease burden and other outcomes (Williams & McCorkle, 2011). Caregivers’ abilities and their own health or any related symptoms may prohibit them from fulfilling the role of caregiver, such as in the example of the husband with Parkinson disease and rheumatoid arthritis who cares for his wife, who has lung cancer. Symptoms and perhaps clusters of symptoms (e.g., sleep disturbance, fatigue, depression) that caregivers may experience are analogous to the “tip of the iceberg” and hint at their underlying stress and burden. Table 7-3 shows examples of family caregiver assessment of burden and distress.
### TABLE 7-3 Family Caregiver Assessment

<table>
<thead>
<tr>
<th>Assessment Domain</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caregiving situation</td>
<td>How did you happen to become a caregiver?</td>
</tr>
<tr>
<td>• Relationship to care recipient</td>
<td>How do you and your care recipient get along?</td>
</tr>
<tr>
<td>• Relationship quality</td>
<td>What kind of care do you provide for your loved one?</td>
</tr>
<tr>
<td>• Living situation</td>
<td>Where do you live?</td>
</tr>
<tr>
<td>• Resources</td>
<td>Are there others living with you?</td>
</tr>
<tr>
<td></td>
<td>What help do you have?</td>
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<tr>
<td></td>
<td>Do you have transportation?</td>
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<tr>
<td></td>
<td>Do you have a telephone?</td>
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<tr>
<td>Ability to provide care</td>
<td>What is your overall health?</td>
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<tr>
<td></td>
<td>What are you able to do?</td>
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<tr>
<td></td>
<td>What limits you?</td>
</tr>
<tr>
<td></td>
<td>Do you have a primary care provider?</td>
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<tr>
<td></td>
<td>Physical health: Assess the caregiver’s stamina, range of motion, vision,</td>
</tr>
<tr>
<td></td>
<td>strength, and comorbidities.</td>
</tr>
<tr>
<td></td>
<td>Mental health: Screen for anxiety, depression, sleep disorder, and coping</td>
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<tr>
<td></td>
<td>skills.</td>
</tr>
<tr>
<td></td>
<td>Cognitive abilities: Assess the caregiver’s judgment and memory.</td>
</tr>
<tr>
<td>Competing demands</td>
<td>What are your household responsibilities?</td>
</tr>
<tr>
<td></td>
<td>Do you have dependents (children, disabled or elderly relatives)?</td>
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<tr>
<td></td>
<td>What is your employment situation?</td>
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<tr>
<td></td>
<td>What other responsibilities do you have (e.g., school, religious/volunteer</td>
</tr>
<tr>
<td></td>
<td>activities)?</td>
</tr>
<tr>
<td>Knowledge and skill</td>
<td>Do you have any prior experiences with caregiving?</td>
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<tr>
<td></td>
<td>What is your understanding of the care recipient’s disease?</td>
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<tr>
<td></td>
<td>What information and/or skills training is needed to perform the required</td>
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<tr>
<td></td>
<td>tasks of caregiving (e.g., patient pain management, nutrition, skin care,</td>
</tr>
<tr>
<td></td>
<td>assistance with mobility)?</td>
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<tr>
<td></td>
<td>What coping strategies do you use?</td>
</tr>
<tr>
<td></td>
<td>What self-care actions do you perform?</td>
</tr>
<tr>
<td></td>
<td>Are you aware of available resources and respite care?</td>
</tr>
</tbody>
</table>

Note. Based on information from Family Caregiver Alliance, 2012; Leenerts et al., 2007; Northouse et al., 2012.

In research as well as clinical practice, measurement of caregiver burden should be done using multidimensional tools. Reviews about the impact of caregiving have included a number of scales designed to assess a variety of caregiver outcomes in research (Van Durme, Macq, Jeanmart, & Gobert, 2012), such as burden, needs, and QOL (Deeken, Taylor, Mangam, Yarbroff, & Ingham, 2003). A resource inventory of selected caregiver assessments for practitioners is available through the Family Caregiver Alliance (2012). Many of the tools that measure objective burden include components such as the number and type of caregiving tasks encompassing physical care, instrumental care, and time demands. While these tools itemize the amount of care that caregivers provide, they do not measure the impact and distress that caregivers experience and may not truly identify caregivers at risk for adverse outcomes from the demands of providing care.

Subjective measures of caregiver burden also need to be part of the assessment. How caregivers feel about their caregiving role, responsibilities, and the distress they experience may be more revealing than just objective measures. For example, one may be providing heavy
personal caregiving activities but find meaning and reward in being a caregiver. The converse may apply if one is not able to keep up and views caregiving as an imposition. Instruments identified in the reviews by Deeken et al. (2003) and Van Durme et al. (2012) were validated in various caregiving populations and had 1–200 items. Simpler and shorter tools are less burdensome and most practical for clinical situations, particularly in primary care or family practice. Ideally, a brief screening tool for clinical practice should include measures of both objective and subjective burden items, for example, asking caregivers to specify a patient concern or task they perform for their loved one and then ask to rate the amount of distress or how much difficulty they experience related to the concern or task (Honea et al., 2008). One very simple tool for caregivers to complete is the Distress Thermometer (DT) (National Comprehensive Cancer Network®, 2014). Zwahlen, Hagenbuch, Carley, Recklitis, and Buchi (2008) found the DT to have good diagnostic utility in screening for depression and anxiety relative to the Hospital Anxiety and Depression Scale in a sample of more than 300 family caregivers of patients with cancer. Bevans et al. (2011), however, found the DT to be of less diagnostic utility in their study of family caregivers in the transplant setting when the DT was compared to the emotional subscales of the Brief Symptom Inventory (Derogatis & Spencer, 1993) and the Multidimensional Fatigue Symptom Inventory (Stein, Jacobsen, Blanchard, & Thors, 2004).

A useful guide for practitioners is available through the Family Caregiver Alliance website at https://caregiver.org/caregivers-count-too-s3-nuts-bolts-caregiver-assessment. After completing the assessment, nurses can then target and prioritize interventions for caregivers according to the needs or issues identified.

Evidence-Based Interventions

Interventions have been designed to address caregiver burden, preparedness, self-efficacy/competence, and other outcomes affecting caregiver QOL. Opportunities arise at various times across the cancer disease trajectory for providers to initiate interventions to assist caregivers in their myriad challenges. Most intervention trials have been conducted around diagnosis (even advanced-stage disease) and within months of active treatment onset (Clark et al., 2013; Jepson et al., 1999; Northouse et al., 2013; Rexilius, Mundt, Megel, & Agrawal, 2002) or conversely, at the end of life (Hudson, Thomas, Quinn, Cockayne, & Braithwaite, 2009; McMillan et al., 2006; O’Hara et al., 2010). Both ends of the trajectory continuum are times of uncertainty and threatened by anticipated grief and loss (Choi et al., 2012), while times of transition after active treatment are also fraught with uncertainty and new challenges for caregivers (Given, Sherwood, & Given, 2011).

Targets of interventions have been directed to the patient and caregiver as a dyad, to the caregiver alone, or in groups of caregivers with or without their care recipients (Northouse, Katapodi, Song, Zhang, & Mood, 2010). So far, some interventions significantly, albeit with small to medium effect sizes, reduce caregiver burden or improve other caregiver outcomes. Evidence-based interventions aimed at improving caregiver outcomes, including those in cancer populations, are gradually mounting in number. Thus, in 2013, a total of 10 systematic reviews and three meta-analyses were found from the past decade (see Table 7-4). Recent intervention trials for caregivers not found in the reviews are included in Table 7-5. The three primary approaches to caregiver interventions are (a) psychotherapy/therapeutic counseling, (b) psychoeducation and skills training, and (c) psychosocial/supportive. More comprehensive integration of a combination of these approaches is referred to as a multicomponent intervention (Sorensen, Pinquart, & Duberstein, 2002).
### TABLE 7-4  Systematic Reviews and Meta-Analyses of Interventions and Caregiver Outcomes

<table>
<thead>
<tr>
<th>Source</th>
<th>Type (SR/MA) and Number of Articles (K)</th>
<th>Population and Outcome(s)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martire et al., 2004</td>
<td>MA K = 70</td>
<td>Patients with chronic illness, including cancer</td>
<td>Significant but small effect sizes for reducing CG burden, depression, and anxiety were found. Effects were strongest in nondementing illnesses and for psychosocial interventions that targeted the individual family member and that addressed relationship issues.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Depression, anxiety, relationship satisfaction, CG burden</td>
<td></td>
</tr>
<tr>
<td>Hudson, 2005</td>
<td>SR K = 13</td>
<td>Patients with cancer receiving palliative/ EOL care</td>
<td>Of the 13 studies found, 5 were deemed to have reasonable evidence without methodologic flaws and with sufficient data on support- and information-focused interventions for family CGs, yet none were specifically in palliative care. Interventions were delivered mostly in the home and/or via telephone for individuals, although one was via group. Dose of interventions varied from 3–6 sessions. Positive outcomes from interventions in 2 studies indicated greater confidence in ability and/or greater satisfaction in providing care. One study with no effect found a trend that CGs with physical problems were more burdened.</td>
</tr>
<tr>
<td>McMillan, 2005</td>
<td>SR K = 21</td>
<td>Patients with cancer or dementia at EOL</td>
<td>Both educational and supportive interventions were tested using both telephone and in-person sessions, but it was still unclear which approach is best. Mixed results occurred across studies, where some showed little or no impact on improving CG depression and others reported improved CG QOL, reduced depression and burden, and greater knowledge and mastery postintervention.</td>
</tr>
<tr>
<td>McLean &amp; Jones, 2007</td>
<td>SR K = 5</td>
<td>Patients with cancer at EOL</td>
<td>Psychosocial interventions focused on couples’ relationship quality and other perceptions of distress. One descriptive study and 2 RCTs showed positive effects in reducing distress and improving couples’ relationship quality and QOL. In both RCTs, positive effects were noted at 3 months, but they were not sustained at 6 months when measured again in one of the RCTs.</td>
</tr>
<tr>
<td>Honea et al., 2008</td>
<td>SR K = 12</td>
<td>Patients with cancer CG burden or strain</td>
<td>Psychoeducational, psychotherapy, and supportive interventions had significant but small effect sizes that are likely to reduce CG burden across cancer settings and applied to individuals or groups. Multicomponent interventions may be most beneficial for CGs reporting greater burden and to CGs who are older, are female, and report more subjective burden. Interventions have a stronger effect at reducing burden when relationship issues between the patient and CG are addressed. A number of studies were able to report positive psychosocial outcomes yet did not show reduction in CG burden.</td>
</tr>
</tbody>
</table>

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TABLE 7-4  Systematic Reviews and Meta-Analyses of Interventions and Caregiver Outcomes (Continued)

<table>
<thead>
<tr>
<th>Source</th>
<th>Type (SR/MA) and Number of Articles (K)</th>
<th>Population and Outcome(s)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorenz et al., 2008</td>
<td>SR, K = 122</td>
<td>Patients with cancer and other terminal or chronic illnesses receiving palliative/EOL care</td>
<td>Although small effect sizes were noted, weak to moderate evidence suggests CG interventions, particularly when comprehensive and individually targeted, can improve various measures of CG burden. Moderate evidence existed for palliative care interventions to improve CG satisfaction.</td>
</tr>
<tr>
<td>Hartmann et al., 2010</td>
<td>MA, K = 52</td>
<td>Patients with chronic illness (cancer, cardiovascular disease, arthritis, and others)</td>
<td>Interventions were categorized as either psychoeducational or family relationship–focused. Statistical significance was noted with small to moderate effect sizes for improved physical and mental health, QOL, and self-efficacy with sustained effect up to 7 months or more. Higher effects of benefit were seen in relationship-focused interventions compared to psychoeducational interventions with regard to health outcomes for both patients and families.</td>
</tr>
<tr>
<td>Hudson et al., 2010</td>
<td>SR, K = 14</td>
<td>Patients with cancer receiving palliative care</td>
<td>Most interventions were aimed at coping training. Comparison groups were used. Psychosocial supportive interventions aimed at partner-guided pain management increased self-efficacy and lowered depression; with regard to sleep behaviors, lower depression rates and improved sleep quality were noted. Psychoeducational interventions improved CG preparedness, competence, and rewards and reduced the number of unmet needs.</td>
</tr>
<tr>
<td>Northouse et al., 2010</td>
<td>MA, K = 29</td>
<td>Patients with cancer</td>
<td>Psychoeducational, skills training, and counseling interventions had small to medium effects, yet they significantly reduced CG burden, improved coping ability, enhanced QOL, and increased self-efficacy.</td>
</tr>
<tr>
<td>Candy et al., 2011</td>
<td>SR, K = 11</td>
<td>Patients with cancer in terminal phase of disease</td>
<td>Most interventions (k = 9) included psychological support of CGs and advice on caring and helped in the short term to buffer against psychological distress, although with small effect size. Other interventions (k = 2) provided indirect support for CGs by addressing patient care needs. Overall, CGs receiving an intervention compared to those in a control group had marginally better QOL and ability to cope with their CG role, although the difference was not statistically significant.</td>
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<table>
<thead>
<tr>
<th>Source</th>
<th>Type (SR/MA) and Number of Articles (K)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Harding et al., 2012</td>
<td>SR K = 33</td>
<td>Patients with cancer receiving palliative/EOL care CG burden/stress, preparedness, self-efficacy, coping skills, psychological distress, problem-solving ability, social support, and QOL, among others</td>
<td>One-on-one psychotherapeutic and psychoeducational interventions addressing coping improved competence, rewards, and preparedness ratings and reduced depression; when psychotherapy was administered to patient-CG dyads, CGs reported less uncertainty, greater communication and self-efficacy, improved QOL, and reduced stress and depression. Respite improved QOL and patient symptoms, although not all the studies showed an effect.</td>
</tr>
<tr>
<td>Northouse et al., 2012</td>
<td>SR K = 5 MAs</td>
<td>Patients with chronic illness, including cancer Multiple CG well-being outcomes</td>
<td>Categories of interventions were (1) psychoeducational: managing patient symptoms and other aspects of care; skills training for coping, communication, and problem solving; and (2) therapeutic counseling with focus on strengthening relationships, managing conflict, or dealing with loss. Interventions had positive effects on CG and patient outcomes whether addressed to CGs alone or jointly with patients. Interventions that addressed relationship issues with the patient-caregiver dyad, particularly about communication and joint problem solving, had more positive effects in the cancer population, which was thought to be due to synergy that influences the well-being of both in the dyad. Longer interventions (dose) were more likely to improve CG coping, and those designed to improve CG knowledge had larger effects on both patient and CG outcomes than those designed to decrease depression in CGs.</td>
</tr>
<tr>
<td>Waldron et al., 2013</td>
<td>SR K = 6 RCTs</td>
<td>Patients with cancer CG QOL</td>
<td>All studies were classified as skills training interventions using a cognitive behavioral approach that included psychoeducation; most were delivered by nurses in person, via telephone, or in combination. Small to nil effect sizes were found. Those with larger effect sizes targeted CGs’ problem-solving and communication skills.</td>
</tr>
<tr>
<td>Source</td>
<td>Population</td>
<td>Characteristics for Intervention</td>
<td>Findings</td>
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<tr>
<td>Hudson et al., 2005</td>
<td>Patients receiving palliative/end-of-life care (N = 106)</td>
<td>A psychoeducational and supportive nurse-delivered intervention with 2 in-home visits and 1 telephone call between visits used to prepare CG for care of self and patient Guidebook and audiotape used to complement nurse interactions Randomized to usual care or usual care plus new intervention</td>
<td>No significant effects were found related to preparedness, self-efficacy, competence, or anxiety, although subjects in intervention group reported a significantly more positive CG experience.</td>
</tr>
<tr>
<td>Carter, 2006</td>
<td>Patients with advanced cancer (N = 30)</td>
<td>A brief behavioral caregiver sleep intervention delivered in two 1-hour sessions Elements included information about stimulus control, relaxation, cognitive therapy, and sleep hygiene. Randomized between intervention and attention control group</td>
<td>All CGs improved scores in sleep, QOL, and depression over time. CGs in the sleep intervention group, though, had greater improvements in sleep and depression than the control group.</td>
</tr>
<tr>
<td>Collinge et al., 2007</td>
<td>Patients with mixed cancers (N = 99 CGs and patients)</td>
<td>A 6-hour session providing instruction in massage and touch therapy to groups of patient and CG couples aimed to build CG efficacy Pre- and post-test design Elements included discussions about touch in caregiving and concerns, as well as the role of communication.</td>
<td>CGs with high sense of burden were least likely to report higher self-efficacy in massage; however, those with lower schedule burden reported higher self-efficacy predicted by more frequent massage during the week and showed increasing self-efficacy over time.</td>
</tr>
<tr>
<td>Hudson et al., 2008</td>
<td>Patients with cancer and a few other illnesses receiving home-based palliative care (N = 74, with n = 44 completing all three data collection sets)</td>
<td>Psychoeducational group intervention delivered in 3 consecutive weekly sessions Nonrandomized</td>
<td>Positive effects were found for preparedness for role, competence, rewards, and having information needs met from baseline to program completion and maintained at 2-week follow-up.</td>
</tr>
<tr>
<td>O’Hara et al., 2010</td>
<td>Patients with advanced cancer receiving palliative care (N = 198 CGs)</td>
<td>Patient-focused ENABLE II aimed at increasing patient QOL, decreasing symptom intensity, and lowering depressed mood, thereby decreasing CG burden Delivered by nurse specialist in 4 weekly phone sessions Randomized between intervention and usual care</td>
<td>No significant differences in CG burden were noted between groups.</td>
</tr>
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### TABLE 7-5 | Intervention Trials With Caregiver Outcomes (Continued)

<table>
<thead>
<tr>
<th>Source</th>
<th>Population</th>
<th>Characteristics for Intervention</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Savundra-nayagam, Montgomery, Kosloski, &amp; Littler, 2011</td>
<td>Patients with Alzheimer disease/dementia, multiple sclerosis, Parkinson disease, cancer, stroke, or heart or endocrine disease (N = 115 intervention, N = 95 comparison)</td>
<td>Psychoeducational Powerful Tools for Caregivers (PTC) tested for effectiveness in reducing 3 types of CG burden: stress, objective, and relationship. Nonrandomized between PTC and comparison group.</td>
<td>Intervention group had lower stress burden and objective burden but no effect on relationship burden.</td>
</tr>
<tr>
<td>Sherwood et al., 2012</td>
<td>Patients with advanced cancer (N = 169 dyads)</td>
<td>Problem-solving intervention aimed at increasing CG assistance with symptom management. Randomized between a nurse-delivered symptom management intervention and a coach-led group.</td>
<td>No significant main effect of the problem-solving intervention in symptom assistance was noted at 10 weeks; however, CGs with lower depressive symptoms were more likely to be assisting with symptom management at 10 weeks if they had received nurse-delivered interventions; spousal CGs who provided assistance at baseline were less likely than nonspouses to provide assistance at 10 weeks.</td>
</tr>
<tr>
<td>Chih et al., 2013</td>
<td>Patients with advanced breast, lung, or prostate cancer (N = 235 patient-CG dyads)</td>
<td>Online symptom reporting system: Comprehensive Health Enhancement Support System, with or without use of Clinician Report symptom reporting system.</td>
<td>Pooled analysis from 2 randomized controlled trials comparing outcomes at 6 and 12 months. Less negative mood was noted for those in the group with Clinician Report; no significant difference was seen in physical burden at either time point.</td>
</tr>
<tr>
<td>Clark et al., 2013</td>
<td>Patients with advanced cancer receiving radiotherapy and their CGs (N = 131)</td>
<td>Randomized between usual care and a 6-session (90 min. each) structured multidisciplinary intervention that addressed 5 domains of QOL, plus 10 brief structure phone counseling sessions. CGs were invited to attend 4 of the 6 sessions.</td>
<td>Intervention was primarily aimed at addressing patient QOL and did not impact CGs in this study. CG QOL was maintained at a low level across time in both intervention and control groups.</td>
</tr>
<tr>
<td>Source</td>
<td>Population</td>
<td>Characteristics for Intervention</td>
<td>Findings</td>
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<tr>
<td>Collinge et al., 2013</td>
<td>Patients with cancer (any stage or treatment) and their CGs (N = 97 dyads)</td>
<td>Psychoeducational intervention using multimedia: DVD and print manual (no direct instructions) for home-based instruction on touch, caring, and cancer. Included topics on attitudes, communication about touch in cancer, psychological preparation for giving and receiving touch, safety precautions, massage techniques for comfort and relaxation with practice in the home setting over 4 weeks. Randomized to massage group or attention control (reading) group (with suggested sessions lasting 5–20 minutes three times/week)</td>
<td>Significant gains were reported for intervention group CGs in confidence, comfort, and self-efficacy in using touch/massage as forms of caregiving. Patients reported significant reductions in all symptoms after both activities (reading or massage).</td>
</tr>
<tr>
<td>McLean et al., 2013</td>
<td>Patients with end-stage cancer and their CGs (N = 42 dyads)</td>
<td>8 couple-based, emotionally focused therapy intervention sessions delivered by psychologist Data collected at baseline, post-intervention, and 3 months postintervention Randomized to intervention or standard care</td>
<td>Significant improvement in marital functioning for emotionally focused therapy group. No significant differences were seen for the Caregiver Burden Scale, Beck Depression Inventory, or Beck Hopelessness Scale.</td>
</tr>
<tr>
<td>Northouse et al., 2013</td>
<td>Patients with advanced cancer (stages III–IV) and their CGs (N = 484 dyads)</td>
<td>Randomized between control group and two intervention group programs: Brief (3 sessions) versus Extensive (6 sessions) delivered over 10 weeks Experimental condition based on the FOCUS Program using a combination of in-home and telephone visits offering information and support</td>
<td>A significance in group by time interactions revealed at 3 months an improvement in dyadic coping (less avoidant coping), self-efficacy, and social QOL for those receiving the intervention, though not maintained at 6 months. Dyads receiving the Brief intervention showed significant increase in use of healthy behaviors at 3 months, though also not maintained at 6 months. CGs in both intervention groups had significantly improved emotional QOL (p &lt; 0.05) that was maintained from the 3-month to 6-month time points.</td>
</tr>
</tbody>
</table>

CG—caregiver; QOL—quality of life
Recommended for Practice

The challenge in determining and making recommendations for practice must be weighed against what is statistically significant (evidence-based) versus what is clinically significant. Clinical significance is usually regarded as an individual’s return to normal function (Jacobson, Roberts, Berns, & McGlinchey, 1999), whereas statistical significance requires large sample sizes to show a large effect. Many of the studies to date have had small to medium effect sizes in measured outcomes. The recommendations for practice versus what is likely or unlikely to be helpful to ease caregiver burden, depression, or anxiety and improve other outcomes such as preparedness, self-efficacy, and ultimately QOL are based on the literature. However, clinicians need to judge what is clinically meaningful and important in their practice when making recommendations to individual caregivers or dyads. Therapeutic counseling, psychoeducation and skills training, and psychosocial interventions, especially in combination, are recommended for practice (Northouse et al., 2010).

Psychotherapy/Therapeutic Counseling

The development of a therapeutic relationship between a caregiver and a mental health professional is a hallmark of psychotherapy and therapeutic counseling (Norcross & Lambert, 2011). Such rapport and counseling help individuals to explore the feelings and thoughts associated with the issues of caregiving and learn certain skills and strategies for managing overwhelming feelings and thoughts. Therapeutic counseling can also be used to assist with strengthening the relationship between the patient and the caregiver (Northouse et al., 2010). Cognitive behavioral therapy is an abbreviated type of psychotherapy that focuses on present thinking, behavior, and communication rather than on past experiences, and it is directed toward problem solving. These interventions can help caregivers work through difficulty with issues of time management, workload burden, and emotional reactivity and to find ways to adapt and reframe their thinking so as to reengage in positive experiences.

Psychoeducational and Skills Training

Psychoeducational interventions in general are structured programs aimed at providing information. Information can be about the care recipient’s disease process, treatment, and symptom management, as well as resources or services for family caregivers (Lorenz et al., 2008). Skills training involves interventions that aim to prepare caregivers to address specific clinical problems with the care recipient, such as pain management, mobility, skin care, massage, anorexia, or diarrhea. Caregivers can learn to identify helpful strategies for coping, communication, and problem solving, such as dealing with fears and performance of self-care. Psychoeducation and skills training interventions demonstrated significant, although small to moderate, effect sizes; those targeting caregiver communication skills and problem solving had larger effect sizes (Waldron, Janke, Bechtel, Ramirez, & Cohen, 2013). Delivery can be in groups or individually with a caregiver.

Carter (2006) conducted a randomized controlled trial to test a brief behavioral caregiver sleep intervention that was delivered over two one-hour sessions. Caregivers were randomized between the intervention and an attention control group. Elements of the psychoeducation intervention were information about stimulus control, relaxation, cognitive therapy, and sleep hygiene. While all caregivers improved scores in sleep, QOL, and depression over time, the caregivers in the sleep intervention group had greater improvements in sleep and depression than those in the control group.
Psychosocial/Supportive Interventions

Psychosocial refers to the interrelationship between a person and his or her social network or environment. Support can be in the form of financial, instrumental, physical, emotional, spiritual, or social support. Psychosocial/supportive interventions, then, are those that bring a caregiver together with others. This type of intervention allows for a forum for discussion of issues, successes, and feelings regarding caregiving (Hudson, Remedios, & Thomas, 2010).

Psychosocial interventions include teaching caregivers how to use problem-solving skills to meet their caregiving demands. One such intervention tested by Cameron, Shin, Williams, and Stewart (2004) was a one-hour in-person intervention delivered to caregivers alone in the clinic, which introduced a five-step problem-solving approach/techniques and encouraged caregivers to COPE (be Creative, Optimistic, Plan, and Obtain expert information). When retested at four weeks postintervention, the caregivers showed decreased emotional tension and increased confidence and problem-solving ability.

Support is especially effective when caregivers are able to identify exactly what they need in the way of help. When able to identify specific needs and ask for help, caregivers may subsequently experience a greater sense of control, peace of mind, and relief from stress even when the situation is less than ideal. Effects of psychosocial interventions may be stronger when targeted to the individual family member and when relationship issues are addressed (Martire, Lustig, Schulz, Miller, & Helgeson, 2004).

Multicomponent Interventions

Multicomponent interventions have been found to be most effective in reducing caregiver burden and other caregiver outcomes (Honea et al., 2009). Using a combination of therapeutic counseling, psychoeducation and skills training, and psychosocial support in interventions provides a comprehensive approach.

Effectiveness Not Established

Skills Training Directed at Patient Symptom Control

Several studies conducted were not able to establish effectiveness in improving caregiver outcomes for those at greatest risk of burden. Possible explanations for this may be the content, timing, or dose of intervention, or even the selected outcome measured. For example, a psychoeducational/skills training intervention about symptom control was delivered to 237 patient-caregiver dyads. In what may appear to be a sufficient dose of contacts (five in-person plus five over the telephone over a 20-week period), results did not show effectiveness in reducing caregiver depression over that time (Kurtz, Kurtz, Given, & Given, 2005).

Skills Training in Massage and Touch Therapy

Collinge, Kahn, Yarnold, Bauer-Wu, and McCorkle (2007) conducted skills training in massage and therapeutic touch for patient and caregiver couples to build caregiver self-efficacy. Included in the six-hour session were discussions about touch in caregiving and concerns, as well as the role of communication. The researchers found that those with a high sense of burden were the least likely to report self-efficacy in massage, and those with lower schedule burden reported higher self-efficacy, which predicted more frequent massage during the following week, increasing caregivers’ perceived self-efficacy over time. Collinge et al. (2013) later updated their intervention to be delivered via a multimedia DVD and print manual for home-based instruction and practice, leading to positive results for both care recipients and caregivers.
Respite

Support can provide *respite*, that is, a temporary relief from the stress of caregiving. Respite can be in the form of concrete services, such as care or companionship for the care recipient at home or in a convalescent center or adult daycare center. Services can also be those that provide for role tasks and activities previously performed by the care recipient such as meal preparation, home maintenance, repair, or yardwork. Although it is helpful on a temporary basis, respite has not been found to be effective in significantly reducing overall caregiver burden (Honea et al., 2008). Respite can be viewed not just as concrete services, but also as activities that caregivers can incorporate that do not require them to leave their loved one. Such activities, defined by the caregiver as those that allow a bit of respite within the midst of chaos, could include reading, watching a movie, listening to music, taking a long bath, or visiting with family or friends (Honea, 2012).

Family/Caregiver Teaching Points

Four general categories of caregiver needs are information, coping skills, communication, and self-care (Given et al., 2012; Honea, 2012). Caregivers need information about the disease, prognosis, treatment, expected side effects and their management, hands-on care skills, and accessing and navigating the healthcare system, including resources. They may need to be coached in healthy coping strategies and communication. The relationship between the caregiver and care recipient affects how they cope and communicate with each other. It can take time and practice to develop good communication skills with others, especially when one is not used to dealing with healthcare providers. Nurses and other providers need to partner with family caregivers by keeping communication open with both the caregiver and the care recipient, encouraging teamwork between them (Bowman, Rose, Radziwiecz, O’Toole, & Berila, 2009). Nurse navigators and case managers, for example, may be available and are a valuable resource to help caregivers negotiate, and they can advocate on behalf of caregivers. Successful partnerships between healthcare providers and caregivers can foster caregivers’ self-care abilities and enhance their self-care activities to improve health (Teel & Leenerts, 2005).

It is important for nurses to keep in mind the context of the caregiving situation and where on the illness trajectory the care recipient is. Both of these concurrent processes color the stress and stress appraisal processes and, ultimately, the caregiver’s psychobehavioral and physiologic responses. For example, Williams and Bakitas (2012) reminded nurses and other providers of beneficial and important topics to include in interactions with caregivers such as (a) reinforcing positive aspects of caregiving, (b) cultivating open communication, and (c) acknowledging the prior experiences and social foundation of the caregiver’s life that can be supportive or burdensome.

Evidence-based interventions to reduce caregiver burden are therapeutic counseling, psychoeducational and skills training, and psychosocial supportive interventions (Honea et al., 2008, 2009; Northouse et al., 2010). Key elements to specifically include are assistance with

- Strategies for coping
- Communication
- Problem-solving skills.

Although there may be a current lack of evidence to support reductions in caregiver burden, depression, or other outcomes at this time, the following should be tailored to individual situations.
Skills training directed at patient symptom control
Training in massage and therapeutic touch
Respite (exploring what concrete services and/or activities are acceptable forms of respite for an individual caregiver)

Such interventions should not be discarded offhandedly. Certainly, when dealing with individual caregivers and their care recipients, it is important to employ interventions that are evidence based and those that have yet to show statistical significance but that may be clinically meaningful in each unique caregiving situation.

Expected Patient Outcomes

The expected outcomes are obvious in theory but not always as obvious to achieve. Combinations of intervention approaches are targeted to reduce or improve the negative outcomes of caregiving. Caregiver burden, whether viewed as objective, subjective, or relationship burden, may not necessarily be recognized as such by caregivers. Yet, hints of caregiver burden may manifest in symptoms of sleep difficulties, depression, anxiety, tension, panic, or behaviors that adversely affect a caregiver’s health. Skills competency, problem solving, and coping skills can be learned, which may reduce caregiver burden and ultimately enhance caregiver QOL.

Need for Future Research

There is a continued need for intervention studies that target caregiver burden in its manifested symptoms and behaviors. Intervention studies are needed that address caregiver burden across the cancer disease trajectory. Because of the scarce literature on reducing caregiver burden and improving caregiver QOL during times of remission, this may be fertile ground for understanding, as caregivers usually continue aspects of the role during this phase. Novel approaches need to be designed to bring interventions where caregivers can benefit most with regard to dose and time for interventions. Testing of interventions delivered through the use of technology such as the Internet and telecommunications should be explored to allow those unable to attend on-site individual or group interventions because of time commitments or transportation issues to participate and therefore be less isolated.

Conclusion of Case Study

R.M. has others in the home with her, yet she has many responsibilities. She is responsible for overseeing her husband’s medical appointments, medications, and nutrition. She works to provide the family income and health insurance. Assessing what resources she may have through her employer can help her decide how to take time off from work through the Family and Medical Leave Act. She also supervises her mother, though she does not live with her. R.M. could use help to identify other resources that may be available to her, such as informing her about nurse case managers with the insurers to help coordinate and facilitate medical care. She complains that she is not sleeping well and has mentioned skipping her needed medications and meals. She could use a referral to a social worker and to support groups available in her area or online. She should be assessed.
for other important potential health problems, such as nutrition, coping strategies, and problem-solving, communication, and relationship issues. Reviewing sleep hygiene guidelines with her may help her enhance her sleep. Giving her permission to seek care for herself is important in helping her prioritize her self-care. Exploring her relationships with her husband and the rest of her family may help identify communication issues or interpersonal conflicts that may be present, and referrals for counseling could be offered.

**Conclusion**

Caregivers of a loved one with cancer are overwhelmed by the myriad activities and responsibilities of caregiving. Competing responsibilities, uncertainty, anxiety, fear, and the sense of not being prepared or competent to fulfill their role as caregiver create significant stress. Caregiver burden, whether as objective, subjective, or relationship burden, is spawned by these factors. Assessment is essential to identify burden and other negative consequences of caregiving so that nurses can apply targeted interventions that may reduce caregiver burden, anxiety, or depression and improve other caregiver outcomes, including QOL.

**References**


Given, B.A., Given, C.W., & Sherwood, P.R. (2012). Family and caregiver needs over the course of the cancer trajectory. *Journal of Supportive Oncology, 10*, 57–64. doi:10.1016/j.suponc.2011.10.003


CHAPTER 8

Chemotherapy-Induced Nausea and Vomiting

Carrie Tompkins Stricker, PhD, RN, AOCN®, and Susan W. Wesmiller, PhD, RN

Case Study

L.M. is a 43-year-old woman with stage II invasive ductal breast cancer. Her breast cancer is node positive, estrogen-receptor and progesterone-receptor negative, and negative for HER2/neu oncogene overexpression. Her oncologist plans chemotherapy with four cycles of doxorubicin and cyclophosphamide (AC) every two weeks, to be followed by four cycles of paclitaxel every two weeks. She presents to the office today for her first cycle of chemotherapy, and the nurse meets with her to discuss her antiemetic regimen.

Overview

Despite significant advances in the prevention and management of nausea and vomiting, these symptoms remain two of the most severe and distressing for individuals undergoing chemotherapy and lead to decreased adherence to cancer therapies and a reduction in quality of life (QOL) and daily functioning (Fernández-Ortega et al., 2012; Pirri et al., 2013; Viale, Grande, & Moore, 2012). Fortunately, a growing arsenal of effective agents is available to prevent and treat chemotherapy-induced nausea and vomiting (CINV) and can be used in combination to block the multiple pathways that contribute to CINV. When used appropriately in combination, agents such as dexamethasone, serotonin (5-HT₁) receptor antagonists, and neurokinin-1 (NK₁) receptor antagonists can prevent as much as 70%–80% of vomiting with even the most emetogenic chemotherapy treatments, although management of nausea remains a greater challenge (Bouganim et al., 2012).

Despite pharmacologic advances, inconsistent prescription of and adherence to appropriate antiemetic therapy remain significant barriers to CINV prevention and management (Fatigoni & Roila, 2013; Gilmore et al., 2013). Oncology nurses have the opportunity and responsibility to play a critical role in ensuring optimal management of CINV by helping to identify patients with the greatest risk and by applying national and international guidelines for CINV prevention and management (Basch et al., 2011; Multinational Association of Supportive Care in Cancer [MASCC], 2004; National Comprehensive Cancer Network® [NCCN®], 2014; Roila,
There is some indication that computerized physician order entry systems will increase adherence to guidelines (Kadakia et al., 2014); however, expert oncology nursing care remains indispensable in reducing the incidence of and suffering associated with CINV by helping to ensure that patients receive evidence-based interventions. Prevention is clearly the best management for these debilitating symptoms.

The sensation of nausea and the act of vomiting are important reflexes that protect the gastrointestinal (GI) tract from toxic substances (Navari, 2013). Nausea is “a subjective phenomenon of an unpleasant sensation in the epigastrium and in the back of the throat that may or may not culminate in vomiting” (Dibble, Israel, Nussey, Casey, & Luce, 2003, p. E40). Vomiting is “a physical protective reaction to the ingestion of toxins resulting in the expulsion of gastric contents through the mouth” (Dibble, Casey, Nussey, Israel, & Luce, 2004, p. E1). Retching is the unsuccessful attempt to expel contents from the stomach (Janelins et al., 2013).

CINV typically is classified into categories of acute, delayed, anticipatory, breakthrough, or refractory CINV (see Table 8-1) (Jordan, Gralla, Jahn, & Molassiotis, 2014; Irwin, Lee, Rodgers, Starr, & Ralph-Webber, 2012). Delayed CINV is more than twice as common as acute CINV in individuals receiving moderately or highly emetogenic chemotherapy regimens that include agents such as cisplatin and doxorubicin (Ballatori et al., 2007; Boccia, Grunberg, Franco-Gonzales, Rubenstein, & Voisin, 2013). The pattern of delayed CINV is dependent on the chemotherapy drug involved. It may start the first day after chemotherapy and last for a few days. At other times, for example with cisplatin, after an acute peak in the first 24 hours, CINV may be delayed until the second or third day after chemotherapy administration and last for three days or longer (Jordan et al., 2014).

Anticipatory CINV is very difficult to manage, and prevention of acute CINV is the best strategy for avoiding this extremely challenging clinical phenomenon (Irwin et al., 2012). The trigger for anticipatory CINV may be only a thought, smell, or sight of something reminiscent of chemotherapy. As with anticipatory CINV, both breakthrough and refractory CINV often develop as a result of inadequate control of acute or delayed CINV, again underscoring the importance of preventing CINV with optimal antiemetic therapy starting with the first cycle of chemotherapy treatment.

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Acute</td>
<td>Nausea or vomiting that occurs within the first 24 hours of receiving chemotherapy</td>
</tr>
<tr>
<td>Delayed</td>
<td>Any nausea or vomiting that occurs more than 24 hours after chemotherapy administration; typically peaks 48–72 hours and may last as long as 7 days</td>
</tr>
<tr>
<td>Anticipatory</td>
<td>A conditioned response to chemotherapy based on prior CINV experience, leading to nausea and/or vomiting when the patient is exposed to stimuli associated with the chemotherapy and related nausea and vomiting</td>
</tr>
<tr>
<td>Breakthrough</td>
<td>CINV that occurs despite using prophylactic medications and requires the use of “rescue” therapies</td>
</tr>
<tr>
<td>Refractory</td>
<td>CINV that occurs after subsequent cycles of chemotherapy after the use of prophylactic and breakthrough medications have failed</td>
</tr>
</tbody>
</table>

Note. Based on information from Basch et al., 2011; Jordan et al., 2014.
Prevalence

Although clinical trials of antiemetic therapy report control rates for nausea and vomiting to be as high as 70%–80%, these statistics likely do not reflect the actual control rates in clinical practice because of both patient and provider factors (Ruhlmann & Herrstedt, 2012). In patient surveys, up to 30% of individuals receiving highly emetogenic chemotherapy reported acute-phase vomiting and nearly half reported delayed vomiting, whereas with moderately emetogenic chemotherapy, 10%–25% of patients reported acute-phase vomiting and 28%–40% reported delayed vomiting (Jordan et al., 2014; Molassiotis et al., 2014). Rates of nausea are even higher, with acute nausea occurring in up to 52% of individuals receiving moderately or highly emetogenic chemotherapy and delayed nausea occurring in 52%–82% of individuals (Boccia et al., 2013; Molassiotis et al., 2014).

Delayed CINV continues to be a greater clinical challenge than acute CINV, with nausea being the greatest challenge (Flaherty, 2013). Although rates of acute CINV have markedly decreased in the past 20 years with the introduction of the 5-HT\textsubscript{3} receptor antagonists (e.g., granisetron, ondansetron, palonosetron), delayed nausea and vomiting remains problematic and is often underestimated (Viale et al., 2012). In a prospective study of 89 women receiving anthracycline-based adjuvant chemotherapy (e.g., AC) for breast cancer, the majority of whom received a 5-HT\textsubscript{3} receptor antagonist and/or dexamethasone for prevention of delayed CINV, daily rates of nausea were as high as 63% two to five days following treatment (Stricker & Velders, 2005). Recent studies have reported a similar incidence of delayed CINV, confirming the clinical challenge it presents (Fernández-Ortega et al., 2012). However, new evidence supports that palonosetron, a second-generation serotonin antagonist, may improve control rates (Boccia et al., 2013; Schwartzberg et al., 2014).

Anticipatory CINV remains one of the most difficult chemotherapy-related symptoms to manage. The incidence of anticipatory CINV did not decrease with the introduction of 5-HT\textsubscript{3} receptor antagonists and remains approximately 6%–7% for anticipatory vomiting and up to 30% for anticipatory nausea by the fourth cycle of chemotherapy (Kamen et al., 2014). The newest class of antiemetics, the NK\textsubscript{1} receptor antagonists, are not effective in the prevention of anticipatory CINV (Kamen et al., 2014). The National Cancer Institute (2013) cites Pavlovian classical conditioning as the theoretical mechanism that best describes anticipatory nausea, so it is not surprising that antiemetic medications are not effective, and the best treatment is the prevention of acute and delayed CINV.

Pathophysiology

The understanding of the pathophysiology of CINV continues to evolve as more research is focused on the neurotransmitter and emetic pathways. Currently, it is believed that CINV is caused by interactions among both peripheral and central mechanisms, neurotransmitters (serotonin, dopamine, substance P), and receptors (5-HT\textsubscript{3} and NK\textsubscript{1}) (Wickham, 2012). Although serotonin, dopamine, and substance P play the primary roles in inducing CINV, other neurotransmitters are implicated in CINV (see Figure 8-1) and include gamma-aminobutyric acid (known as GABA), histamine, and acetylcholine.

The sensory pathways that stimulate nausea and vomiting include vestibular, area postrema, and forebrain inputs, but the GI tract vagal afferent component of this system likely is the most influential factor (Horn, 2014). Following the administration of chemotherapy, neurotransmitters are released in both the GI tract and the brain where receptors for these neurotransmitters are found, predominantly serotonin (5-HT\textsubscript{3} receptors), substance P (NK\textsubscript{1} receptors), and possibly dopamine and γ-aminobutyric acid (GABA).
receptors), and dopamine (dopamine receptors). It is believed that the neurotransmitters may act independently or in combination to induce nausea and/or vomiting by binding to the target receptors and stimulating CINV-related neural pathways (Bayo et al., 2012). Chemotherapy and its metabolites activate receptors in the area postrema (the chemoreceptor trigger zone [CTZ]), the GI tract, and the cerebral cortex (mostly responsible for anticipatory nausea), which send impulses to the vomiting center (VC). The VC is now understood to be a cluster of neurons that comprise the vomiting motor circuitry, near the nucleus tractus solitarius in the medulla (Horn, 2014; Wickham, 2012). In response, efferent impulses are sent to the heart, lungs, cranial nerves, GI tract, and the abdominal muscles involved in emesis (Navari, 2013). Individuals may respond differently to the same stimulation of the VC, which helps to explain why some patients experience CINV and others do not.

In summary, it is now believed that CINV is caused by the interchange of the peripheral and central mechanisms; although definitely interwoven, they are also somewhat unique in their contribution to CINV.

**Peripheral Pathway**

Stimulation of nausea and vomiting peripherally in the GI tract is largely related to serotonin release, which is predominantly responsible for the development of acute CINV (Horn, 2014). As shown in Figure 8-2, enterochromaffin cells line the GI tract and house most of the body’s serotonin. When chemotherapy comes into contact with enterochromaffin cells, either directly from oral ingestion or indirectly via the bloodstream, damage occurs and serotonin is released. Serotonin subsequently binds to the 5-HT<sub>3</sub> receptors prevalent in the gut and transmits a potent signal to the VC in the brain via the vagal afferent fibers. Urinary levels of 5-hydroxyindoleacetic acid (5-HIAA), the main serotonin metabolite, return to baseline within 24 hours following high-dose cisplatin chemotherapy but may remain elevated beyond 24 hours following moderate-dose cisplatin and other moderately emetogenic agents. These data provide evidence that serotonin may play a role in the causation of delayed CINV in some cases, in addition to its predominant role in the pathogenesis of acute emesis (Hesketh, Van Belle, et al., 2003; Higa et al., 2006). The neurotransmitter substance P also is also found in the enterochromaffin cells of the gut (Horn, 2014), although its role in CINV via the peripheral pathway is considered to be secondary (Janelinsins et al., 2013).

**Central Pathway**

Stimulation of central neural pathways plays a critical role in the pathophysiology of CINV. The CTZ is located in the brain stem in an area that is not protected by the blood-brain barrier, so it has the ability to detect emetic agents in both cerebrospinal fluid and blood (Feyer & Jordan, 2011). NK<sub>1</sub> receptors with high affinity for substance P (an endoge-
nous ligand for NK₁ receptors) are concentrated in the nucleus tractus solitarius and, like serotonin, appear to be activated by chemotherapy (Janselsins et al., 2013). Once these receptors are activated, signals are transmitted via the vagal afferent nerves to the CTZ and then to the VC, mediating the induction of vomiting. Levels of substance P in the bloodstream are elevated more than 24 hours following chemotherapy and thus are believed to be associated with delayed CINV, although substance P may play a role in the pathogenesis of acute CINV as well (Higa et al., 2006).

Early preclinical studies have found a possible synergistic action between 5-HT₃ and NK₁ receptors, which may lead to improved treatment strategies for CINV (Darmani, Chebolu, Amos, & Alkam, 2011). Current research is focusing on receptor “crosstalk.” Though not yet entirely understood, there is evidence that the activation of 5-HT₃ receptors and NK₁ receptors may affect the cellular responses of the other system. The receptor crosstalk is believed to be the mechanism behind the increased success of second-generation serotonin antagonists, such as palonosetron (Rojas, Raje, Tsukamoto, & Slusher, 2014).

The understanding of nausea is less well defined than for emesis, but it is clearly a unique symptom that often occurs independently of vomiting or retching. Chemotherapy-induced vomiting is more successfully controlled than nausea, supporting evidence that other neural pathways are involved in nausea. Recent studies have shown that olanzapine, an antipsychotic that blocks transmission of multiple neurotransmitters at their receptor sites, includ-
ing dopamine, serotonin, catecholamines, acetylcholine (muscarinic), and histamine, may significantly aid the prevention and treatment of nausea (Navari, Gray, & Kerr, 2011).

**Impact**

Given the prevalence of CINV, careful examination of its impact is necessary. Symptom distress, physiologic consequences, and negative effects on QOL, functional status, and treatment adherence are all pertinent concerns. More recently, research began documenting the negative economic consequences of CINV.

**Symptom Distress**

Although patient perceptions of CINV have changed over time as antiemetic therapy has improved, both nausea and vomiting remain among the top five symptoms ranked as most severe by heterogeneous samples of individuals with cancer, as documented by a series of similar descriptive studies conducted in the 1980s and 1990s to determine patients’ perceptions of the severity of chemotherapy side effects (Coates et al., 1983; de Boer-Dennert et al., 1997; Lindley et al., 1999). Since that time, other studies continued to demonstrate that although the incidence and severity of vomiting have decreased, control is not yet optimal, and nausea related to chemotherapy has replaced vomiting as the more distressing problem (Feyer & Jordan, 2011; Russo et al., 2013). In a recent study, Rosenblum et al. (2013) analyzed the symptoms experienced by 159 women with ovarian cancer in current chemotherapy treatment. When they compared the women who experienced chemotherapy-induced nausea (n = 89) with the women who did not (n = 70), they found significant differences between the groups in terms of other symptoms experienced. Those women who reported nausea experienced significantly more abdominal bloating, bowel disturbances, lack of appetite, dizziness, fatigue, depression, and weight loss (Rosenblum et al., 2013).

**Physiologic Consequences**

Nausea and vomiting related to chemotherapy can lead to a number of negative physiologic consequences, including impaired nutritional intake, electrolyte imbalances, dehydration, and pulmonary and GI complications (Horn, 2008; Navari, 2013). Impaired nutrition and weight loss are present in as many as 40%–85% of patients with cancer (Paccagnella, Morassutti, & Rosti, 2011) and may be exacerbated as a result of decreased oral intake and inadequate caloric consumption. Impaired nutrition may result in weight loss, inadequate protein stores, and loss of muscle mass and can lead to a wasting cycle that is difficult to reverse (Davidson et al., 2012). CINV results in other adverse consequences. Vomiting, in particular, can lead to significant electrolyte abnormalities, acid-base imbalances, and dehydration. Reduced oral intake contributes to these adverse consequences, but the primary cause is the loss of gastric fluid rich in potassium, sodium, chloride, magnesium, water, hydrochloric acid, and bicarbonate. Emesis can result in metabolic acidosis because of bicarbonate loss or, in cases of severe vomiting, metabolic alkalosis because of loss of hydrogen ions. Other serious potential physiologic consequences of chemotherapy-induced vomiting include aspiration pneumonia and mucosal or submucosal tears of the lower esophagus or esophagogastric junction, known as Mallory-Weiss syndrome (Merinopoulos, Merinopoulos, & Evans, 2012). Although these complications are rare, they underscore the importance of CINV prevention and control in individuals receiving emetogenic chemotherapy.
Research clearly documents the negative effects of CINV on QOL and daily functioning. In the early 1990s, one of the first major studies to address this issue found that patients who experienced emesis related to chemotherapy had significant declines in QOL in the three days following chemotherapy, whereas QOL remained stable in those individuals without emesis (Lindley et al., 1992). Participants perceived that both nausea and vomiting substantially interfered with their ability to complete meals, spend time with family and friends, and maintain daily functioning, including social activities. Since that time, there has been an explosion of research that has continued to demonstrate the negative impact of CINV on QOL and functioning (Fernández-Ortega et al., 2012; Haiderali, Menditto, Good, Teitelbaum, & Wegner, 2011). One prospective longitudinal study of 200 newly diagnosed patients with cancer found that CINV, and especially nausea, had the greatest impact on the deterioration in health-related QOL scores, specifically in the areas of physical, role, and social functioning; fatigue; appetite loss; and overall physical health (Pirri et al., 2013). A number of studies have used the Functional Living Index—Emesis (FLIE) instrument to examine the impact of CINV on daily functioning across diverse cancer populations residing in various countries. Greater duration, intensity, and frequency of CINV were associated with a negative impact of CINV on daily functioning in these studies, and individuals experiencing both acute and delayed CINV had the greatest declines in daily functioning (Ballatori et al., 2007; Bloechl-Daum, Deuson, Mavros, Hansen, & Herrstedt, 2006; Cohen, de Moor, Eisenberg, Ming, & Hu, 2007; Haiderali et al., 2011). Even individuals who escape acute CINV are at risk for functional declines related to delayed symptoms. In one multinational sample of 298 individuals, nearly one-fourth of individuals who did not have acute CINV nonetheless reported a significant negative impact of delayed CINV on their daily lives, with nausea causing a greater impact than vomiting (Bloechl-Daum et al., 2006).

**Effects on Antineoplastic Treatment Adherence**

Prior to the introduction of newer antiemetic agents such as the serotonin antagonists, up to 20% of individuals with cancer either postponed or discontinued chemotherapy because of nausea and/or vomiting (Herrstedt, 2002). Thanks to the introduction of more effective antiemetic medications over the past two decades, CINV now less frequently affects adherence to antineoplastic therapy, according to an Oncology Nursing Society survey of 577 members on adherence to oral chemotherapy (Roop & Wu, 2013). The results showed the two strongest barriers to treatment adherence were the cost of therapy and adverse events. The results from another study that focused on adjuvant chemotherapy decisions in 54 older women with breast cancer indicated that the top reason women chose not to have adjuvant chemotherapy was the apprehension of side effects (Harder, Ballinger, Langridge, Ring, & Fallowfield, 2013). Chemotherapy dose reductions of greater than 25% have long been known to compromise efficacy and decrease cancer survival (Bonadonna & Valagussa, 1981), underscoring the importance of CINV management.

**Economic Outcomes**

Nausea and vomiting related to chemotherapy may result in negative economic consequences. CINV elevates the costs of care associated with cancer therapy, including both outpatient and hospital charges, as well as personal and societal economic consequences, such as work loss (Haiderali et al., 2011). Medical costs are higher for individuals with CINV. In
a study of 2,071 insurance beneficiaries with cancer, total monthly medical costs were significantly greater, by $2,619, for those with uncontrolled CINV compared to those with controlled CINV (Shih, Han, Zhao, & Elting, 2005). Individuals with uncontrolled CINV also lost more days from work (8.9 versus 7.2 days). Unplanned hospital visits for CINV also have an impact on economic outcomes. Several studies have reported that CINV ranks among the top three reasons for emergency department (ED) visits that frequently result in an unplanned admission (Aprile et al., 2013; Mayer, Travers, Wyss, Leak, & Waller, 2011). In a recent study, Kreys, Kim, Delgado, and Koeller (2014) reported on two years of data for 3,191 patients receiving chemotherapy. They found 799 ED visits for CINV in this group, resulting in an overall cost of $3.6 million.

**Risk Factors**

Given the significant deleterious impact of CINV on QOL, preventing nausea and vomiting is paramount. As the number, efficacy, and cost of antiemetic agents continue to increase, clinicians face a growing demand to use these agents in efficacious and cost-effective ways. The most effective antiemetic regimens must be targeted toward individuals with the highest risk for CINV. The greatest determinant of CINV risk is the emetogenicity of the chemotherapy regimen, defined as its potential for causing nausea and vomiting (Basch et al., 2011). National and international guidelines recommend specific antiemetic therapy based on categories of emetic risk (NCCN, 2014; Roila et al., 2011). In the case of highly emetogenic chemotherapy, use of the most aggressive antiemetic prophylaxis clearly is indicated. In the case of moderately emetogenic chemotherapy, however, clinician judgment plays a greater role, as antiemetic guidelines offer a number of pharmacologic options for CINV prevention. Individual risk factors can help clinicians to choose the best antiemetic therapy for the individual patient.

**Treatment-Related Risk Factors**

The likelihood and severity of CINV are related directly to the specific chemotherapy regimen administered because individual chemotherapeutic agents vary widely in their emetogenicity. Chemotherapy agents are assigned to categories based on their likelihood of inducing acute vomiting when prophylactic antiemetic medications are not administered (see Table 8-2). Agents are classified into four levels of emetogenic risk: high (greater than 90%), moderate (30%–90%), low (10%–30%), and minimal (less than 10%) (Basch et al., 2011; Roila et al., 2011). A major goal of this classification system is to guide the choice of pharmacologic agents for prevention and management of CINV. Algorithms have been proposed for calculating the emetogenicity of combined chemotherapy regimens by adding up modified scores for individual chemotherapy agents (Hesketh et al., 1997). Although potentially quite clinically useful, this algorithm has not been validated for routine use in clinical practice. Nonetheless, it highlights the importance of considering the potential additive effects of chemotherapy agents in increasing the likelihood of developing CINV.

One regimen combining moderately emetogenic chemotherapy agents has received particular attention for its high emetic risk, largely because of data concerning its use in women with breast cancer who have an elevated risk for developing CINV. The AC regimen historically was classified as moderately emetogenic based on the emetogenicity of its individual chemotherapy agents (Hesketh et al., 1997), but this categorization was recently changed in most guidelines. Both NCCN and the American Society of Clinical Oncology (ASCO) defined AC as
Chapter 8  Chemotherapy-Induced Nausea and Vomiting

either doxorubicin or epirubicin in combination with cyclophosphamide and classified it as a highly emetogenic regimen in its antiemesis guidelines (Basch et al., 2011; NCCN, 2014). Although MASCC/European Society for Medical Oncology (ESMO) still classifies AC as moderately emetogenic, they recognize the elevated CINV risk of this regimen (Jordan et al., 2014).

Experiencing acute CINV is one of the most important risk factors for delayed CINV. Individuals who have acute CINV are more likely to experience nausea and vomiting in the delayed setting (Jordan et al., 2014). Furthermore, the incidence of CINV generally increases over time across cycles of chemotherapy (Bouganim et al., 2012). Fortunately, the NK₁ receptor antagonist aprepitant has been able to reduce the cumulative impact of treatment cycles on the CINV experience (Grunberg et al., 2009).

### Patient Risk Factors

Although the emetogenicity of the chemotherapy regimen is the most important risk factor for CINV, patient experiences vary widely within these categories of risk. Identifying patients who are at higher risk for CINV at baseline before chemotherapy treatment is imperative because CINV is more difficult to manage once established, especially anticipatory CINV. Figure 8-3 lists a number of individual characteristics associated with an increased risk

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### TABLE 8-2 Classification of Chemotherapy Agents by Their Potential for Acute Emetogenicity

<table>
<thead>
<tr>
<th>Level of Emetogenicity</th>
<th>Rate of Emesis</th>
<th>Chemotherapy Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (Level 4)</td>
<td>Emesis in nearly all patients (&gt; 90%)</td>
<td>Carmustine, Cisplatin ≥ 50 mg/m², Cyclophosphamide &gt; 1,500 mg/m², Dacarbazine, Mechlorethamine</td>
</tr>
<tr>
<td>Moderate (Level 3)</td>
<td>Emesis in 30%-90% of patients</td>
<td>Carboplatin, Cytarabine &gt; 1 g/m², Cyclophosphamide ≤ 1,500 mg/m², Doxorubicin, Epirubicin, Ifosfamide, Irinotecan, Oxaliplatin</td>
</tr>
<tr>
<td>Low (Level 2)</td>
<td>Emesis in 10%-30% of patients</td>
<td>Capecitabine, Doxorubicin hydrochloride liposomal, Etoposide, Gemcitabine, Methotrexate, Mitomycin, Mitoxantrone, Taxanes, Topotecan</td>
</tr>
<tr>
<td>Minimal (Level 1)</td>
<td>Emesis in &lt; 10% of patients</td>
<td>Bleomycin, Busulfan, Fludarabine, Vinca alkaloids</td>
</tr>
</tbody>
</table>

for CINV. A recent study showed that women who did not experience postoperative nausea and vomiting following breast cancer surgery were at lower risk for experiencing CINV than those women with postoperative nausea and vomiting (Oddby-Muhrbeck, Öbrink, Eksborg, Rotstein, & Lönnqvist, 2013).

**Potential Genetic Risk Factors**

The most recent ASCO guidelines indicate that the goal for management of treatment-induced nausea and vomiting (whether from surgery, chemotherapy, or radiation) should be complete antiemetic response (Basch et al., 2011). However, the best protocols result in 70%–80% response, leading many researchers to believe there may be another explanation for why 20%–30% of patients do not respond to antiemetic therapy. Several candidate genes have been studied in an attempt to discover a genetic predictor for CINV. Because serotonin plays an important role as a neurotransmitter in the CINV pathway, and serotonin antagonists are always included as part of antiemetic protocols, it is logical that research has focused on variability of genes of the serotonin pathway. Genetic variability of the serotonin receptor subunit genes \( HTR3A \), \( HTR3B \), \( HTR3C \), and \( HTR3D \) is thought to be involved in mediation of nausea and vomiting caused by chemotherapy agents (Hammer et al., 2010). One study found that patients with breast cancer who were homozygous (meaning that both alleles are a variant from the wild type) for a deletion variant in the \( HTR3C \) gene had significantly more vomiting and nausea following chemotherapy (Fasching et al., 2008). Another study found that serotonin transport gene polymorphisms 5-HTTLPR and rs25531 were associated with nausea and vomiting caused by chemotherapy agents before they began adjuvant therapy, putting them at greater risk for CINV once adjuvant chemotherapy was initiated (Wesmiller et al., 2014). Another focus of pharmacogenetics and CINV research has been with CYP2D6, a member of the cytochrome P450 (CYP450) family. CYP2D6 is a hepatic enzyme that is responsible for the metabolism of more than 25% of all medications, including many antiemetics (ondansetron, tropisetron, palonosetron, and dolasetrion) and opioids used frequently for cancer pain (Candiotti et al., 2005; Janicki, Schuler, Jarzemowski, & Rossi, 2006). Multiple studies have found that patients who are ultra-rapid or poor CYP2D6 metabolizers have an altered response to antiemetic medications (Trammel, Ro-
Now that CYP2D6 testing has been approved by the U.S. Food and Drug Administration (FDA) and is widely accessible, there is a growing movement to provide testing for CYP2D6 for the 20%–30% of patients who experience breakthrough CINV (Trammel et al., 2013).

**Continuation of Case Study**

Recall L.M., the 43-year-old woman with stage II invasive ductal breast cancer who has been prescribed four cycles of AC every two weeks followed by four cycles of paclitaxel every two weeks. What risk factors does L.M. have for CINV?

L.M. is younger than 50 years old and female, both factors that put her at greater risk for developing CINV. Furthermore, NCCN (2014) recognizes AC as a highly emetogenic regimen. L.M.’s antiemetic therapy should be tailored according to these risks.

**Assessment**

Assessment of CINV in the clinical setting is indispensable to optimal prevention and management. Without routine assessment of nausea and vomiting experienced by individuals undergoing chemotherapy, oncology nurses will be misinformed about the patient experience, as individuals with cancer tend to underreport their symptoms if not clearly prompted to fully report them (Johnson, Moore, & Fortner, 2007), and suboptimal management of CINV may result. Assessment of delayed CINV is especially critical given that delayed symptoms typically occur when the healthcare team no longer has the opportunity for direct observation. The phenomenon of “out of sight, out of mind” may, in part, explain why oncology nurses and physicians are able to accurately estimate the incidence of acute CINV experienced by patients receiving both highly and moderately emetogenic chemotherapy and yet significantly underestimate the incidence of delayed CINV (Grunberg, 2012). Provider assumptions about the efficacy of modern antiemetic regimens may hinder assessment practices, as clinicians may have a false sense of reassurance about their effectiveness (Grunberg, 2012). Another barrier to optimal control of CINV is practitioner underestimation of the occurrence of CINV in their patients and patient underreporting of their symptoms (Hawkins & Grunberg, 2009). Nurses need to integrate regular assessment of CINV and other chemotherapy-related symptoms into routine practice.

**Risk Assessment**

As with any symptom, nurses should first conduct a risk assessment to determine the individual’s likelihood of developing CINV (Ropka, Padilla, & Gillespie, 2005). Risk assessment involves an evaluation of treatment-related factors and patient-related characteristics that could influence CINV risk. First, the level of emetogenicity of the prescribed chemotherapy regimen should be determined, as this is central to establishing the appropriate prophylactic antiemetic regimen (NCCN, 2014). The ASCO, NCCN, and MASCC/ESMO antiemesis guidelines provide useful tables classifying the emetic risk of chemotherapy agents. Table 8-2 provides an abbreviated summary of common chemotherapy agents and their corresponding emetic risk. Individuals receiving highly emetogenic regimens should be prescribed the most aggressive antiemetic prophylaxis available, consisting of agents from at least three
different classes of antiemetic therapy (NCCN, 2014). For patients receiving moderately emetogenic chemotherapy regimens, however, other treatment- and patient-related characteristics play a particularly important role in determining optimal therapy. Patients with risk factors such as younger age, female gender, prior experience with CINV, and high pretreatment expectations of developing CINV may warrant additional therapies beyond the minimum recommended antiemetic medication regimen. Risk assessments should take place with each new cycle of chemotherapy, as an individual’s risk may change based on his or her evolving symptom experience.

Symptom Assessment

Assessment of nausea and vomiting related to chemotherapy should happen before the first day of the first cycle of chemotherapy and continue throughout the entire course of treatment. The first pretreatment assessment should include a thorough review of known risk factors to determine if patients are at increased risk. Assessment of CINV relies on both objective and subjective data and should encompass not only the symptoms of nausea and vomiting but also evaluation of potential related consequences, such as impaired nutrition and hydration (Horn, 2008) or decreased adherence to the treatment plan (Di Maio et al., 2013). Because nausea is a subjective symptom, assessment relies on patient self-report data. Assessment of vomiting incorporates objective data when the clinician is able to directly observe the patient, but it typically relies heavily on self-report because most chemotherapy-related vomiting will occur in the delayed setting, when the patient typically is not clinically observable. Reliable and validated methods of assessment, such as the MASCC Antiemesis Tool (MAT) (MASCC, 2004; Molassiotis et al., 2007), are therefore essential.

Because patient self-report of nausea and vomiting is the cornerstone of CINV assessment, oncology nurses should inquire about the number, onset, duration, and severity of episodes of nausea and vomiting, as well as the use and perceived efficacy of interventions undertaken by the patient to manage CINV. A number of reliable and valid questionnaires are available for assessing CINV and its impact on QOL and functioning, including the Morrow Assessment of Nausea and Emesis; the Rhodes Index of Nausea, Vomiting, and Retching; the FLIE; and the chemotherapy-induced nausea and emesis QOL questionnaire (Martin, A.R., et al., 2003; Martin, Rubenstein, Elting, Kim, & Osoba, 2003; Morrow, 1992; Rhodes & McDaniel, 1999). These instruments, however, were developed for use in research studies, whereas in the clinical setting, visual analog scales or verbal numeric scales are frequently used. Questionnaire length and the time needed for completion and scoring are barriers to their clinical use.

In contrast, the MAT (MASCC, 2004) was designed specifically for use in clinical practice and is a reliable and validated assessment tool (Molassiotis et al., 2007). The MAT is a short self-report instrument that assesses both acute and delayed nausea and vomiting. The MAT should be filled out by the patient only twice per chemotherapy cycle—once 24 hours following chemotherapy to capture acute CINV and then again four days after chemotherapy to capture delayed nausea and vomiting. The MAT can be freely downloaded from MASCC’s website (www.mascc.org/mat) and is recommended for the assessment of CINV in clinical practice (Molassiotis et al., 2007). Use of CINV tools such as the MAT helps to facilitate discussions between clinicians and patients about the CINV experience, thereby affording opportunities to adjust a patient’s antiemetic therapy on an ongoing basis throughout the entire course of chemotherapy. Notably, the MAT was included in a recent review of patient-reported outcome measures for patients experiencing multiple GI symptoms, including nausea and vomiting. The Center for Outcomes Research and Education patient-reported outcomes library (www.researchcore.org/gipro) is an excellent
source for assistance in selecting CINV measures for both clinical and research purposes (Khanna et al., 2014).

**Objective Assessment and Related Complications**

For patients experiencing CINV, especially those with emesis, clinicians should perform a thorough objective assessment to evaluate for adverse consequences of nausea and vomiting. Nutrition assessment should include a diet history; evaluation of height and weight, a physical examination to detect signs of dehydration, sarcopenia, or muscle wasting; vital signs; and laboratory work (Davidson et al., 2012). A body mass index less than 17 kg/m² is indicative of malnutrition and requires further evaluation. A serum albumin level less than 3.5 mg/dl and serum transferrin level less than 200 mg/dl indicate depleted protein stores, and a prealbumin level of 15 mg/dl or less points to altered protein synthesis (Watterson et al., 2009). All are indicative of cachexia (see Chapter 6) and necessitate additional evaluation and intervention. Electrolytes should be evaluated for patients who are experiencing emesis, especially of a severe or persistent nature, because vomiting of gastric contents can lead to hypokalemia, hyponatremia, hypochloremia, and hypomagnesemia. If metabolic alkalosis or acidosis is suspected, particularly in severe cases of emesis, bicarbonate levels should be checked and arterial blood gases drawn to evaluate arterial blood pH level (Marston, Kehl, Copp, Nourbakhsh, & Rifkin, 2014).

**Differential Diagnosis**

Persistent or refractory nausea and vomiting after chemotherapy should always raise suspicion for additional abnormalities. Differential diagnoses include brain metastases, tumor infiltration of the bowel, other GI abnormalities including gastroparesis, and nausea and vomiting related to other comorbidities (Basch et al., 2011). In addition, chemotherapy and concomitant medications, including corticosteroids, may exacerbate gastritis or gastroesophageal reflux disease (Grunberg, 2012).

**Evidence-Based Interventions**

**Overview and Goals of Management**

The primary goals of managing CINV are prevention and treatment of symptoms, maintenance of QOL, and avoidance of complications, including hospitalizations. Prevention is the most important goal. The Oncology Nursing Society (ONS) Putting Evidence Into Practice (PEP) resource on CINV summarizes effective interventions for the prevention and treatment of CINV (Irwin et al., 2012). When planning CINV prevention for a patient receiving chemotherapy, practitioners need to identify the optimal combination of pharmacologic agents to achieve these goals and also must consider appropriate behavioral interventions and complementary therapies.

The cornerstone of CINV management is pharmacologic antiemetic therapy. The pharmacologic management of CINV has evolved remarkably over the past two decades. The introduction of two of the most effective classes of antiemetics, the 5-HT₃ receptor antagonists and NK₁ receptor antagonists, has revolutionized the control of CINV. Further, the introduction of a second generation 5-HT₃ receptor antagonist, palonosetron, was a hallmark advance of this past decade (Navari, 2013).
Pharmacologic Management

Several key principles guide pharmacologic therapy for CINV (Basch et al., 2011). First and foremost, prevention of both nausea and vomiting is the primary goal of antiemetic therapy, as CINV is more difficult to treat once established. The prescribed antiemetic regimen must cover the entire period of risk, which corresponds to a minimum of four days following administration of highly or moderately emetogenic chemotherapy (Basch et al., 2011). The emetogenicity of the prescribed chemotherapy regimen should be the primary factor guiding the choice of prophylactic antiemetic therapy, which should be initiated before chemotherapy administration. Finally, combination therapy, such as concurrent dexamethasone and ondansetron (with or without aprepitant), is superior to single-agent therapy and is essential for highly and moderately emetogenic chemotherapy regimens (Basch et al., 2011).

Historically, dopamine receptor antagonists, such as metoclopramide, and corticosteroids, such as methylprednisolone, were the first medications found to be helpful in treating CINV (Roila et al., 1987). Before the advent of serotonin antagonists, high-dose metoclopramide and methylprednisolone often were combined to treat CINV associated with cisplatin-based regimens, despite the significant toxicity associated with high-dose regimens including extrapyramidal reactions, disorientation, and sedation. Now their usefulness is limited primarily to treatment of established nausea and emesis and not for CINV prevention (Navari, 2013). Phenothiazines, such as prochlorperazine and chlorpromazine, were a mainstay of CINV treatment in the 1980s (Wiser & Berger, 2005). These agents are now considered useful only for prevention of CINV with minimally emetogenic chemotherapy regimens or as adjunctive therapy for refractory CINV and are inappropriate for use alone with highly and moderately emetogenic chemotherapy (NCCN, 2014).

Corticosteroids remain a cornerstone of antiemetic therapy. Given that a greater volume of data is available on its efficacy and tolerability compared to other corticosteroids, dexamethasone is now considered the corticosteroid of choice for combination antiemetic therapy (Basch et al., 2011). A meta-analysis of 32 studies documented the superiority of dexamethasone over placebo in both the acute and delayed settings when used with moderately and highly emetogenic regimens (Ioannidis, Hesketh, & Lau, 2000). In addition to its clear antiemetic and antinausea effects, dexamethasone may improve CINV prevention and treatment through amelioration of anorexia and fatigue (Inoue et al., 2003).

Palonosetron is the newest 5-HT\textsubscript{3} receptor antagonist and is considered a second-generation agent in this class. It has a 100-fold higher binding affinity compared to other 5-HT\textsubscript{3} antagonists, has a half-life of about 40 hours, and is only available as an IV formulation (Aapro et al., 2006). Two separate randomized studies in individuals receiving moderately emetogenic therapy showed superiority of palonosetron to both ondansetron and dolasetron in control of delayed CINV (Eisenberg et al., 2003; Gralla et al., 2003). When studied in patients receiving highly emetogenic chemotherapy regimens, palonosetron was equivalent to ondansetron for prevention of acute CINV but superior for control of delayed CINV (Aapro et al., 2006; Saito et al., 2009).

Evidence supporting the use of first-generation 5-HT\textsubscript{3} antagonists as prophylaxis for delayed CINV is lacking. Given their superb ability to prevent acute CINV, they commonly were assumed to be effective in preventing delayed CINV as well (Rojas et al., 2014). Although individual studies have documented improved control of delayed emesis of these agents compared to placebo, a meta-analysis of 32 studies did not support this conclusion and found...
the pooled difference to be marginal—risk of vomiting was reduced by only 8.2% (Geling & Eichler, 2005).

First-generation 5-HT\textsubscript{3} receptor antagonists were no better than prochlorperazine at controlling delayed CINV in a study of 691 patients receiving doxorubicin in community oncology settings (Hickok et al., 2005). Also, the addition of a 5-HT\textsubscript{3} receptor antagonist to dexamethasone was not superior to dexamethasone alone for prevention of delayed emesis, according to the aforementioned meta-analysis (Geling & Eichler, 2005). Therefore, use of first-generation 5-HT\textsubscript{3} antagonists in combination with dexamethasone in preventing delayed emesis is not warranted, although they are still recommended as monotherapy for prevention of CINV following moderately emetogenic chemotherapy, as well as for treatment of breakthrough CINV (NCCN, 2014). Data on palonosetron are much more supportive of its use in prevention of delayed CINV (Navari, 2013). Differences in binding and effects on receptor function likely explain these differences in efficacy compared to first-generation 5-HT\textsubscript{3} receptor antagonists. See Table 8-3 for recommended doses of serotonin antagonists.

Although 5-HT\textsubscript{3} antagonists are in common use thanks to their efficacy in controlling acute CINV, several potential side effects warrant attention. A small risk of electrocardiogram (ECG) changes exists, specifically prolonged QT interval on ECG (Doggrell & Hancox, 2013; Schnell, 2003). A potential increased risk for ventricular arrhythmias and cardiac arrest was observed with dolasetron but not with ondansetron or granisetron (Schnell, 2003). IV dolasetron was removed from the U.S. market in 2012 because of the increased risk of developing a prolonged QT interval with IV usage, which may potentially precipitate life-threatening ventricular arrhythmias (Navari, 2013). In 2012, the FDA placed a 16 mg dose restriction on IV ondansetron because of the risk of QT prolongation, although recommended oral dosing was not changed. Considered a second-generation serotonin antagonist, palonosetron used at the dose of 0.25 mg IV resulted in a lower mean post-dose change in QT interval compared to dolasetron or ondansetron (Aapro, Macciocchi, & Gridelli, 2005).

### Table 8-3

**Recommended Doses of Serotonin (5-HT\textsubscript{3}) Receptor Antagonists for Acute Emesis**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolasetron</td>
<td>PO</td>
<td>100 mg</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>Removed from U.S. market because of cardiac safety issues</td>
</tr>
<tr>
<td>Granisetron</td>
<td>IV</td>
<td>1 mg or 0.01 mg/kg</td>
</tr>
<tr>
<td></td>
<td>PO</td>
<td>2 mg (or 1 mg\textsuperscript{a})</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>IV</td>
<td>8 mg or 0.15 mg/kg</td>
</tr>
<tr>
<td></td>
<td>PO</td>
<td>16 mg\textsuperscript{b}</td>
</tr>
<tr>
<td>Palonosetron</td>
<td>IV</td>
<td>0.25 mg</td>
</tr>
<tr>
<td>Tropisetron\textsuperscript{c}</td>
<td>IV</td>
<td>5 mg</td>
</tr>
<tr>
<td></td>
<td>PO</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

\textsuperscript{a} The 1 mg dose was preferred by some panelists based on a small randomized study in moderately emetogenic chemotherapy and a phase II study in highly emetogenic chemotherapy.

\textsuperscript{b} Randomized studies have tested the 8 mg twice-daily schedule.

\textsuperscript{c} Used outside of the United States

*Note.* Based on information from Roila et al., 2011.
Numerous other side effects of 5-HT\textsubscript{3} antagonists can occur in patients, with headache and constipation being most commonly reported (Karch, 2014; Mattiuzzi et al., 2010). When IV palonosetron and ondansetron were compared, headache and constipation were infrequent and occurred at almost identical rates (Gralla et al., 2003; Mattiuzzi et al., 2010). 5-HT\textsubscript{3} antagonists should be used with caution in patients with renal impairment because they could increase the risk of ECG changes (Goodin & Cunningham, 2002).

**Neurokinin-1 Receptor Antagonists**

The FDA approved the first NK\textsubscript{1} receptor antagonist, aprepitant, in its oral form in 2003 and the IV formulation, fosaprepitant dimeglumine, in January 2008 (Merck & Co., Inc., 2008a). Aprepitant is different from and complementary to other available antiemetic agents. It is approved for use in the prevention of CINV with both highly and moderately emetogenic chemotherapy in combination with dexamethasone and a 5-HT\textsubscript{3} antagonist (Merck & Co., Inc., 2008b). Aprepitant works predominantly by blocking substance P within the central nervous system, where most NK\textsubscript{1} receptors are located (Rojas et al., 2014). The addition of three days of aprepitant to ondansetron plus dexamethasone markedly improved the control of CINV in the first five days following administration of cisplatin-based highly emetogenic chemotherapy regimens (Hesketh, Grunberg, et al., 2003; Poli-Bigelli et al., 2003). Aprepitant particularly was effective in preventing delayed CINV, and its use in combination with dexamethasone resulted in an absolute improvement of up to 21% in complete response rates (no emesis and no rescue therapy) in the delayed setting compared to dexamethasone alone (Hesketh, Grunberg, et al., 2003; Poli-Bigelli et al., 2003). When added to ondansetron and dexamethasone, aprepitant improved control of CINV and reduced the impact of CINV on QOL in patients with breast cancer receiving AC chemotherapy (Warr, Hesketh, et al., 2005). The addition of aprepitant to ondansetron and dexamethasone maintained superior control of CINV across all four cycles of chemotherapy (Herrstedt et al., 2005). Similar improvements in efficacy were observed with the addition of aprepitant to ondansetron in patients receiving a diverse assortment of moderately emetogenic chemotherapy regimens, 52% of whom were receiving non-AC-based antineoplastic regimens (Rapoport et al., 2010).

Aprepitant is available in both oral and IV formulations and is generally well tolerated. The use of aprepitant did not result in a significant increase in adverse events compared to standard therapy in the AC chemotherapy trial (Warr, Hesketh, et al., 2005). Use of aprepitant resulted in a slightly increased risk of fatigue or asthenia and hiccups in the highly emetogenic chemotherapy trials (Hesketh, Grunberg, et al., 2003; Poli-Bigelli et al., 2003) and similar rates of adverse reactions as the control arm in trials with moderately emetogenic chemotherapy (Rapoport et al., 2010; Warr, Grunberg, et al., 2005). A number of potential drug-drug interactions can occur with the use of aprepitant. Aprepitant is a substrate, moderate inducer, and moderate inhibitor of the CYP450 enzyme CYP3A4 and also induces CYP2A9 (Karch, 2014; Merck & Co., Inc., 2008b). Thus, aprepitant alters the metabolism and the area under the curve of certain medications, such as dexamethasone and warfarin (Basch et al., 2011). Effects are more pronounced with oral forms of medications.

**Other Classes of Antiemetic Medications**

The newest medication to show substantial effects on the prevention and control of CINV is olanzapine, an antipsychotic that blocks multiple neurotransmitters in the central nervous system, including serotonin and dopamine (Navari, 2013). Guidelines now support the use
of olanzapine as an alternative to aprepitant in the prevention of CINV with highly emetogenic chemotherapy regimens and as an effective agent for the treatment of breakthrough CINV (NCCN, 2014). Olanzapine appears particularly effective for the prevention and control of nausea, which remains a greater clinical challenge than vomiting. Available in generic form, it is an inexpensive agent that is safe and well tolerated when used at doses and over time periods associated with antiemetic efficacy (e.g., 10 mg for three days). Low rates of sedation, weight gain, or induction of significant hyperglycemia were observed in antiemetic trials, effects that have been associated with olanzapine given for longer periods of time. A randomized clinical trial comparing olanzapine to aprepitant, each combined with the standard duet of palonosetron and dexamethasone, showed improved control of nausea with olanzapine versus aprepitant (69% vs. 38% rates of “no nausea”) (Navari et al., 2011). Complete response rates were similar between study arms. Furthermore, in the first phase III trial comparing agents for the treatment of breakthrough CINV, olanzapine was superior to metoclopramide in patients who developed breakthrough emesis or nausea following highly emetogenic chemotherapy despite standard prophylactic therapy (dexamethasone, palonosetron, and fosaprepitant) prechemotherapy plus dexamethasone on days 2–4 (Navari, Nagy, & Gray, 2013). Those randomized to receive olanzapine, 10 mg PO daily for three days, had significantly higher rates of no nausea (68%) and no vomiting (70%) compared to those who received metoclopramide, 10 mg PO TID for three days (28% without nausea and 31% without vomiting).

Cannabinoid neuromodulators are another class of agents with antiemetic properties. Cannabinoids have inhibitory effects on other neurotransmitters and agonist effects on cannabinoid-1 receptors found in the central and peripheral nervous systems, resulting in anti-nausea and antiemetic effects (Davis, Maida, Daeninck, & Pergolizzi, 2007). Pharmaceutical cannabinoids approved for use in managing CINV are nabilone and dronabinol. In a meta-analysis of 30 randomized studies, cannabinoids were superior to both placebo and conventional antiemetics, such as dopamine antagonists and phenothiazines, for the control of nausea and vomiting (Tramèr et al., 2001). However, they have no added benefit compared to serotonin antagonists (Navari et al., 2013). Up to 50% of participants receiving cannabinoids in clinical trials reported dizziness, drowsiness, or somnolence; 35% had a sensation of being high; and 25% experienced hypotension (Tramèr et al., 2001). Their role is limited to the treatment of breakthrough or refractory CINV, and they may be particularly effective for the latter (Davis et al., 2007; NCCN, 2014).

Anxiolytics, such as lorazepam, frequently are used as adjuncts in managing CINV but are not the drugs of choice for prevention (Basch et al., 2011; Navari et al., 2013). Although they do not have direct antiemetic effects, they help to relieve anxiety symptoms that may exacerbate the CINV experience. This class of agents should be used carefully in older adults because of the potential for medication interactions and the propensity to induce adverse effects such as confusion (Roscoe, Morrow, Aapro, Molassiotis, & Olver, 2011).

**Guidelines for Antiemetic Therapy**

Given the growing number and complexity of antiemetic agents available for the prevention and management of CINV, maintaining an up-to-date understanding of how to use them effectively is paramount. Clinical practice guidelines are an excellent resource that health systems and clinicians can use to ensure contemporary evidence-based practice. Three major organizations have guidelines for the prevention and management of CINV: NCCN, an alliance of cancer centers across the United States; ASCO; and MASCC/ESMO. Each of these organizations reviews and updates its guidelines with varying degrees of fre-
quency. NCCN, for example, provides updates as often as one to three times annually depending on evolving data (NCCN, 2014). ASCO updated its guidelines in 2011 to reflect the latest clinical evidence (Basch et al., 2011), and MASCC/ESMO last updated its guidelines in 2010 (Roila et al., 2011).

In an effort to make information regarding interventions for CINV more accessible for clinical use, the ONS PEP resource for CINV (Irwin et al., 2012) lists interventions with varying degrees of evidence for effectiveness. Interventions that are listed under Recommended for Practice are supported by data either from multiple randomized clinical trials or from expert recommendations resulting from a comprehensive and critical analysis of the literature. The resource summarizes guideline-based antiemetic recommendations for pharmacologic therapy, all of which are listed in the category of Recommended for Practice.

**Antiemetic Guidelines: Highly Emetogenic Chemotherapy**

All three major antiemetic guidelines offer consistent recommendations for the prevention of CINV associated with highly emetogenic chemotherapy (Basch et al., 2011; NCCN, 2014; Roila et al., 2011). NCCN’s guidelines for highly emetogenic chemotherapy appear in Figure 8-4. All patients should receive aggressive antiemetic prophylaxis with drugs from three different classes: a corticosteroid, a 5-HT$_3$ receptor antagonist, and either an NK$_1$ receptor antagonist or olanzapine. In addition, NCCN (2014) states that either a histamine-2 blocker or proton pump inhibitor can also be added, which can help with GI protection from the effects of dexamethasone. NCCN and ASCO both recognize AC, defined as the combination of either doxorubicin or epirubicin with cyclophosphamide, as a highly emetogenic chemotherapy regimen and therefore recommend the same triple-drug CINV prophylaxis for individuals receiving AC (Basch et al., 2011; NCCN, 2014). Although the MASCC/ESMO guidelines classify AC as moderately emetogenic chemotherapy, they also recommend triple therapy for women receiving this regimen based on the evidence and because of the particularly high risk of CINV in these women. The NCCN, MASCC/ESMO, and ASCO guidelines differ slightly for antiemetic prophylaxis with AC chemotherapy (see Table 8-4).

**Antiemetic Guidelines: Moderately Emetogenic Chemotherapy**

All the guidelines agree that dual therapy with dexamethasone and a 5-HT$_3$ receptor antagonist should be given on the first day of chemotherapy for the prevention of acute CINV. NCCN guidelines are shown in Figure 8-5. Palonosetron is preferred, but first-generation 5-HT$_3$ receptor antagonists are also appropriate (NCCN, 2014). Both MASCC/ESMO and ASCO recommend that the second-generation agent palonosetron be used but state that a first-generation agent is also appropriate if palonosetron is unavailable (Basch et al., 2011; Roila et al., 2011). Although the MASCC/ESMO guidelines classify AC as a moderately emetogenic chemotherapy, they also recommend triple therapy for women receiving this regimen based on the evidence and because of the particularly high risk of CINV in these women. The NCCN, MASCC/ESMO, and ASCO guidelines differ slightly for antiemetic prophylaxis with AC chemotherapy (see Table 8-4).
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with moderately emetogenic chemotherapy, NCCN, MASCC/ESMO, and ASCO recommend single-agent dexamethasone on days 1–3 (Basch et al., 2011; NCCN, 2014; Roila et al., 2011). Finally, NCCN states that aprepitant may be given alone or in combination with dexamethasone for prevention of delayed CINV in those individuals who received aprepitant for acute CINV (NCCN, 2014).

**Antiemetic Guidelines: Low and Minimal Emetic Risk Chemotherapy**

According to the NCCN guidelines, chemotherapy regimens of low emetogenic potential require prophylaxis with a single agent such as dexamethasone, prochlorperazine, metoclopramide, or a 5-HT₃ receptor antagonist starting prior to chemotherapy and continuing daily for multiday chemotherapy (NCCN, 2014). Therapy with a proton pump inhibitor and/or lorazepam is optional (NCCN, 2014). For agents of minimal emetic risk, no prophylaxis is required, but therapy can be prescribed as per breakthrough CINV recommendations should CINV develop. Figure 8-6 provides an overview of the NCCN guidelines for chemotherapy of low and minimal emetogenic potential.

**Antiemetic Guidelines: Breakthrough Nausea and Vomiting**

Breakthrough nausea and vomiting continues to be a significant clinical challenge. For example, even when patients receiving highly emetogenic chemotherapy are treated with the appropriate triple-drug therapy of aprepitant, dexamethasone, and a 5-HT₃ antagonist, 50% still experience delayed nausea or vomiting (Grunberg, Slusher, & Hugo, 2013). The overarching principle for managing breakthrough CINV is to give an additional agent from a different class of antiemetic medication, such as metoclopramide, prochlorperazine, or a cannabinoid (Basch et al., 2011; NCCN, 2014). Multiple concurrent agents may be necessary. Appropriate medications and their corresponding dosages are listed in the ONS PEP resource (Irwin et al., 2012). If the chosen strategy is effective, the breakthrough medications should be continued on a scheduled rather than an as-needed basis (Basch et al., 2011). If control is not achieved,
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then the clinician should consider changing to higher-level antiemetic prophylactic therapy with subsequent cycles of chemotherapy treatment (Basch et al., 2011).

**Antiemetic Guidelines: Anticipatory Nausea and Vomiting**

Each of the major antiemetic guidelines recognizes that the best strategy for managing anticipatory nausea and vomiting is to use optimal antiemetic therapy to prevent acute and delayed CINV in all cycles of treatment (Basch et al., 2011; NCCN, 2014; Roila et al., 2011). Once anticipatory CINV develops, it is difficult to manage. For the treatment of anticipatory CINV, all three guidelines recommend behavioral and psychological strategies such as systematic desensitization, as well as the use of anxiolytics (Basch et al., 2011; NCCN, 2014; Roila et al., 2011). Anxiolytic agents and doses are included in the comprehensive ONS PEP resource (Irwin et al., 2012).

**Antiemetic Guidelines: Multiday Emetogenic Chemotherapy Regimens**

Patients receiving multiday chemotherapy regimens are at risk for both acute and delayed CINV of prolonged duration, depending on the drug, dose, and schedule of chemotherapy administered (Basch et al., 2011). Clear guidelines do not exist for specific antiemetic agents and the schedules that should be prescribed for multiday chemotherapy regimens; however, each of the major guidelines provided principles for managing antiemetic therapy in this setting. NCCN and ASCO agree that antiemetics appropriate for the chemotherapy agent of highest emetogenic risk should be administered on each day of chemotherapy and thereafter for an additional two to three days, particularly for those agents likely to cause delayed emesis (Basch et al., 2011; NCCN, 2014). These would include the administration of dexamethasone once daily (either PO or IV) on the day of and for two to three days after any day on which a chemotherapy agent of moderate to high emetic risk is administered, as well as a 5-HT₃ antagonist prior to each daily dose of moderately or highly emetogenic chemotherapy (NCCN, 2014). The dexamethasone dose may be modified or omitted when the chemotherapy regimen already includes a corticosteroid. ASCO further notes that the granisetron transdermal patch, which delivers therapy over multiple days, is an alternative to taking a serotonin antagonist daily (Basch et al., 2011). NCCN states that palonosetron may be adequate for onetime administration prior to regimens of three-day duration, rather than repeated daily dosing of first-generation 5-HT₃ antagonists (NCCN, 2014).

**Nonpharmacologic Management**

A number of nonpharmacologic options for the management of CINV have been investigated, and although none are supported by strong and consistent evidence to stand alone or be classified as Recommended for Practice, several are categorized as Likely to Be Effective in the ONS PEP resource for CINV (Irwin et al., 2012). Exceptions exist when nonpharmacologic management may be very beneficial, for example, to prevent anticipatory nausea. Behavioral therapy, including progressive muscle relaxation, hypnosis/guided imagery, music therapy, and acupuncture and acupressure, is recommended by NCCN (2014) for anticipatory nausea and vomiting.

For acute and delayed CINV, these strategies are often categorized as Effectiveness Not Established because of evidence that is somewhat contradictory. But, because no harm is associated with any of these strategies and some clinicians report that they may be helpful, they are certainly options to be used in conjunction with pharmacologic antiemetic therapy. Providing psychoeducational support and information and managing patient expectations are
supported by adequate evidence and were placed in the Likely to Be Effective category according to the PEP classification schema (Irwin et al., 2012).

**Acupuncture and Acupressure**

Acupuncture and acupressure have gained increasing popularity for managing various symptoms related to chemotherapy, including nausea and vomiting. Both modalities involve the stimulation of anatomic points, called *acupoints*, positioned along designated meridians of the body (Deng & Cassileth, 2013). Acupuncture involves the insertion of wire-thin needles into the skin at these acupoints, whereas acupressure is performed using noninvasive digital pressure or by the recipient wearing an elastic wristband with an embedded stud (Deng & Cassileth, 2013). In Chinese medicine, acustimulation modalities are believed to help restore the body to a state of energy balance. Nausea is thought to result from a disruption in Qi, the energy flow of living beings (Lv, Feng, & Li, 2013). The P6 Neiguan acupoint, an area located on the ventral aspect of the wrist approximately three fingerbreadths from the flexor crease, is the most commonly used area for nausea and vomiting control (Towler, Molassiotis, & Brearley, 2013).

A randomized controlled trial of acupressure was undertaken in 160 women with breast cancer receiving moderately to highly emetogenic chemotherapy (Dibble et al., 2007). Digital acupressure at the P6 pressure point was effective in reducing both delayed nausea and vomiting and hastening recovery from nausea (Dibble et al., 2007). Another study focused on the effects of P6 acupressure and nurse-provided counseling, reporting that a synergic effect may exist when the two strategies are provided together to reduce CINV (Suh, 2012). In a meta-analytic review of reviews, Towler et al. (2013) found nine reviews that examined the effectiveness of acupuncture for the treatment of CINV. They found a paucity of rigor in published studies yet still concluded that acupuncture should be considered for symptom relief when limited treatment options are available (Towler et al., 2013).

**Other Complementary Therapies**

Ginger is considered a traditional antiemetic strategy that has been used for centuries (Pertz, Lehmann, Roth-Ehrang, & Elz, 2011), so it seems a logical choice to consider as a modality for the treatment of CINV, and in fact many patients may choose to use it. However, a recent systematic review of 872 subjects from five different studies found insufficient evidence to support the use of ginger alone as a recommended treatment measure for CINV (Lee & Oh, 2013).

Guided imagery, music therapy, and progressive muscle relaxation have been examined as adjunctive therapies for CINV and appear particularly helpful for treating anticipatory CINV (Irwin et al., 2012). A meta-analytic review found both guided imagery and progressive muscle relaxation to be effective in reducing nausea, but no conclusion could be drawn about their effect on vomiting because of low incidence in these studies (Luebbert, Dahme, & Hasenbring, 2001). Another study, however, found progressive muscle relaxation to be effective at reducing the duration of both nausea and vomiting in 71 Chinese women with breast cancer (Molassiotis, Yung, Yam, Chan, & Mok, 2002). With guided imagery, patients are encouraged to think of a favorite or pleasant place in order to mentally block thoughts of prior experiences with chemotherapy. Self-hypnosis, distraction, massage, and aromatherapy are other methods that may be helpful for controlling CINV, but effectiveness has not yet been established by robust data (Irwin et al., 2012). With distraction, patients can watch videos or listen to music to divert attention from a situation that may cause nausea. Although further study is needed to document the effectiveness of these nonpharmacologic methods, they appear to have minimal risk and hold promise as complementary therapies for CINV.
**Need for Future Research**

Despite major advances in the prevention and management of CINV in the past two decades, further research is needed to improve clinicians’ ability to identify patients at risk. Research is needed to determine protocols of combined medications that will best prevent delayed CINV, a persistent problem. Understanding the mechanism of anticipatory CINV also provides a vast area for future research. Protocols that combine biobehavioral and complementary treatment strategies need to be developed and tested. Further research that increases understanding of the pathophysiologic mechanisms underlying CINV, particularly for nausea, would go far in propelling science forward. Future research also should seek to better individualize antiemetic management strategies using previously identified and as yet unknown predictive factors, including potential biomarkers and receptor crosstalk. The ability to tailor CINV management, combining both pharmacologic and nonpharmacologic strategies, to individuals would markedly improve not only the effectiveness but also the cost efficiency of antiemetic therapy. Finally, failure to integrate best practices for the assessment and management of CINV into individual and organization-wide clinical practice remains a major barrier to optimal prevention and management of CINV. More research is needed to examine the best strategies for promoting evidence-based practices in diverse clinical settings so that all patients can benefit from comprehensive and effective antiemetic therapy.

**Conclusion of Case Study**

L.M. has been prescribed the following antiemetic regimen while receiving AC chemotherapy, consistent with guidelines for highly emetogenic chemotherapy (NCCN, 2014). She received the following medications as a plan to both prevent and manage CINV.

- **Day 1:** Palonosetron 0.25 mg IV, dexamethasone 12 mg PO, and aprepitant 125 mg PO
- **Days 2–4:** Dexamethasone 8 mg PO daily plus aprepitant 80 mg PO days 2 and 3

The oncology nurse calls L.M. on day 3 to evaluate how she is tolerating AC chemotherapy. L.M. has moderate nausea, without vomiting, that is interfering with her ability to eat and has made her stay home from work. Clearly, additional therapy is indicated. Although she experienced no vomiting, L.M. is experiencing moderate nausea interfering with daily functioning despite optimal prophylactic antiemetic therapy recommended by national guidelines (NCCN, 2014). A number of options may be considered for managing her breakthrough nausea, including

- Olanzapine 10 mg PO daily for three days
- An oral 5-HT₃ antagonist
- Metoclopramide 10–40 mg PO or IV either every four or every six hours
- Nabilone 1–2 mg PO twice daily, or dronabinol 5–10 mg PO either every three or every six hours
- Prochlorperazine 10 mg PO every six hours.

Several options stand out from among the others. Appropriate management of breakthrough nausea and vomiting should include the addition of an antiemetic from a different class, such as olanzapine, metoclopramide (a dopamine antagonist), or nabilone (a cannabinoid) (Basch et al., 2011; NCCN, 2014). An oral 5-HT₃ antagonist would be the least appropriate choice at this time because L.M. received palonosetron, a 5-HT₃ inhibitor, on day 1, and this agent has a 40-hour half-life. She is already receiving dexamethasone, so additional steroid medication is not advisable. Either olanzapine or metoclopramide would
likely be the best choice for L.M. given the potential for central nervous system and sedative side effects with the use of cannabinoids, particularly because she is trying to preserve her ability to work. Olanzapine was superior to metoclopramide in one study (Navari et al., 2013). A phenothiazine such as prochlorperazine would be another option. Regardless of which agent is selected, if it is effective, it should be given on a scheduled rather than an as-needed basis until nausea has dissipated and then should be added to the prophylactic antiemetic regimen with future cycles of chemotherapy (Basch et al., 2011). L.M. received daily olanzapine (10 mg/day) for three days with excellent relief of symptoms. She was able to return to work within 24 hours, and she experienced much less nausea with future cycles.

Conclusion

Despite major advances in antiemetic therapy and the availability of complementary therapies of varying effectiveness in managing CINV, nausea and vomiting remain two of the most distressing side effects for individuals receiving chemotherapy for cancer treatment. CINV impairs daily functioning and significantly decreases QOL. Therefore, the primary goal of antiemetic therapy is complete prevention of CINV, and a growing armamentarium of pharmacologic agents is available to assist in this effort. The appropriate use of the two newest antiemetic agents, aprepitant and palonosetron, significantly improves the control of CINV compared to prior therapies, and these agents appear particularly promising when used together in combination with dexamethasone for regimens of the highest emetogenic risk. Nonetheless, CINV remains prevalent, and delayed nausea and vomiting are especially problematic. Combination antiemetic therapy covering the entire period of risk is imperative, and the emetogenicity of the chemotherapy regimen along with individual risk factors should guide the choice of antiemetic medications. National and international consensus guidelines are based on a thorough review of the available evidence regarding antiemetic therapy and should be used to guide decisions regarding optimal CINV prevention and management. Lack of routine assessment of CINV in clinical practice and poor use of antiemetic guidelines remain two significant barriers to optimal prevention and management. Oncology nurses can take the lead in efforts to optimize CINV therapy by implementing standards for assessment and management of nausea and vomiting not only in their individual clinical practices but also in their institutional standards. Furthermore, oncology nurses should educate patients about comprehensive strategies for CINV, including antiemetic medications, dietary strategies, and complementary therapies such as acupuncture and progressive muscle relaxation.

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References

Chapter 8  Chemotherapy-Induced Nausea and Vomiting


Case Study

A.M. is a 48-year-old RN who was diagnosed with breast cancer 18 months ago. She received four cycles of doxorubicin and cyclophosphamide every two weeks followed by four cycles of paclitaxel every two weeks. She started daily tamoxifen after her chemotherapy finished. Her menstrual cycle has been irregular since receiving chemotherapy. She is experiencing trouble sleeping and fatigue and reports that she does not feel as mentally sharp as she did prior to her chemotherapy treatments. She has been forgetting names of people she knows well and has trouble coming up with words she wants to use in conversation. She also finds it difficult to multitask on the busy inpatient surgical unit where she works and is very concerned that her performance at work has declined. She is afraid that she may forget something important that could negatively affect one of her patients. A.M. notices she is frequently misplacing items, such as her car keys and her purse. She is having a difficult time keeping track of the activities of her husband and two school-age children. This is a big change for her, as she always has been able to juggle the demands of home and work life. She finds this very upsetting and asks if anything can be done to help her with these issues.

Overview

Nurses play an important role in helping patients with cancer to cope with the short- and long-term effects of cancer therapy, including cancer-related cognitive impairment (CI). CI in adult patients with cancer is a complex phenomenon associated with both cancer and cancer-related treatment. CI is associated with central nervous system (CNS) malignancies because of the effect of direct tissue damage from the cancer, as well as the sequelae of radiation therapy and chemotherapy (Zucchella, Bartolo, Di Lorenzo, Villani, & Pace, 2013). Intrathecal, myeloablative, and standard-dose regimens of chemotherapy also are associated with CI (Ahles & Saykin, 2001; Harder et al., 2004; Jim et al., 2012; Vijayanathan, Gulinello, Ali, & Cole, 2011). Non-CNS tumors appear to be associated with CI prior to administration of chemotherapy (Wefel, Lenzi, Theriault, Davis, & Meyers, 2004). The clinical picture of CI is complicated further by confounding factors such as age, hormonal status, and concomitant cancer-related symptoms such as fatigue, pain, and anemia (Janelsin et al., 2011; Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005; Kurita et al., 2012). Psychosocial factors such as anxiety and depression can complicate the assessment of cognitive function (Jansen et al., 2005).
The body of literature for the examination of CI experienced by patients with cancer who have received chemotherapy continues to grow (Collins, Mackenzie, Tasca, Scherling, & Smith, 2013; Hermelink et al., 2010; Hess et al., 2010; Kohli et al., 2007; Tannock, Ahles, Ganz, & van Dam, 2004; Wefel et al., 2004). Chemotherapy-related CI tends to manifest as a decline in memory, concentration, and multitasking functions and can occur during or after treatment for cancer. Patients with cancer commonly have referred to this experience as “chemobrain” or “chemo fog.” However, patients with cancer who have not received chemotherapy have reported these symptoms as well, thus making the term *chemobrain* a misnomer (Hurria, Somlo, & Ahles, 2007; Wefel et al., 2004). Experts in the field have suggested that the experience of CI be referred to as *cancer- or cancer therapy–associated cognitive change* (Hurria et al., 2007) because many factors could be implicated in the development of this impairment. For the purposes of this chapter, the phenomenon will be referred to as CI.

The majority of the research designed to evaluate CI in adult patients with cancer has focused on women with breast cancer (Ahles, 2013). In recent years, this field of study has broadened and includes research of CI in patients with other solid tumors such as prostate and lung cancer, as well as those with hematologic malignancies. Methodologic challenges in this area of research have made it difficult to generalize results to a broader group of patients with cancer. Some of these challenges include studies with small sample sizes and differing methods of testing cognitive function. In addition, statistical analyses have not been standardized across studies, thereby making comparisons and definitive conclusions about CI in patients with cancer difficult (Shilling, Jenkins, & Trapala, 2006). Despite these methodologic problems and lack of consistent measurement tools, patients with cancer are reporting that CI is problematic. A better understanding of this experience is important because of the negative effects on quality of life and potential interference with work, educational, and personal goals (Mulrooney, 2007; Myers, 2012).

CI has been found across groups of patients with varying cancer diagnoses. In one study, 60% (n = 24 out of 40) of patients with hematologic malignancies treated with bone marrow transplantation after high-dose chemotherapy or total body irradiation were found to have mild to moderate impairment in attention, information processing speed, verbal learning, and memory (Harder et al., 2002). Predictors for CI in this sample included fatigue, overall health status, and higher level of education. In patients with breast cancer treated with chemotherapy, the incidence of CI has been broad, with estimates as high as 75% of participants having measurable CI on neuropsychological testing (Janelsins et al., 2011). CI has been documented prior to and after chemotherapy in patients with non-small cell lung cancer (Whitney et al., 2008) and at baseline and following prophylactic cranial irradiation in patients with small cell lung cancer (Grosshans, Meyers, Allen, Davenport, & Komaki, 2008). CI following chemotherapy has been demonstrated for patients with testicular (Skoogh et al., 2012), ovarian (Correa, 2010; Correa et al., 2010; Hess et al., 2010; Stavraka et al., 2012), and head and neck (Gan et al., 2011) cancers, as well as lymphoma (Ahles & Saykin, 2001) and multiple myeloma (Potrata, Cavet, Blair, Howe, & Molassiotis, 2010). Patients with prostate cancer receiving androgen deprivation therapy (ADT) reported CI (Wu, Diefenbach, Gordon, Cantor, & Cherrier, 2013). Likewise, women with breast cancer receiving hormonal therapy also experienced CI (Bender et al., 2007).

**Descriptions and Consequences of Cognitive Impairment**

The vast majority of the research on CI in patients with cancer has focused on neuropsychological test results with less emphasis on the clinical significance or the impact of CI on
the day-to-day life of patients. However, some qualitative research has been conducted to describe the lived experience of CI-related changes and the impact on daily function and quality of life. Mulrooney (2007) conducted a qualitative study with 10 women who were treated with chemotherapy. The participants of this study described problems with short-term memory, attention, concentration, word retrieval, and multitasking. These incidents of cognitive failures were unpredictable and could happen several times a day one week but just once or twice in another week. Participants often described CI as being part of a “vicious cycle” (p. 115). They shared the experience of being in the middle of a conversation and having trouble coming up with a particular word. Participants noted a feeling of dread followed by anxiety that would make word retrieval nearly impossible. Anxiety was described as a component of the CI experience not only during the occurrence but also when worrying about important things that potentially could be forgotten. CI often resulted in negative consequences both at home and at work. Some of the participants described altered relationships with their families. Family members often would get frustrated and angry with the memory loss experienced by the participants. Changes in employment status were noted. Out of the 10 participants, two retired earlier than they had planned, three reduced their workloads, and two others lost their jobs as a result of CI (Mulrooney, 2007).

Results from other recent qualitative studies conducted with diverse populations of cancer survivors demonstrated similar results (Boykoff, Moieni, & Subramanian, 2009; Fitch, Gray, Godel, & Labrecque, 2008; Mitchell, 2007; Potrata et al., 2010; Skoogh et al., 2012; Wagner, Sweet, Butt, Lai, & Cella, 2009). Negative effects on social relationships and employment were common concerns shared by study participants (Boykoff et al., 2009; Munir, Burrows, Yarker, Kalawsky, & Bains, 2010; Myers, 2012; Von Ah, Haberman, Carpenter, & Schneider, 2013). Additional examples of CI noted in recent research include difficulty with reading comprehension, trouble driving, getting lost, misplacing items, forgetting what they were doing when in the midst of an activity, and forgetting important tasks or appointments (Cappiello, Cunningham, Knobf, & Erdos, 2007; Cheung et al., 2012; Downie, Mar Fan, Houédé-Tchen, Yi, & Tannock, 2006; Mitchell & Turton, 2011; Myers, 2012; Potrata et al., 2010; Raffa & Martin, 2010). The importance of receiving education about the potential for CI prior to receiving treatment, ongoing assessment of cognitive status, and validation of the experience by the healthcare team consistently was demonstrated (Boykoff et al., 2009; Cappiello et al., 2007; Fitch et al., 2008; Myers, 2012; Rust & Davis, 2013; Von Ah et al., 2013). The timing for first recognizing CI, as well as for when participants noticed any improvement, was variable. Not all participants experienced improvement in CI over time.

**Pathophysiology**

CI occurring in patients with cancer is believed to be multifactorial. A panel of experts convened in 2003 to discuss the research on CI in patients with cancer who had received chemotherapy (Tannock et al., 2004). One of the goals of this meeting was to identify the factors that potentially could affect cognitive function in this population. The factors then were incorporated into a model and included endogenous hormones, genetic predisposition, depression, anxiety, fatigue, cytokines, cancer treatment, and clotting in small blood vessels. Since the discovery that CI also occurs prior to cancer therapy, postulation of causal mechanisms has expanded and additional factors are considered. As part of a recent review article, Merriman, Von Ah, Miaskowski, and Aouizerat (2013) developed a model for proposed mechanisms for cancer- and treatment-related cognitive changes that includes both cancer treatment (chemotherapy, surgery, radiation therapy, hormonal therapy) and other
clinical factors (tumor-associated inflammation, physical/psychological stress, attentional fatigue, comorbidities, and concurrent symptoms) (see Figure 9-1). Genetic variations and age are proposed as innate inter-individual differences that moderate CI, as aging is associated with changes in cognition and genetic predisposition is hypothesized to be associated with longer-term CI. Baseline cognitive function is noted as a factor in the outcome of the impact of cognitive changes. This model provides a useful framework to better understand the complexities of CI experienced by patients with cancer. Some of the factors from the model are discussed in greater detail in the following sections.

**Endogenous Hormones: Androgens, Estrogen, and Cognition**

The hippocampus (see Figure 9-2) is one of the areas of the brain responsible for memory and learning. The hippocampus registers new memories that then are stored elsewhere...
in the brain as long-term memories (Lezak, Howieson, Bigler, & Tranel, 2012). Estrogen receptors (alpha and beta) are present in the hippocampus. Evidence is accumulating in support of the role of estrogen receptor–beta in mediating the effects of estrogen on cognition (Liu et al., 2008).

Recent interest has been expressed in the effects of estrogen levels on the prefrontal cortex (see Figure 9-2) because this area of the brain is involved in tasks requiring intact executive function. Estrogen is thought to modulate executive function within the prefrontal cortex (Liu et al., 2008). One component of this hypothesis is the role of estrogen in modulating the neurotransmitters important to executive function, dopamine and norepinephrine (Shanmugan & Epperson, 2014). The impact of estrogen on dopamine levels may be further complicated by the catechol-O-methyltransferase (COMT) genotype and related enzyme activity (Shanmugan & Epperson, 2014).

Complaints of cognitive decline (specifically memory and attention) are common in women during the transition through menopause. Decreasing levels of estrogen are thought to play a role in these cognitive changes; however, the definitive mechanism is still under investigation (Liu et al., 2008). The gradual change in cognition observed during menopause and the normal aging process may be accelerated for women in whom estrogen levels abruptly decrease as a result of surgery or chemotherapy to treat malignancy (Mar Fan et al., 2010). Thus, decreases in estrogen levels may exacerbate the experience of CI for women receiving chemotherapy.

Androgen receptors also are present in the brain, specifically in the hippocampus, amygdala (see Figure 9-2), and prefrontal cortex (Ulubaev, Leet, Purandare, Pendleton, & Wu, 2009). However, the relationship between androgens, such as testosterone, dihydrotestosterone, and dehydroepiandrosterone sulfate, and cognitive ability is not well understood.
Patients with lower levels of testosterone are hypothesized to have lower levels of cognition, but the mechanism by which CI occurs is unclear, and results of studies designed to investigate the relationship of hypogonadism to cognitive decline have been mixed (Ulubaev et al., 2009).

Results of two studies indicated a relationship between low levels of free testosterone and declines in specific domains of cognitive function such as processing speed, spatial ability, and visual memory for patients who have received androgen blockage for the treatment of prostate cancer (Green et al., 2002; Moffat et al., 2002). Indirect effects of androgens on cognition may be due to the modulation of insulin-like growth factor-1 synthesis in the liver (Ulubaev et al., 2009).

Moffat et al. (2002) conducted a longitudinal assessment of serum free testosterone concentration for 407 men aged 50–90 for a mean duration of 9.7 years. Higher levels of free testosterone index were associated with better scores on visual and verbal memory, visuospatial functioning, and visuomotor scanning and lower rates of longitudinal decline in visual memory. The possible beneficial relationship between circulating free testosterone concentrations and specific domains of cognitive performance in older men was suggested, lending support to the hypothesis that androgen deprivation is associated with CI.

Genetic Predisposition

Some studies have explored the hypothesis that the development of CI may be related to a genetic predisposition. Ahles et al. (2003) examined a group of long-term survivors of breast cancer and lymphoma who had been treated with chemotherapy to see if the presence of the epsilon 4 allele of the apolipoprotein E (APOE) gene was associated with a higher degree of CI compared with survivors who did not carry this allele. The presence of the allele has been linked with a higher risk of developing Alzheimer disease, as well as CI following head injuries (both single traumatic brain injuries and injuries sustained with repeated trauma from sports such as boxing or football). Ahles et al. (2003) found that the participants with the epsilon 4 allele scored significantly lower in neuropsychological measures of visual memory (p < 0.03) and spatial ability domains (p < 0.05) compared with the participants who did not have the allele. No group differences were found for fatigue, depression, or anxiety. This study provided preliminary data to support that chemotherapy-related CI may, in part, be related to the presence of the epsilon 4 allele of the APOE gene, and research in this area is ongoing. In subsequent research, Ahles et al. (2014) investigated an interaction effect between APOE, cognitive changes after cancer treatment, and smoking history. The sample included women with breast cancer treated with chemotherapy (n = 55), matched with women with breast cancer not treated with chemotherapy (n = 68) and controls (n = 43). No main effect was seen for APOE and group. However, patients with the epsilon 4 allele (APOE4) who also had a history of smoking demonstrated improved performance on processing speed compared to controls (95% confidence interval [-1.015, -0.064], p = 0.0263). The authors concluded that a history of smoking may have a protective effect on cognition for patients who are positive for APOE4. The proposed explanation is that smoking corrects a deficit in nicotinic receptor functioning in APOE4+ patients and increases dopamine levels. Studies in noncancer populations have shown similar results, and preclinical evidence suggests that brief exposure to nicotine in adolescence may have a long-term impact on brain function (Ahles et al., 2014).

A single nucleotide polymorphism of catechol-O-methyltransferase, COMT158Met, is hypothesized to play a role in changes in cognition (Small et al., 2011). Individuals who possess
a substitution of valine (VAL allele) with methionine (Met) at codon 158 on chromosome 22q11 are called COMT-Val+ carriers. These individuals have higher enzymatic activity and less availability of dopamine. COMT-Val+ carriers have been shown to perform more poorly on neurocognitive tests of attention and executive function than COMT-Val– individuals (Small et al., 2011). Small and colleagues conducted a study with breast cancer survivors who had received radiation therapy (n = 58) and/or chemotherapy (n = 72) and 204 healthy controls. COMT genotyping was accomplished via saliva samples. Performance on neurocognitive tests was compared across the groups. COMT-VAL+ carriers demonstrated poor performance on tests of attention, verbal fluency, and motor speed. VAL+ participants who had received chemotherapy performed more poorly on tests of attention than VAL+ participants in the healthy control group. This allele may confer added risk for cognitive changes associated with chemotherapy. Future genetic characterization may provide important information to identify individuals who are at high risk for CI and lead to further individualization of cancer therapy.

Concurrent Symptoms and Demographic Variance

Individuals with cancer commonly experience the symptoms of depression, anxiety, and fatigue (Jansen et al., 2005; Lezak et al., 2012; Meyers, Albitar, & Estey, 2005). Each of these symptoms has the potential to affect cognitive function (Jansen et al., 2005). Depression and anxiety, also referred to as symptoms of distress, may occur as a result of the psychosocial impact of the diagnosis or as an affective response to the physical symptoms caused by the disease and treatment (Jansen et al., 2005). Fatigue is the most common symptom reported by individuals with cancer during and after treatment (Mehnert et al., 2007; Stricker, Drake, Hoyer, & Mock, 2004). All three symptoms have been associated with the release of proinflammatory cytokines (due to the cancer and chemotherapy) (Myers, 2008).

Bender et al. (2006) found that self-report of CI was associated with depression. Castellon et al. (2004) noted that women who reported higher levels of anxiety, depression, or fatigue reported more cognitive complaints than women who did not have anxiety, depression, or fatigue. However, CI after chemotherapy has been demonstrated even when controlling for depression, anxiety, and fatigue (Ahles & Saykin, 2002; Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003; Schagen et al., 2002; van Dam et al., 1998).

Lehto and Cimprich (1999) found that higher levels of anxiety were correlated with poor ratings on a self-report measurement of attentional function (the Attentional Function Index) in women with newly diagnosed breast cancer who were about to undergo surgery. However, anxiety did not correlate significantly with standard neuropsychological measurement of attentional function. Cimprich (1999) showed that the most common symptoms experienced and reported by women with newly diagnosed breast cancer prior to any treatment were insomnia, mood disturbance, fatigue, and inability to concentrate. Greater numbers of symptoms were significantly correlated with lower cognitive function (subjectively rated) and mood disturbance (as measured by the Profile of Mood States). In contrast, Tchen et al. (2003) found no significant correlation between CI and higher levels of fatigue, menopausal symptoms, or poorer quality of life.

Conflicting evidence exists as to whether anxiety, depression, and fatigue are associated with objective neuropsychological measures of CI or whether these symptoms are only associated with subjective self-reports of perceived CI. Regardless, these concurrent symptoms have the potential to exacerbate problems with cognitive performance and should be a component of ongoing assessment during and after cancer therapy and targeted for appropriate interventions.
Patients with cancer frequently experience chronic pain and anemia (Grant et al., 2013; Swarm, 2013). These concurrent symptoms are associated with difficulties in attention and concentration (McCracken & Iverson, 2001; Meyers, 2000). Anemia (hemoglobin levels of 12 mg/dl or less) is associated both with fatigue and changes in cognitive functioning (Jacobsen et al., 2004). As with depression, anxiety, and fatigue, chronic pain and anemia should be addressed with appropriate interventions (see Chapters 3 and 20).

Complaints of forgetfulness and memory concerns are common among the aging population (Mol et al., 2007), and older adults may be at greater risk for cancer-related cognitive changes. However, Cimprich, So, Ronis, and Trask (2005) published research results indicating that younger age may be associated with an increased perception of changes in cognitive function and, therefore, CI may have a greater impact on quality of life. Higher levels of education and intelligence are hypothesized to be associated with high baseline function and cognitive reserve that may mitigate the effects of cancer and cancer treatment on cognitive performance (Jansen, Miaskowski, Dodd, & Dowling, 2007).

Cytokines

Cytokines are proteins secreted by cells of the immune system that help to regulate immunity, the inflammatory process, and hematopoiesis. Interleukins (ILs) and interferons are examples of cytokines that occur naturally and yet can be administered as a type of biotherapy to treat certain types of cancer. Although the naturally occurring cytokines are released peripherally, they can act upon the CNS. The exact mechanism is unclear, but various pathways appear to allow cytokines to cross the blood-brain barrier, travel to the brain, and induce behavioral changes. Dantzer (2001) discussed the term sickness behavior, whereby the release of proinflammatory cytokines can induce a decrease in general activity, exploratory behavior, oral intake, and brain stimulation, as well as impair memory and learning.

In a study designed to assess cytokine-associated emotional and cognitive disturbances in healthy young men, Reichenberg et al. (2001) injected the participants (N = 20) with an endotoxin and drew blood samples hourly to measure cytokine levels. Neuropsychological testing was performed at various time points (one, three, and nine hours) after the injection of the endotoxin. The results showed a transient significant increase in anxiety (p = 0.009) and depression (p = 0.003) at one to two hours postinjection and a significant global decrease in verbal and nonverbal memory functions (p values ranging from 0.01 to 0.008) on neuropsychological testing. High cytokine levels were significantly correlated with greater levels of anxiety and depression and lower memory performance.

In patients with cancer, cytokines have been associated with the development of many symptoms, including anorexia-cachexia, asthenia, pain, sleep disturbances, mood disturbances, and fatigue (Dunlop & Campbell, 2000). The cognitive impact of exogenous administration of cytokines is well documented for patients with cancer receiving high doses of interferon-alpha and IL-2 (Capuron, Ravaud, & Dantzer, 2001). Cognitive changes have been seen for spatial and temporal disorientation, decreased processing speed, verbal memory, and executive function for patients receiving exogenous cytokines.

Naturally occurring proinflammatory cytokines (such as IL-1, IL-6, and tumor necrosis factor-alpha [TNF-α]) are released because of the body’s response to cancer or because of the damage caused by the cancer (Miller, 2003). These cytokines have been shown to play a role in cancer progression and metastases (Dunlop & Campbell, 2000). Proinflammatory cytokine release also is associated with some treatments for cancer, such as chemotherapy (Niiya et al., 2003; Wichmann et al., 2003; Zaks-Zilberman, Zaks, & Vogel, 2001). The release
of cytokines in response to cancer and chemotherapy is hypothesized to play a role in the development of CI (Ahles & Saykin, 2007; Merriman et al., 2013).

Cancer Therapy and Cognition

Chemotherapy

Numerous hypotheses have been postulated as to the causal mechanism(s) for chemotherapy-related CI, including direct injury to cerebral gray and white matter, microvascular injury (Wefel et al., 2004), DNA damage and oxidative stress (Ahles & Saykin, 2007; Chen, Jungsuwadee, Vore, Butterfield, & St. Clair, 2007), cytokine-induced inflammatory response (Ahles & Saykin, 2007), chemotherapy-induced anemia (Mancuso, Migliorino, De Santis, Saponiero, & De Marinis, 2006; Massa, Madeddu, Lusso, Gramignano, & Mantovani, 2006), and chemotherapy-induced menopause (Jansen et al., 2005).

Preclinical investigation highlighted a potential relationship among injury to neural progenitor cells, impaired maintenance of white matter integrity, and subsequent CI (Dietrich, Han, Yang, Mayer-Pröschel, & Noble, 2006; Dietrich, Monje, Wefel, & Meyers, 2008). Dietrich et al. (2006) noted that self-renewing, lineage-committed neural progenitor cells and nondividing mature oligodendrocytes (myelin-forming cells) are the most vulnerable cell populations to chemotherapeutic agents. Repetitive exposure to chemotherapeutic agents exceeded cellular repair potential and resulted in long-term suppression of cell division and apoptosis in the subventricular zone, hippocampus, and major white matter tracts of the CNS in animal models (Dietrich et al., 2006).

Some chemotherapeutic agents, such as etoposide (Wood et al., 2006) and the taxanes (Ahles & Saykin, 2007), are associated with the release of proinflammatory cytokines and may be associated with a secondary inflammatory response that results in CI. In vitro work with chemotherapeutic agents demonstrated production of proinflammatory cytokines in various cancer cell lines (Maier & Watkins, 2003; Niiya et al., 2003; Wichmann et al., 2003; Zaks-Zilberman et al., 2001).

Ganz et al. (2013) recently conducted a longitudinal prospective trial designed to evaluate whether a relationship exists between recent chemotherapy exposure in women with early-stage breast cancer and proinflammatory cytokines. Women younger than age 65 who had completed surgery, radiation, and/or chemotherapy but who had not yet initiated hormonal therapy were assessed for self-reported and objective measures of CI and levels of four inflammatory markers (N = 93). Participants were assessed for fatigue, depression, and sleep disturbance. The mean plasma level for a surrogate marker for TNF-α (soluble TNF receptor type II, or sTNF-RII) was elevated at baseline for the women who had received chemotherapy (n = 49). Higher levels of sTNF-RII were correlated with memory complaints. Participants (n = 49) who received chemotherapy also had significantly more fatigue (p = 0.003). A high correlation was demonstrated for fatigue, memory complaints, and depression. The authors concluded that a common underlying biologic process may mediate these symptoms. Declines in sTNF-RII were associated with improvements in self-reported memory. Interestingly, significant correlations (r = –0.55, p = 0.02) were seen for sTNF-RII levels and cerebral metabolic changes per neuroimaging, despite lack of correlation with objective neuropsychological tests. These results lend further support to the importance and accuracy of patients’ self-report of CI.

Oxidative stress occurs when the generation of reactive oxygen and nitrogen species exceed cellular adaptive and repair capacities (Chen et al., 2007). Numerous chemotherapeutic agents are reported to induce oxidative stress. Some of these agents include the anthra-
cyclines, cyclophosphamide, 5-fluorouracil, cisplatin, busulfan, mitomycin, cytarabine, and bleomycin. Oxidative stress associated with doxorubicin therapy (an anthracycline) occurs in nontargeted tissues and leads to injury of normal tissues (Chen et al., 2007). Doxorubicin, like other chemotherapeutic agents administered in standard doses, was believed not to cross the blood-brain barrier. However, doxorubicin has been associated with increased circulating levels of TNF-α in animal models. TNF-α can penetrate the blood-brain barrier and activate glial cells in the CNS to produce more TNF-α in the brain. Synthesis of TNF-α in the CNS is related to the induction of nitric oxide synthase (Chen et al., 2007; Joshi et al., 2010). As a result, the generation of reactive nitrogen species, including nitric oxide, increases (Tangpong et al., 2007). Additionally, the neurotoxicity associated with doxorubicin-induced TNF-α resembles the free radical mechanisms implicated in Alzheimer disease (Tangpong et al., 2007).

Commonly used chemotherapeutic agents, such as 5-fluorouracil, methotrexate, vinca alkaloids, and taxanes, have been known to affect the nervous system in a variety of ways. Choi et al. (2001) documented cognitive problems in a group of women who had developed leukoencephalopathy as a result of treatment for breast cancer with 5-fluorouracil. Patients with breast cancer treated with a high-dose chemotherapy regimen that included high doses of methotrexate were shown to have a higher incidence of CI (32%) than women treated with standard-dose chemotherapy (17%) or healthy controls (9%) in a historical study (van Dam et al., 1998). Methotrexate also has been associated with encephalopathy when it is administered in high doses or intrathecally. In a small study (N = 18) conducted to assess the cognitive effects of treatment with intrathecal methotrexate and whole brain radiation therapy (WBRT) to treat primary CNS lymphoma, researchers found that 21% of the sample (n = 4) developed severe cognitive dysfunction after therapy (Harder et al., 2004).

Chemotherapy can affect cognitive function via a more indirect route. For example, chemotherapy given to premenopausal women may result in altered or complete cessation of ovarian function. This cessation of ovarian function may result in complete menopause. Historical reports indicated that adjuvant chemotherapy induces menopause in up to 77% of premenopausal women receiving treatment for breast cancer (Bender, Paraska, Sereika, Ryan, & Berga, 2001). Research in women receiving polychemotherapy regimens, including doxorubicin and taxanes, has demonstrated substantial cessation of menses for women 20–45 years old (41%) (Sukumvanich et al., 2010). This cessation can be a temporary or permanent condition, and the resulting drop in estrogen levels potentially could affect cognitive function (Bender et al., 2001).

**Hormone Therapy**

The use of hormonal agents to treat breast and prostate cancer may be associated with CI, although study results have been mixed. Anastrozole, an aromatase inhibitor used to treat estrogen receptor-positive postmenopausal breast cancer, works by reducing plasma estrogen levels. Bender et al. (2007) found that women with early-stage breast cancer who were taking anastrozole scored significantly lower on tests of verbal and visual learning and memory (n = 15, p < 0.01) than women who were taking tamoxifen (n = 16). Tamoxifen, an estrogen receptor modulator with both agonist and antagonist effects, prevents the uptake of estrogen by blocking the estrogen receptors on breast cancer cells (Castellon et al., 2004). Some evidence has pointed to an antagonistic effect of tamoxifen in the brain (Sumner et al., 1999). Phillips et al. (2010) reported better cognitive function for women receiving the aromatase inhibitor letrozole (n = 65) compared to those treated with tamoxifen (n = 55). Follow-up results one year after cessation of endocrine therapy indicated that performance
on objective neuropsychological tests improved (N = 100) (Phillips et al., 2011), but participants’ self-report of perceived CI did not improve (N = 100) (Ribi et al., 2012).

Schagen et al. (1999) and Ahles et al. (2002) found no significant differences on measures of cognitive function in women with breast cancer who had received tamoxifen after chemotherapy compared to those who had not received tamoxifen. Similar results were noted by Paganini-Hill and Clark (2000) and Hermelink et al. (2008). However, results of other studies have shown an association between tamoxifen and poorer performance on tests of verbal learning, language, visuospatial functioning, and verbal memory (Castellon et al., 2004; Eberling, Wu, Tong-Turnbeaug, & Jagust, 2004).

Breckenridge, Bruns, Todd, and Feuerstein (2012) examined women with breast cancer with past or current exposure to aromatase inhibitors or tamoxifen (n = 77) to women with breast cancer with no history of hormonal therapy (n = 56). Exposure to hormonal therapy was not associated with performance on objective neuropsychological tests. However, significant correlation was seen for self-reports of perceived CI (p < 0.05). Self-reports of perceived CI were associated with fatigue, depression, and anxiety (R^2 change range: 0.28–0.37).

Results from a number of studies demonstrated a significant effect of ADT on cognition (Bussiere, Beer, Neiss, & Janowsky, 2005; Cherrier, Aubin, & Higano, 2009; Green et al., 2002, 2004; Jenkins, Bloomfield, Shilling, & Edginton, 2005; Wu et al., 2013). Declines in spatial reasoning, spatial abilities, and working memory were significant for the men receiving ADT. In a few studies, deterioration was seen for some neuropsychological tests while improvement was seen in other tests, leading the researchers to conclude that testosterone decline is associated with selective cognitive domains (Almeida, Waterreus, Spry, Flicker, & Martins, 2004; Salminen, Portin, Koskinen, Helenius, & Nurmi, 2004, 2005). In contrast, other study results did not demonstrate a significant impact of ADT on cognition for men with prostate cancer (Almeida et al., 2004; Joly et al., 2006; Salminen et al., 2003, 2004). Interesting results were seen by Chao et al. (2012). Men with prostate cancer (N = 30) receiving ADT (n = 15) or not (n = 15) were evaluated by neuropsychological tests and functional magnetic resonance imaging (fMRI) during a memory test. Although no differences in neuropsychological tests were seen for men receiving ADT, statistically significant associations were seen between ADT and decreased medial prefrontal cortical activation by fMRI (p = 0.009). Other neuroimaging study results have indicated that self-report of CI and changes in cerebral activation may precede evidence of CI as assessed by current available neuropsychological tests (Saykin et al., 2006). Larger longitudinal studies are needed to further explore the potential effects of ADT on cognition.

Radiation Therapy

WBRT has been known to cause leukoencephalopathy, which is characterized by damage to the myelin found in the cerebral white matter of the brain. Leukoencephalopathy tends to occur 6–24 months after treatment with WBRT, and the results on cognitive function can be profound (Aoyama et al., 2007). Reports of emotional dysfunction and declines in memory and attention have been documented. More severe effects include dementia, stupor, and coma (Aoyama et al., 2007). Delayed effects of radiation therapy to the CNS may be due to vascular injury, demyelination of white matter, and necrosis (Correa, 2010). Risk factors for delayed effects of radiation therapy include greater tissue volumes exposed to radiation therapy, higher total doses, concomitant chemotherapy, advanced age (older than 60), and vascular risk factors (Correa, 2010).

Prophylactic cranial irradiation (PCI) continues to be a treatment offered to patients with small cell lung cancer to prevent brain metastasis. Patients with small cell lung cancer were
evaluated with neuropsychological testing after chemotherapy and prior to and following PCI. The researchers found that 47% of the participants had evidence of CI before receiving PCI (Grosshans et al., 2008). A transient drop in performance on tests of executive function and language skills occurred with PCI, but performance improved over time (Grosshans et al., 2008). In a study of older adult patients with glioblastoma multiforme (GBM), the use of focal radiation therapy of daily fractions of 1.8 gray (Gy) for a total weekly dose of 50 Gy plus supportive care significantly increased survival without damage to cognitive function (Keime-Guibert et al., 2007).

CNS lymphomas frequently are treated with combined modalities of high-dose methotrexate and WBRT. CNS damage is produced through vascular injury, neuronal loss, inflammation, demyelination, and necrosis, as well as disruption of hippocampal neurogenesis (Collins et al., 2013). Correa et al. (2012) found that patients receiving high-dose methotrexate without WBRT (n = 26) experienced reduced levels of CI (p < 0.001) compared to patients receiving the combined-modality therapy (n = 24).

Gan et al. (2011) investigated cognitive functioning after radiation or chemoradiation for a small sample of patients (N = 10) with head and neck cancer. Significant correlation was seen between the severity of memory impairment and radiation dose to the temporal lobes of the brain (p = 0.03).

Conducting research to determine the causal mechanisms of CI is complicated by the potential impact of the various therapies for treating malignancies. Research is further complicated further when the damage related to primary and secondary brain tumors is taken into account.

**Brain Tumors**

Patients with brain tumors experience unique challenges. Tumors may have a direct effect on CNS function, including cognitive function. Factors such as tumor size and location, tumor histology, and treatment regimen may play a part in the presence of CI in patients with brain tumors (Zucchella et al., 2013).

The location of the brain tumor may affect cognition. Patients with frontal tumors scored lower overall on cognitive testing (Kaleita et al., 2004) and may exhibit difficulties with impulse control, information retrieval, reaction time, and facial recognition (Klein, Duffau, & De Witt Hamer, 2012). Patients with tumors of the left hemisphere experience more depressive symptoms and memory impairment (Hahn et al., 2003) and may have difficulties with executive function and concentration (Correa, 2006). Tumors in the right hemisphere are associated with visual and spatial cognitive deficits (Klein et al., 2012). However, tumor location was not associated with nonverbal memory scores or any other cognitive domain scores in a study conducted by Correa et al. (2007).

Histology of the brain tumor may or may not affect cognition. Hahn et al. (2003) found that patients with GBM scored lower on tests of psychomotor function and visual scanning compared to patients who did not have a GBM histology. However, Kayl and Meyers (2003) found no differences on neuropsychological testing between patients with GBMs and those with anaplastic astrocytomas.

Results from one study demonstrated that surgery and radiation did not appear to be significant predictors of cognitive function for patients with brain tumors (Kaleita et al., 2004). When evaluating differences between WBRT with or without radiosurgery, researchers found control of disease to be the most important factor in maintaining cognitive function (Aoyama et al., 2007) and that the tumor itself was more detrimental to cognitive function than the treatment. Talacchi, Santini, Savazzi, and Gerosa (2011) noted that the decompres-
sive effects of surgery and decreased intracranial pressure improved cognitive function for 24% of the patients in their study (N = 29, n = 7) compared to 38% of patients who had CI postoperatively (n = 11). Of note, postoperatively, the impact of residual tumor, radiation, chemotherapy, and surgical resection on cognition is very difficult to disentangle (Talacchi et al., 2011).

As with other patients with non-CNS cancer, age, fatigue, sleep disturbance, depression, and anxiety can influence the degree of CI. Neuropsychological testing in these patients showed that younger patients scored better than middle-aged or older patients (Kaleita et al., 2004). Depression, fatigue, sleep disturbance, CI, and pain have been found to be a symptom cluster in patients with high-grade gliomas (Fox, Lyon, & Farace, 2007). Long-term survivors of GBM were found to have significant CI, anxiety, depression, and decreased social functioning and ability to work. However, the quality-of-life scores of this group of GBM survivors generally were reported to be good (Steinbach et al., 2006). Because of the nature of CNS malignancies and direct tissue invasion from primary and secondary brain tumors, healthcare professionals may be more apt to assess patients for changes in cognition. Recognition of the cognitive sequelae for treatment of non-CNS malignancies is important to providing quality cancer care. However, assessment of subtle changes in cognition related to cancer and cancer therapy has proved to be very challenging.

Assessment

Domains of Cognition and Standard Neuropsychological Testing

Cognition involves complex thought processes, which can be classified in various ways. The five broad components of general cognitive function include (a) receptive abilities, (b) memory, (c) expressive functions, (d) thinking, and (e) mental activity variables (Lezak et al., 2012). Receptive abilities are the ways in which individuals receive, classify, and integrate information. Memory involves the storage and retrieval of information. Expressive functions refer to the ability to communicate information. Thinking includes the ability to form concepts and organize information. Mental activity variables comprise behavioral characteristics that are intimately involved in cognitive operations and include level of consciousness, attentional functions, and activity rate. The ability to direct attention is necessary for each of these classes of cognitive functioning to operate efficiently. Activity rate refers to the mental processing speed, as well as the speed of motor responses.

In addition to cognitive functions, another important concept for mental performance is executive function. Executive function consists of the ability to “engage successfully in independent, purposeful, self-directed, and self-serving behavior” (Lezak et al., 2012, p. 37), including the ability to decide upon a desired action followed by outlining and executing the necessary steps to achieve the desired outcome. Neuropsychological testing generally is performed to test levels of functioning in all aspects of cognition.

A typical battery of neuropsychological testing can take up to eight hours to complete, with many of the measures used to assess more than one cognitive domain. An overview of the domains of cognition, the functions associated with each domain, and examples of neuropsychological tests that are used to assess each domain is provided in Table 9-1. Global assessment measures are tools used to assess multiple areas of cognitive function and often are used to quickly screen for abnormalities. One such global assessment tool, the High Sensitivity Cognitive Screen (HSCS), can predict (but not mea-
sure) how cognitively intact a person will be in six domains of cognition (Fogel, 1991). The HSCS takes approximately 25 minutes to administer and initially was developed to screen for mild delirious states. As the HSCS was not developed to detect changes in cognitive function in patients with cancer, the HSCS may not be the most accurate tool to use in this setting.

Interpretation of research results is complicated by the lack of consistency in selection of neuropsychological tests and the cognitive domains that are evaluated. The International Cognition and Cancer Task Force (ICCTF) published recommendations for a core set

<table>
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<tr>
<th>Domain of Cognition</th>
<th>Definition</th>
<th>Examples of Neuropsychological Tests</th>
</tr>
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<tbody>
<tr>
<td>Abstract reasoning</td>
<td>The ability to solve complex problems by generating a hypothesis and incorporating feedback that may then modify the problem-solving effort</td>
<td>D-KEFS Card Sorting Test</td>
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<tr>
<td>Attention and concentration</td>
<td>The ability to focus on direct attention to a particular problem and ignore extraneous stimuli not required to solve the problem. This domain also includes the ability to multitask, or concentrate on more than one task at a time.</td>
<td>CPT&lt;br&gt; D-KEFS subtests (Trail Making, Color-Word Interference, Verbal Fluency)&lt;br&gt; P3SAT</td>
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<tr>
<td>Information processing speed</td>
<td>Refers to how quickly one can internalize and assess information</td>
<td>D-KEFS Trail Making Tests&lt;br&gt; Digit Symbol-Coding (WAIS-III)&lt;br&gt; P3SAT</td>
</tr>
<tr>
<td>Language and verbal skills</td>
<td>Refers to both receptive and expressive skills. Enables one to comprehend directions and correctly respond using verbal abilities</td>
<td>D-KEFS Verbal Fluency Tests&lt;br&gt; WASI Vocabulary subtest&lt;br&gt; WRAT-3 Reading subtest</td>
</tr>
<tr>
<td>Learning and memory</td>
<td>The ability to commit new information to memory so that it may be retrieved. Tests assessing this domain will assess both long- and short-term memory function as well as verbal and nonverbal learning and memory.</td>
<td>CVLT and CVLT-II&lt;br&gt; Faces I and II (WMS-III)&lt;br&gt; Logical Memory I and II (WMS-III)</td>
</tr>
<tr>
<td>Motor skills</td>
<td>Tests of motor skills assess the speed and dexterity of motor functioning, as well as how quickly the brain can signal the body to perform tasks that vary in complexity</td>
<td>D-KEFS Trail Making Tests&lt;br&gt; Digit Symbol-Coding (WAIS-III)&lt;br&gt; Grooved pegboard</td>
</tr>
<tr>
<td>Visuospatial and visuoconstrucional skills</td>
<td>Visuospatial and visuoconstrucional abilities include the capacity to process visual features of a stimulus and to coordinate motor output to construct or reproduce visual stimuli.</td>
<td>WASI Block Design subtest</td>
</tr>
</tbody>
</table>

CPT—Continuous Performance Test; CVLT—California Verbal Learning Test; D-KEFS—Delis-Kaplan Executive Function System; PASAT—Paced Auditory Serial Addition Test; WAIS-III—Wechsler Adult Intelligence Scale, Third Edition; WASI—Wechsler Abbreviated Scale of Intelligence; WMS-III—Wechsler Memory Scale, Third Edition; WRAT-3—Wide Range Achievement Test, Revision 3

Note. Based on information from Lezak et al., 2012.
of neuropsychological tests, criterion to define CI, and study methods to improve research
design (Wefel, Vardy, Ahles, & Schagen, 2011). ICCTF recommended specific tests for the
measurement of learning and memory, processing speed, and executive function, including
Hopkins Verbal Learning Test–Revised (Benedict, Schretlen, Groninger, & Brandt, 1998),
the Trail-Making Test (Reitan, 1992), and the Controlled Oral Word Association of the Mul-
tilingual Aphasia Examination (Benton & Hamsher, 1989).

One of the problems with using standard neuropsychological testing in patients with can-
cer is that these tests were not developed specifically for the CI reported by this population.
Such tests may not fully identify subtle changes that an individual finds very meaningful. In
a study conducted to assess cognitive function in patients with ovarian cancer who were re-
cieving chemotherapy, researchers found that women with more education perceived mem-
ory and concentration declines despite testing in the normal ranges on neuropsychological
testing (Hensley et al., 2006).

A number of self-report instruments are available for the assessment of perceived cog-
nitive function. Two of the available instruments that have been validated for use with the on-
cology population are the Attentional Function Index (Cimprich, Visovatti, & Ronis, 2011)
and the Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog) (Wag-
nier et al., 2009). The Attentional Function Index is designed to measure the perceived ef-
fectiveness in activities requiring attention and working memory, such as the ability to for-
mulate plans, carry out tasks, and function effectively in daily life. The FACT-Cog includes
subscales for perceived cognitive impairments, perceived cognitive abilities, and the impact
of perceived cognitive impairments on quality of life.

Self-report of CI in the face of normal neuropsychological testing results has been asso-
ciated with depression (Bender et al., 2006; Castellon et al., 2004), anxiety (Castellon et al.,
2004; Schagen et al., 2008), fatigue (Castellon et al., 2004; Downie et al., 2006), menopausal
symptoms (Downie et al., 2006), distress (Schagen et al., 1999; Shilling & Jenkins, 2007), and
self-report of poor quality of life (Shilling & Jenkins, 2007). Little correlation has been seen
between objective neuropsychological tests and self-report instruments. Some have speculat-
ed that these two types of testing may measure different constructs (Hermelink et al., 2010;
Pullens, De Vries, & Roukema, 2010).

Research results indicated that self-report of cognitive changes may precede evidence of
CI measured by neuropsychological testing. Saykin et al. (2006) used neuroimaging to com-
pare gray matter volume for older adults with mild CI and individuals with self-reported cog-
nitive complaints with that of healthy controls. They noted that the individuals with cog-
nitive complaints demonstrated similar patterns of gray matter loss as the individuals with
documented mild CI. However, those individuals with cognitive complaints performed with-
in normal limits on neurocognitive testing. These findings highlighted the importance of
self-report.

The oncology nurse may not have access to neuropsychological testing or self-report
assessment instruments for patients with cancer. The best method for nurses to use when
evaluating patients with reports of CI may be to ask them to describe details of their ex-
perience. Jansen (2013) developed a practical algorithm for nurses to use when decid-
ing if referral to a neuropsychologist is needed (see Figure 9-3). She suggested respond-
ing to patients’ reports (or those of family/friends) of CI by ruling out other potential
treatable confounders such as psychological factors (depression, anxiety), comorbidities,
medications, laboratory abnormalities, and lifestyle factors. If treatable confound-
ers are identified, clinicians should implement appropriate measures to treat the un-
derlying cause. If no confounders are identified, nurses should consider referral to a
neuropsychologist.
Radiologic Findings

Radiologic studies most commonly are used to evaluate primary or secondary CNS involvement and have not been a standard part of the workup for CI. However, radiologic studies to assess for changes in the brains of patients with cancer have been used in a number of studies. Magnetic resonance imaging (MRI) studies were used to assess the brains of pa-
tients with lung cancer who had completed chemotherapy (Ciszkowska-Lyson et al., 2003). The MRI results indicated areas of neuronal loss and demyelination. Similar abnormal findings of the brain also have been found in patients with breast cancer. Functional positron-emission tomography scans were used to evaluate the brains of women with breast cancer treated 5–10 years prior with chemotherapy with or without tamoxifen and to compare the results with healthy controls. The researchers found significant alterations in the activity of the frontal cortex, cerebellum, and basal ganglia in the breast cancer group (Silverman et al., 2007).

Research results documenting evidence of cognitive changes prior to cancer therapy (Grosshans et al., 2008; Hermelink et al., 2007; Wefel et al., 2004) are being supported by results from neuroimaging studies. Scherling, Collins, Mackenzie, Bielajew, and Smith (2011) examined neurofunctional differences during working memory tasks for patients with breast cancer and healthy controls after surgery and prior to chemotherapy. No significant differences were seen between the groups for performance on neuropsychological tests or estrogen and cortisol levels; however, significant differences were noted by fMRI related to brain activation during visuospatial working memory tests. McDonald, Conroy, Ahles, West, and Saykin (2012) used fMRI to document differences in frontal lobe activation in women with breast cancer prior to therapy compared with controls. Increased bifrontal and decreased left parietal activation was noted for patients with cancer at baseline. Additional changes in activation were noted after chemotherapy, and some recovery was seen one year after completion of therapy.

Neuroimaging work is producing intriguing information about individuals’ ability to compensate for cancer-related cognitive changes. Ferguson, McDonald, Saykin, and Ahles (2007) studied female monozygotic twins with fMRI during a memory task. One twin was a survivor of breast cancer who had received chemotherapy. Her sister had no history of malignancy. Both twins performed within normal limits on the memory task. However, the fMRI results indicated that the breast cancer survivor recruited more memory circuitry (as evidenced by broader activation noted in the bilateral frontal and parietal regions of the brain); in other words, she had to work harder to achieve the same result. This study and others provide evidence that fMRI can be more sensitive to functional differences than behavioral measures (Reuter-Lorenz & Cimprich, 2013).

Structural changes in the brain also have been demonstrated by neuroimaging studies. McDonald, Conroy, Ahles, West, and Saykin (2010) documented decreases in brain gray matter density shortly after chemotherapy for breast cancer, with some recovery in density occurring one year after the completion of therapy. The study of fMRI to document changes in neural activity patterns over time is ongoing.

**Evidence-Based Interventions**

The study of interventions for CI in patients with cancer is relatively new. Most of the research to date assessing interventions for CI has focused on patients with breast cancer. Both pharmacologic and nonpharmacologic interventions are under investigation. At this time, no interventions have achieved the evidence-based practice status of Recommended for Practice (Allen, 2011). However, initial positive results have been seen for some neurostimulants, a cholinesterase inhibitor, and exercise, and cognitive behavioral therapy (CBT) recently was categorized as Likely to Be Effective in the Oncology Nursing Society Putting Evidence Into Practice resource (Von Ah, Allen, Jansen, & Wulff, 2014). Qualitative research has yielded patients’ suggestions for coping strategies and behavioral changes to mitigate
the impact of CI. Although not based on randomized controlled studies, these suggestions may be of assistance to those challenged by CI.

Pharmacologic Interventions

Neurostimulants

Neurostimulants have been used to treat attention deficit/hyperactivity disorder (ADHD) and narcolepsy. Three neurostimulants have been investigated for potential use in treating cancer-related CI and fatigue and include dexamphetamine, methylphenidate, and modafinil. Dexamphetamine and methylphenidate work by blocking the uptake of dopamine and increasing dopamine and norepinephrine levels and are approved for use with ADHD (Butler et al., 2007). Modafinil is approved for use to treat narcolepsy, obstructive sleep apnea, and shift work sleep disorder and is associated with the release of norepinephrine, dopamine, and histamine (Gehring et al., 2012). Results of studies with these agents as interventions for cancer-related CI have been mixed.

Butler et al. (2007) investigated the prophylactic use of escalating doses of d-threo-methylphenidate (5–15 mg twice daily) versus placebo in 68 patients with primary brain tumors receiving radiation therapy. Assessments for fatigue and cognitive function were conducted at baseline and 4, 8, and 12 weeks after therapy. No difference in fatigue or cognitive performance was seen for either group. Another comparison of d-methylphenidate to placebo on fatigue and cognitive dysfunction was performed by Mar Fan et al. (2008) in women with breast cancer receiving adjuvant chemotherapy. This trial closed early because of slow recruitment and the reluctance of women to take additional medication, specifically methylphenidate. The study therefore was underpowered and no improvements were seen for cognitive function, quality of life, or fatigue. In both of the aforementioned studies, cognitive function was assessed with the Mini-Mental State Examination, a test designed to assess gross cognitive function. The Mar Fan et al. (2008) study also included the HSCS, a test now known to have significant practice effects. Lower et al. (2009) published results of a multicenter, randomized, placebo-controlled, parallel group study to evaluate the effect of d-methylphenidate on fatigue after chemotherapy (N = 154). Fatigue was improved significantly for participants receiving methylphenidate, but no improvements were seen in cognitive function. However, cognitive function was a secondary endpoint, and the study was not powered for this endpoint. Both the Mini-Mental State Examination and the HSCS were used as instruments to measure CI. Adverse events for participants receiving methylphenidate included dry mouth, headache, nausea, and feeling jittery.

Positive results were demonstrated when modafinil and two formulations of methylphenidate (immediate versus sustained release) were compared over four weeks for 24 patients with primary brain tumors (Gehring et al., 2012). Benefits were seen for test performance in processing speed and executive function requiring divided attention. Some differential inconsistencies were noted, with one measure of attention favoring methylphenidate and one measure of processing speed favoring modafinil. A general beneficial effect was noted for patient-reported measures of fatigue, mood, and quality of life for both drugs (and both formulations of methylphenidate).

Significant improvements in some memory speed (Speed of Memory Index, mean change 240.003 seconds; p = 0.0073) and attention skills (Digit Vigilance Test, mean change 1.623 U; p = 0.0014) in fatigued patients with breast cancer were associated with the use of modafinil in a secondary analysis conducted by Kohli et al. (2007). The primary study was designed to evaluate the use of modafinil to treat cancer-related fatigue. Participants were within one month of having received chemotherapy and/or radiation therapy.
Lundorff, Jønsson, and Sjøgren (2009) studied modafinil in 28 patients who self-reported fatigue. Statistically significant improvements were seen in neuropsychological tests for psychomotor speed and attention when modafinil was compared to placebo. Improvement also was noted for depression and drowsiness.

Blackhall, Petroni, Shu, Baum, and Farace (2009) evaluated the use of modafinil in 26 fatigued patients with cancer. Testing was administered for fatigue, depression, quality of life, functional status, and neurocognitive function. Significant improvements were demonstrated for one neuropsychological test designed to assess the attention and cognitive flexibility components of executive function (Trail Making Test B). However, most of the improvement noted during the study was related to fatigue. The authors concluded that if improvements in the Trail Making Test B could be replicated, modafinil may have an effect on cancer-related CI similar to the effects seen with ADHD (Blackhall et al., 2009).

Because of the mixed results and limitations of the studies conducted to date, the effectiveness of neurostimulants to treat cancer-related CI has not been established.

**Cholinesterase Inhibitor**

Donepezil is a reversible acetylcholinesterase inhibitor approved for use with mild to moderate dementia in patients with Alzheimer disease (Shaw et al., 2006). Preclinical work demonstrated the effectiveness of donepezil in reducing chemotherapy-induced cognitive deficits for laboratory animals exposed to methotrexate and 5-fluorouracil (Winocur, Binns, & Tannock, 2011). The following small clinical studies have yielded mixed results.

Donepezil was shown to improve attention/concentration, verbal memory, and figural memory for 24 patients with primary brain tumors who received daily doses of 5 mg for six weeks (Shaw et al., 2006). Assessment was conducted at baseline and at 12 weeks, the end of treatment (24 weeks), and 30 weeks. Other benefits included improvement in health-related quality of life and a trend toward improved emotional and social functioning.

Inconclusive results were found by Jatoi et al. (2005) when they attempted to evaluate a combination of donepezil and vitamin E for patients with small cell lung cancer who had completed cancer therapy, including PCI. The study was closed because of insufficient enrollment (9 of 104 participants), so no conclusions could be drawn. The researchers attributed the low enrollment to restrictive eligibility criteria (complete response or minimal residual disease following cancer therapy that included PCI) and patients’ reluctance to accept trial participation after the completion of therapy. Further research is needed to evaluate the effectiveness of donepezil for cancer-related CI.

**Other**

Memantine is an N-methyl-D-aspartate receptor antagonist approved for moderate to severe Alzheimer disease. Exciting results from a recent Radiation Therapy Oncology Group trial were presented at the 2012 American Society for Radiation Oncology meeting (Brown et al., 2012). Patients (N = 508) with brain metastases receiving WBRT were randomized to receive memantine versus placebo over the course of 24 weeks. Participants receiving memantine had significantly longer time to cognitive decline (p = 0.02) compared to those receiving placebo. The results of the study did not demonstrate significance for the endpoint of improvements in delayed recall (p = 0.059). However, this study provided evidence to support further investigation. The researchers were hopeful that further translational analysis would identify predictive biomarkers for cognitive decline and memantine benefit (Brown et al., 2012).

Initial research indicated that the use of erythropoietin to raise hemoglobin levels might be beneficial for mitigating the effects of anemia (hemoglobin less than 12 g/dl) on cogni-
tion (Massa et al., 2006). However, because of concerns about cardiovascular and thrombovascular events, as well as the potential to shorten overall survival due to tumor progression, the use of erythropoietin for cancer-related CI is not recommended for practice (Allen, 2011).

One study has been conducted to evaluate the use of granulocyte macrophage–colony-stimulating factor (GM-CSF) and/or granulocyte–colony-stimulating factor (G-CSF) treatment for cancer-related CI (Jim et al., 2012). The researchers noted that endogenous GM-CSF is released in individuals with rheumatoid arthritis, and individuals with rheumatoid arthritis rarely suffer from Alzheimer disease. The researchers also noted that exogenous administration of GM-CSF into laboratory mice reduced amyloid deposition and restored normal cognitive function. Jim et al. performed a longitudinal analysis with 95 patients receiving hematopoietic stem cell transplantation. Neuropsychological testing was administered 6 and 12 months post-transplant. GM-CSF plus G-CSF therapy was associated with greater cognitive improvements than G-CSF alone. The researchers are proceeding with randomized controlled trials to further evaluate the effectiveness of colony-stimulating factors.

**Nonpharmacologic Interventions**

**Cognitive Behavioral Therapy**

CBT is a form of psychotherapy that is based on the idea that perceptions and beliefs held by an individual affect how the individual feels emotionally about a particular situation. CBT tends to be goal oriented and can be completed in a relatively short amount of time (i.e., over several weeks to months). In CBT, the focus is on learning and practicing a variety of coping skills with an emphasis on behavioral coping strategies. CBT can be used to assist individuals in coping with stressful situations, as well as a medical illness such as cancer. CBT has been used successfully to assist in the rehabilitation of people with head injuries, stroke, and Alzheimer disease (Gehring et al., 2009).

More recently, CBT has been investigated as a potential intervention for individuals experiencing cancer-related CI. CBT also may be referred to as cognitive rehabilitation. Three common approaches are employed: (a) retraining to retrieve cognitive abilities, (b) teaching compensatory strategies and alternative ways of performing cognitive tasks, and (c) using holistic methods to address social, emotional, and functional issues related to CI (Fardell, Vardy, Johnston, & Winocur, 2011).

A form of CBT was found to improve cognitive function in patients with breast cancer who reported CI following chemotherapy (Ferguson, Ahles, et al., 2007). A CBT-based program titled “Memory and Attention Adaptation Training” (MAAT) was delivered to 29 patients with breast cancer who reported CI and were an average of eight years after therapy. Treatment consisted of the use of a workbook, a series of office visits, and telephone contacts to teach participants compensatory strategies to cope with the CI they had been experiencing. The participants were highly satisfied with the treatment, and significant improvement occurred in neuropsychological testing, self-reported cognitive function, and quality of life. Results of this study suggest that intervening with a form of CBT aimed at teaching coping strategies may be helpful to women treated for breast cancer who are experiencing CI.

A number of more recent studies have been conducted to investigate the use of CBT for cancer-related CI. Gehring et al. (2009) randomized 140 adults with low-grade and anaplastic gliomas to a CBT intervention group or control group. The CBT included computer-based attention retraining and compensatory skills training for attention, memory, and executive functioning. Objective and subjective measures were used for assessment at baseline, at completion of the program, and at a six-month follow-up. Immediately following the in-
tervention, significant improvements were seen on the subjective tests, but not the objective tests. However, at the six-month follow-up assessment, improvements were seen for neuropsychological tests of attention and verbal memory, and participants reported less mental fatigue.

Ferguson et al. (2012) continued their work in this area of research. They randomized 40 women with early-stage breast cancer to a MAAT intervention group or the control group. Participants were assessed at baseline, at eight weeks (post treatment), and at a two-month follow-up visit. The MAAT group demonstrated significant improvements on verbal memory but not in self-report of cognitive complaints. Improvements were noted for the spiritual well-being subscale and the quality-of-life measure.

Schuurs and Green (2013) recruited participants for three groups: intervention (n = 23), a comparison group of cancer survivors (n = 9), and a community sample with no history of malignancy (n = 23). The intervention group received four weeks of cognitive rehabilitation treatment. The intervention was effective in improving overall cognitive function, visuospatial/constructional performance, and immediate and delayed memory. Improvements were not attributed to practice effect and were maintained at three months.

Von Ah et al. (2012) conducted a three-group, single-blind, randomized controlled trial to compare memory training and speed-of-processing training to a wait-list control. A sample of 82 postmenopausal women with breast cancer who reported cognitive concerns after chemotherapy for nonmetastatic disease were recruited. The memory and speed-of-processing training groups participated in 10 one-hour sessions over six to eight weeks. Assessments took place at baseline, postintervention, and at two-month follow-up. The memory training group and speed-of-processing training group experienced domain-specific improvements. Both groups demonstrated improvements in perceived cognitive function, symptom distress, and quality of life.

In contrast, Poppelreuter, Weis, and Bartsch (2009) saw no effects for two types of neuropsychological interventions directed at improving functional attention and memory that were provided to women with breast cancer who had received adjuvant chemotherapy. In this study, 96 women on an inpatient oncology rehabilitation unit were randomized to one of two CBT interventions versus control. No significant intervention effects were seen, as all three groups demonstrated improvements during the study. However, a subset of participants had clinically relevant deficits at six-month follow-up. The researchers speculated that the lack of effect of the interventions could have been due to the overall recuperative process at the end of adjuvant chemotherapy, an unspecific effect of inpatient rehabilitation, or practice effects for the neuropsychological tests.

Taken together, the results of the research described in this section support continued investigation of CBT for cancer-related CI.

Exercise

The body of evidence is growing in support of exercise as an intervention for a variety of cancer-related symptoms, including cancer-related fatigue and CI (Mustian, Peppone, et al., 2009; Mustian, Sprod, et al., 2009). Two very interesting preclinical studies have been published that provide mechanistic support for the use of exercise as an intervention for CI. Fardell, Vardy, Shah, and Johnston (2012) exposed laboratory rodents to 5-fluorouracil and oxaliplatin (agents commonly used to treat colorectal cancer). Cognitive deficits were observed (impaired memory as measured by novel object recognition, and hippocampal-dependent tasks). Physical activity (four weeks of overnight wheel running) was shown (p < 0.05) to prevent the CIs experienced by control animals exposed to chemotherapy without the opportunity for exercise.
In a similar study, Wong-Goodrich et al. (2010) studied laboratory mice who received WBRT or sham therapy. The mice that were provided the opportunity for daily wheel running did not experience the marked decline in spatial memory retention observed months after radiation (tested by previous training in a Barnes maze prior to irradiation and subsequent performance after radiation). Additional benefits of exercise included partial restoration of neurons and increased expression of brain-derived vascular endothelial growth factor and insulin-like growth factor-1 in spite of increased levels of hippocampal proinflammatory cytokines.

Erickson et al. (2011) noted that deterioration of the hippocampus leads to memory impairment in older adults. Erickson et al. also noted that aerobic exercise is a promising treatment to improve neurocognitive function, has been shown to enhance learning and improve retention, and is associated with increased cell survival and proliferation in the hippocampus of laboratory animals. Aerobic exercise also has been associated with increased volumes of white and gray matter in older adults. Older adults without dementia (N = 120) were randomized to moderate-intensity aerobic exercise three days a week or to a control group who participated in stretching and toning exercises. The results of this study showed that the adults in the aerobic exercise group demonstrated improvements in spatial memory, and hippocampal volume was increased by 2%. Increases in brain-derived neurotrophic factor, a mediator of neurogenesis, also were demonstrated in the exercise group. Results of this study indicate that aerobic exercise reverses hippocampal volume loss and improves memory function.

Recent small studies have been published in which the effects of yoga (Galantino, Greene, Archetto, et al., 2012; Galantino, Greene, Daniels, et al., 2012), tai chi (Reid-Arndt & Cox, 2012), medical Qigong (Oh et al., 2012), and resistance training (Baumann et al., 2011) were evaluated for their impact on cognitive function in cancer survivors. The results of these studies are encouraging for the use of exercise as a viable intervention strategy. The most robust of these studies was conducted by Oh et al. (2012), in which 81 patients with cancer were randomized to receive a combination of gentle exercise and meditation or to a control group. The exercise group participated in a 10-week program and was measured for self-report of cognitive function with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 cognitive functioning subscale (EORTC-QLQ-C30-CF) and the FACT-Cog. Quality of life and C-reactive protein, as a biomarker of inflammation, also were measured. Significant improvements were seen for the exercise group for cognitive function on all instruments. Further research is needed to confirm the effectiveness of exercise for cancer-related CI and to establish effective types of exercise, as well as the dose, duration, and timing of the intervention (i.e., before, during, and/or after cancer treatment).

**Complementary Therapy**

The use of ginkgo biloba has been studied as a potential intervention for cancer-related CI because of its antioxidant properties. Barton et al. (2013) investigated the use of ginkgo biloba for the prevention of chemotherapy-related CI in women receiving therapy for breast cancer. A two-arm, randomized, placebo-controlled, double-blind, phase III clinical trial was conducted. Women (n = 166) were randomized to ginkgo biloba or placebo prior to initiation of chemotherapy. No differences were observed in neuropsychological test results or toxicities between the two arms of the study.

Attia et al. (2012) conducted an open-label phase II trial of ginkgo biloba for patients with brain tumors who had completed radiation therapy at least six months prior to enrollment. Patients received ginkgo biloba for 24 weeks followed by a six-week washout period.
Assessments were conducted at baseline and 12, 24 (end of treatment), and 30 weeks (end of washout). Significant improvements were noted in executive function \((p = 0.007)\), attention/concentration \((p = 0.002)\), and nonverbal memory \((p = 0.001)\) at 24 weeks. Some improvements were noted in quality of life. However, study limitations included a 44% dropout rate and lack of control group, so results should be viewed with caution.

**Other Potential Interventions Under Investigation**

Preliminary work has been conducted to examine the use of hyperbaric oxygen treatment for patients who have hypoperfused tissue following neurosurgery and radiation therapy. Hyperbaric oxygen treatment stimulates neovascularization and may improve the function of damaged tissue. One small study of 10 patients with brain tumors who experienced severe compromise after treatment provided some evidence of improvements as measured by electroencephalographic amplitudes (Schellart, Reits, van der Kleij, & Stalpers, 2011).

Other exciting preliminary preclinical work has been done with the transplantation of neural stem cells into the hippocampus of laboratory rats after radiation therapy to the head (Acharya et al., 2009, 2011). Superior performance was demonstrated on hippocampal-dependent cognitive tasks four months following irradiation, with significant stem cell survival documented at one and four months after transplant.

Currently, sufficient evidence to support a standard-of-care intervention for CI is not available. However, early results from studies designed to investigate the efficacy of CBT, exercise, and memantine appear promising.

**Patient Teaching Points**

Many patients with cancer trying to deal with CI have developed their own coping strategies. Mulrooney (2007) conducted a small qualitative study to evaluate the lived experience of breast cancer. The following suggestions have been provided by patients with breast cancer who participated in this study.

Common strategies to cope with CI include writing down important information, keeping calendars, using lists and notes to jog the memory, and participating in relaxation activities such as listening to music. Doing “brain exercises” such as crossword and Sudoku puzzles is believed to improve concentration, but this has not been formally studied. The breast cancer survivors interviewed for this study reported they had to put greater effort into planning certain activities so that memory lapses did not impede the task at hand. Some concrete examples include using lists to go grocery shopping and placing items next to the door if the item would be needed on an outing. Frequently used items such as car keys, pocketbooks, and calendars should be kept in the same place so that they are easy to locate. The individuals found that keeping detailed notes about work-related activities helped to preserve their competency at work (Mulrooney, 2007).

Self-talk can be an important strategy when anxiety occurs during an incident of CI. Many of the breast cancer survivors in the study stated that if they were experiencing a memory lapse or difficulty finding words, they would talk to themselves, take deep breaths, and tell themselves that everything was all right and that they were doing fine. This would help them to calm down and reduce their anxiety. Once calm, they could sometimes (but not always) do what they needed to do, whether it be recalling a word or remembering how to drive to a familiar place (Mulrooney, 2007).

A relationship between social support, either through family, friends, or coworkers, and the ability to cope with CI was found (Mulrooney, 2007). Those participants with little sup-
port seemed to keep their experiences and frustrations with CI to themselves and thus felt they did not cope well with CI. Those who reported having strong support were more apt to divulge the experience of cognitive problems and enlist the assistance of family and friends, and reported much better coping. Ensuring that patients with cancer have a social support network, either through family, friends, or a support group, may be a helpful strategy for helping patients to cope with CI.

Mulrooney’s findings have been corroborated by additional qualitative work (Boykoff et al., 2009; Cheung et al., 2012; Fitch et al., 2008; Munir et al., 2010, 2011; Myers, 2012; Potratz et al., 2010; Rust & Davis, 2013; Skoogh et al., 2012; Von Ah et al., 2013; Wagner et al., 2009). Additional coping strategies for women with breast cancer include exercising, getting enough rest, giving themselves permission to make mistakes, focusing on one thing at a time, and not rushing (Myers, 2012).

Until interventions supported by the highest level of evidence are developed, patients may consider implementing the strategies listed in Figure 9-4. Patients who experience CI have emphasized the need for ongoing assessment and validation of the experience by healthcare professionals (Mulrooney, 2007; Myers, 2012). Nurses can play an important role in identifying cognitive concerns. Nurses also are key to evaluating a patient’s support network and ensuring that patients are referred to outside networks, such as support groups, as necessary.

**Need for Future Research**

Much work remains to be done to confirm the causal mechanisms for CI and to discover effective interventions for CI experienced by patients with cancer. Clinically meaningful neuropsychological tests and screening tools are necessary for the appropriate assessment of cancer-related CI. The relationship between common symptoms experienced by patients with cancer (e.g., depression, anxiety, fatigue) and CI warrants further investigation. Promising areas of research for potential interventions include CBT, exercise, and pharmacologic agents such as memantine.

**Conclusion of Case Study**

Recall that A.M. was a patient with breast cancer who, following treatment, has experienced significant levels of CI. The oncology nurse provides a list of suggestions (see Figure 9-4) that A.M. can use in coping with this change in her cognition. The nurse also refers A.M. to the cancer center psychologist who is conducting a clinical trial with CBT to see if she meets eligibility criteria and is interested in participating. The oncology nurse shares the current evidence supporting regular exercise to help decrease fatigue. The oncologist is notified of the cognitive changes the patient is experiencing and also is informed of A.M.’s sleep disturbances.

A.M. returns to the clinic in four months for follow-up. She is participating in the CBT study. She has implemented some of the strategies she learned from the oncology nurse and is walking for 30–60 minutes three times a week. A.M. always places her keys and her purse by the door when she arrives home so as not to misplace these items. She has a large calendar on her kitchen wall where she keeps track of her children’s extracurricular activities and her husband’s travel schedule. She is using lists at work to remember tasks she must accomplish. A.M. describes having more energy since beginning to exercise, and
### FIGURE 9-4 Strategies for Coping With Cognitive Impairment

“**A place for everything and everything in its place.**”

- Make sure you put frequently used items back in the same place all the time. For example, hang car keys in the same place, and keep your purse or wallet on the kitchen counter.
- If you are going to need to bring something out of the house with you, place it close to the door. For example, if books need to be returned to the library, place them in a bag on the doorknob.

**Get organized.**
- Keep to-do lists, and start to rely on grocery lists.
- Use a day planner or calendar to write things down.
- Sticky notes may be helpful reminders.
- Keep detailed notes.

**Keep a journal.**
- Track to see if patterns exist of when cognitive impairment occurs. This may help you to plan accordingly.
- Monitor the frequency and characteristics of your symptoms, and share them with your healthcare provider.

**Enlist your coworkers, friends, and family to help.**
- Read your journal so that you can identify where you need help.
- Try to offload some responsibilities, both at home and at work.
- Have friends call and remind you of plans you have made together.
- Share your experience with those around you so that they can understand how you feel and what is happening to you.

**Work your mind.**
- Crossword and Sudoku puzzles may help with concentration and word-finding skills.
- Try to do math problems in your head, like multiplication tables or figuring out the change you will receive when paying for a purchase.

**Work your body.**
- Exercise helps to fight fatigue, which has been associated with cognitive impairment.
- Exercise can help you to sleep better, which in turn may help with cognitive impairment.

**Take good care of yourself.**
- Use a pill box to organize your medications.
- Ask your healthcare provider if you can record conversations so you do not forget important information.
- Take notes at healthcare visits.

**Try to fix any underlying problems.**
- Report any depression, anxiety, fatigue, or sleep problems to your healthcare provider to receive the appropriate treatment.
- Have your blood tested for anemia or thyroid problems.

**Try self-talk.**
- If an episode of cognitive impairment occurs, rather than feeling anxious and upset about it, try to talk to yourself and calm yourself down. Some survivors of cancer have found this helpful, as anxiety only makes the impairment worse.

**De-stress.**
- Try yoga, exercise, reading, meditation, listening to calming music, and other quiet activities.
- Laugh!

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Note. Based on information from Mulrooney, 2007.
she reports sleeping better. She thinks that her decreased fatigue and her CBT participation have helped her to concentrate better. Although she does not feel as though she is back to her baseline, she does feel more in control of her life and less fearful of making mistakes at work.

**Conclusion**

The presence of CI has been found across patients with varied cancer diagnoses. CI tends to manifest as a change in attention, concentration, memory, and multitasking abilities. CI can negatively affect many dimensions of a cancer survivor’s life. Multiple factors are thought to play a role in the development of CI. These include endogenous hormones, genetic predisposition, depression, anxiety, fatigue, cytokines, and cancer therapy, as well as the cancer itself. Debate is ongoing about how best to evaluate patients who report CI, and research examining interventions is growing. Future directions in this field of research must address how best to evaluate CI, examine the relationships between CI and other associated factors, and develop more treatment options. Nurses can play an important role in identifying patients with CI and providing suggestions and support to patients reporting this experience.

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**References**


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CHAPTER 10

Depression

Terry A. Badger, PhD, PMHCNS-BC, RN, FAAN, and Mark Lazenby, PhD, APRN, AOCNP®

Case Study

A.B., a 58-year-old married woman, found a lump in her left breast during her monthly breast self-examination two and a half months ago, just weeks after her first grandchild was born. A biopsy revealed infiltrating ductal carcinoma. She underwent a left modified radical mastectomy and left axillary node dissection and is now in the infusion center receiving her third dose of every-two-week dose-dense ACT (doxorubicin, cyclophosphamide, and paclitaxel). During the infusion, the nurse asks Amelia how she has been feeling over the two weeks since her last treatment. A.B. replies, “I’m very tired. I feel as if it takes everything out of me just to get out of bed. When will I get my energy back?” The nurse probes a bit more, and A.B. also reveals that she is having trouble thinking and gets upset at every little thing. A.B. starts to cry.

Overview

Depression is a major mental health problem affecting 25 million Americans and their families (National Institute of Mental Health [NIMH], n.d.). By 2020, the World Health Organization (WHO, n.d.) estimates that depression will be the second leading cause of disability worldwide. However, depression in patients with cancer is different from depression in the general population, as depression in cancer is part of the distress continuum as defined by the National Comprehensive Cancer Network® (NCCN®) (NCCN, 2014). Distress, according to NCCN, is a multifactorial unpleasant emotional experience of a psychological (cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis. (p. DIS-2)

Given this definition, it is important to differentiate which symptoms are caused by depression and which symptoms might be caused by other psychosocial problems, such as spiritual crisis or anxiety (see Chapters 4 and 11). The symptoms of depression and other psychosocial problems may overlap, but knowing the cause will help determine the focus of any refer-
ral or intervention. It is equally important to differentiate the causes of physical symptoms that may accompany depression. For example, is the fatigue caused by the cancer treatment, depression, or both? NCCN has published standards of care for distress management, which are applicable but not specific to depression (see Figure 10-1). The complete distress management guideline is available at www.nccn.org/professionals/physician_gls/PDF/distress.pdf (NCCN, 2014).

### Risk Factors and Associated Incidence

A number of biopsychosocial risk factors are associated with depression in cancer. Studies have found biologic factors that place a person at risk for developing depression during cancer, including female gender, younger age, family history of depression, personal history of depression, cancer-related factors (disease severity and physical burden), and tumor sites (e.g., pancreas, head and neck, lung, brain; Hodgkin disease) (Miller & Massie, 2010).

The lifetime risk for depression in women is nearly twice that of men. About 20% of women report depression during their lifetime compared to about 12% of men (Kessler & Bromet, 2013). Although in general women suffer from depression at increased rates compared to men, some research has found that men and women are equally likely to develop depression when faced with a highly stressful circumstance such as cancer (Miller et al., 2011). In any given year, approximately 6.7% of the U.S. population age 18 and older suffers from

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**FIGURE 10-1** Standards of Care for Distress Management

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*Note. Reproduced with permission from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Distress Management V.2.2014. © 2014 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. National Comprehensive Cancer Network®, NCCN®, NCCN Guidelines®, and all other NCCN content are trademarks owned by the National Comprehensive Cancer Network, Inc.*
major depressive disorder, with 2% of those classified as suffering from severe depression (NIMH, n.d.).

Prevalence rates of depression in patients with cancer vary by type of cancer, time since diagnosis, prognosis, and other variables such as symptom burden. In one of the largest studies of patients with cancer (N = 4,496), Zabora, BrintzenhofeSzoc, Curbow, Hooker, and Piantadosi (2001) reported that the overall prevalence of distress was 35.1%, which varied from 29.6% for patients with gynecologic cancers to 43.4% for those with lung cancer. Overall, most surveys have found that 20%–47% of patients with newly diagnosed or recurrent cancer show significant distress that negatively influences their quality of life (QOL) (NCCN, 2014). In a 2011 meta-analysis, Mitchell et al. reported that 30%–40% of patients with cancer have some combination of mood disorders. Yet, the majority of these patients are not being treated for their depression and related distress, especially among underrepresented populations such as African Americans (Traeger, Cannon, Pirl, & Park, 2013).

Psychological risk factors include perceptions of low social support, less optimism, ambivalence about expressing emotions, and low self-esteem (Miller & Massie, 2010). Social risk factors include poorer social functioning, recent losses and stressful life events, history of trauma or abuse, and substance abuse. Often, while talking with patients, nurses will hear statements indicating that the patient does not have people who are helpful or supportive during illness or that the patient is in crisis because of other events (e.g., divorce, deaths, family issues, unemployment, spouse or family member with substance abuse issues). These factors all increase the risk for developing depression during cancer. Nurses can ascertain many of these factors when assessing the patient’s health history.

When long-lasting with moderate to severe intensity, depression can negatively influence all aspects of the person’s life (e.g., work, family relationships, role functioning). Depression, along with musculoskeletal disorders, has been found to have the highest level of disability at the individual level among all commonly occurring disorders (e.g., cancer, heart disease, diabetes) (Kessler & Bromet, 2013). In the WHO World Mental Health Survey (Kessler & Üstün, 2008), depression was found to predict overall loss of work performance, with an estimated value of these losses ranging from $30.1 billion to $51.5 billion per year.

Depression is also associated with impaired marital and parental role functioning (Kessler & Bromet, 2013). People living with family members with depression report greater health problems, with family members often being sufficiently distressed themselves to require therapeutic intervention (Abela, Zinck, Kryger, Zilber, & Hankin, 2009; Ahlström, Skärsäter, & Danielson, 2009). Of those diagnosed with depression in the general population, only about half receive treatment, and the majority of people are treated in primary care (NIMH, n.d.). Of those receiving treatment, it is estimated that about 38% are receiving only minimally adequate treatment (NIMH, n.d.).

Untreated psychological distress has been linked to QOL impairments (Fann et al., 2008; Jacobsen & Jim, 2008), decreased immune function (Spiegel, Giese-Davis, Taylor, & Kraemer, 2006), increased healthcare use (Bambauer et al., 2006), reduced long-term survival (Giese-Davis et al., 2011), and suicide (Misono, Weiss, Fann, Redman, & Yueh, 2008). Depression affects patients’ ability to adhere to treatment (DiMatteo, Lepper, & Croghan, 2000); in fact, nonadherence to treatment is three times greater in depressed than in nondepressed patients with cancer (NCCN, 2014). Depressed patients (a) have greater difficulty compared to nondepressed patients in making decisions, (b) have poorer compliance with surveillance screenings, and (c) are less likely to participate in healthy behaviors, such as smoking cessation and exercising (Carmack, Basen-Engquist, & Gritz, 2011).
These manifold negative consequences of untreated depression highlight the need for improved education, additional screening, and increased interventions for depression. Oncology nurses are ideally positioned within the healthcare team for early detection of and intervention for depression in patients with cancer. Interventions, including medications to alleviate depression, will be discussed later in this chapter.

Pathophysiology

Depression is currently recognized as having a neuroanatomical, neuroendocrinologic, or neurophysiologic basis (Musselman, Miller, Royster, & McNutt, 2010), although more research is needed before a biologic diagnostic test is developed for this disorder. Strong evidence suggests that factors such as temperament (negative affectivity), adverse childhood experiences, stressful life events, genetic predisposition, or having a chronic or disabling medical condition can all place a person at risk for depression (American Psychiatric Association [APA], 2013). Chronic stress can cause changes in hypothalamic-pituitary-adrenal (HPA) axis function that contributes to depression (Booij, Bouma, de Jonge, Ormel, & Oldehinkel, 2013).

Research on depression includes genetic and biologic marker studies (Holmans et al., 2007; Raison, Capuron, & Miller, 2006). The four research approaches to the genetics of mood are (a) familial loading studies (e.g., comparing families with depression to families without the disease), (b) studies evaluating the inheritability of mood disorders (e.g., twin studies), (c) studies of the incidence of people with the risk for, but not yet ill from, mood disorders to determine biologic or psychological antecedents, and (d) studies using genetic probes to determine which relatives and which phenotypes are associated with the genetic contributors to mood disorders. Evidence is increasing from genetic studies on the genetic inheritance of depression (Gibb, Benas, Grassia, & McGeary, 2009; Holmans et al., 2007; Kendler, Gatz, Gardner, & Pedersen, 2005; Lazary, Gonda, Benko, Gacser, & Bagdy, 2009). For example, a study by Burkhouse, Gibb, Coles, Knopik, and McGeary (2011) found that, under the same environmental influences, children carrying two copies of certain alleles in involved in the genes that help control transport of serotonin were more likely to exhibit signs of depression than children who did not.

Biologic marker studies have focused on growth hormone, serotonergic and other neurotransmitter receptors, sleep, and HPA function (Raison et al., 2006; Sunderajnan et al., 2010; Uher & McGuffin, 2010). Changes in HPA function (i.e., aberrations in cortisol) have been linked to depression (Spiegel, 2012). More recently, Raison and Miller (2011, 2013) have proposed that inflammatory processes may play a role in causing depression.

Thus, knowing a person’s familial history of depression (i.e., did both parents have depression?) and personal history is important. An individual with first-degree relatives with major depression has a two-to fourfold higher risk compared to the general population (APA, 2013). In addition, the risk of depression during illness is higher in individuals who had a more severe episode of depression when younger or who have had recurrent episodes. Evidence suggests that abnormalities in biologic markers persist throughout the life span and that these depression-causing abnormalities may worsen when individuals are facing an illness such as cancer (Reyes-Gibby et al., 2013).

The medications used for cancer treatment have been implicated as the cause of depression symptoms, including chemotherapy agents (especially vinca alkaloids), immunomodulatory agents (thalidomide), biologics (interferon), and corticosteroids, all of which are part of cancer treatment. Indeed, many antidepressant medications may interact with antineo-
plastic drugs (Miguel & Albuquerque, 2011). Other medications include but are not limited to antihypertensives, anticonvulsants, antiarrythmics, beta-blockers (Andrade, 2013), histamine-2 receptor blockers, digoxin, antiparkinsonian drugs, antihistamines, nonsteroidal anti-inflammatory drugs, psychoactive drugs, and antifungal medications such as fluconazole (Lemachatti, Levêque, Beretz, & Bergerat, 2009). When anticancer medications are added to medications prescribed for another illness and these medications have been implicated in causing depressive symptoms, patients require additional evaluation for depression to determine the additive effect of multiple medications.

A special case is tamoxifen. Not only do 25% of women with breast cancer report depression (Fann et al., 2008), but the estrogen blocker tamoxifen has been associated with an increased rate of depression in women with breast cancer (Danhauser et al., 2013). However, selective serotonin reuptake inhibitor (SSRI) antidepressant medications can reduce tamoxifen’s efficacy (Breitbart, 2011). In fact, paroxetine use by women on tamoxifen is associated with increased mortality (Kelly et al., 2010).

Assessment

Depression can be categorized as major depressive disorder or as persistent depressive disorder (formerly called dysthymia) (APA, 2013). Major depressive disorder is described as having five or more of the criterion symptoms in Figure 10-2 (APA, 2013). These symptoms must be present nearly every day and for almost all day, for at least two weeks, and must represent a change from previous functioning. At least one of the criterion symptoms must be either (a) depressed mood or (b) loss of interest or pleasure in usual activities. These symptoms can be remembered easily using the mnemonic A SAD FACES (see Figure 10-3) (Montano, 1994).

Persistent depressive disorder can be diagnosed when an individual has depressed mood for most of the day and for more days than not, for at least two years in adults and one year in children, plus two of the criterion symptoms when depressed (APA, 2013, p. 168). In both major depressive disorder and persistent depressive disorder, the symptoms cause clinically significant distress and impairment in social, occupational, or other important areas of functioning.

Some healthcare providers believe that depression is a normal response to cancer; therefore, depression is often undiagnosed and untreated (Fallowfield, Ratcliffe, Jenkins, & Saul, 2001). This belief is a major barrier to depression screening and treatment. In the Institute of Medicine (IOM) report Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs

<table>
<thead>
<tr>
<th>FIGURE 10-2</th>
<th>Criterion Symptoms for Diagnosing Major Depressive Disorder</th>
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<tbody>
<tr>
<td>• Depressed mood (irritable mood in children and adolescents)</td>
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<tr>
<td>• Marked diminished interest or pleasure in usual activities</td>
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<tr>
<td>• Weight gain or loss without dieting, or decrease or increase in appetite</td>
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<tr>
<td>• Insomnia or hypersomnia</td>
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<tr>
<td>• Psychomotor agitation or retardation</td>
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<tr>
<td>• Fatigue or loss of energy</td>
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<tr>
<td>• Feelings of worthlessness or excessive or inappropriate guilt</td>
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</tr>
<tr>
<td>• Difficulty thinking, concentrating, and making decisions</td>
<td></td>
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<tr>
<td>• Recurrent thoughts of death or suicidal ideation</td>
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</table>

Note. Based on information from American Psychiatric Association, 2013.
A new, twofold standard of care was outlined: (a) psychosocial services must be an integral part of quality cancer care and (b) screening for depression or psychological distress must be a routine part of care. Following IOM’s evidence-based quality care standard, the American College of Surgeons Commission on Cancer (2012) has mandated that all cancer centers it accredits must screen patients for distress. The case is clear: All oncology healthcare providers should screen for depression or distress.

The use of self-report measures for screening has a number of advantages, such as ease of administration, scoring of the tool by individuals who have not had extensive training, and the speed in which the tools can be completed by patients (Badger, 2005). Furthermore, self-report screening tools can provide a relatively quick assessment of depression before a clinical interview is conducted, quantifying the severity of the depression and identifying changes over time (Passik & Lowery, 2011). A lengthier evaluation should be scheduled for those who score above the established cutoff scores on screening tools for depression. For these reasons, Figure 10-4 includes written self-report screening tools specifically designed to measure depression; these tools have evidence of reliability, validity, sensitivity, and specificity in patients with cancer. Reliability refers to the consistency of the responses, and validity refers to its correlation with an accepted gold standard (e.g., clinical interview). Sensitivity is the ability to correctly identify those who are depressed, and specificity is the ability to correctly identify those who are not depressed. The figure does not include items or subscales from other multidimensional symptom or QOL scales, such as the Functional Assessment of Cancer Therapy (Yanez, Pearman, Lis, Beaumont, & Cella, 2013). For readers looking for specific interview approaches, Trask (2004) provides an excellent review of clinical interview scales.

In 2005, Badger reviewed the available screening tools for depression for the Oncology Nursing Society (ONS). Since that review, Vodermaier, Linden, and Siu (2009) and Pirl (2010) conducted systematic reviews of depression scales and came to similar conclusions and recommendations. Among the tools listed, the Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and the Center for Epidemiologic Studies Depression Scale (Eaton, Muntaner, Smith, Tien, & Ybarra, 2004; Radloff, 1977) are both considered excellent, although the BDI must be purchased. The Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983), also good, is probably one of the most widely used scales throughout the world. Although the Patient Health Questionnaire-9 (PHQ-9) (Kroenke, Spitzer, & Williams, 2001) and the Distress Thermometer (NCCN, 2014) have been used more frequently in the past few years to screen for depression and distress, there have been

<table>
<thead>
<tr>
<th>FIGURE 10-3</th>
<th>A SAD FACES Mnemonic</th>
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<tbody>
<tr>
<td>A</td>
<td>Appetite</td>
</tr>
<tr>
<td>S</td>
<td>Sleep (insomnia or hypersomnia)</td>
</tr>
<tr>
<td>A</td>
<td>Anhedonia (loss of interest or pleasure in usual activities)</td>
</tr>
<tr>
<td>D</td>
<td>Depressed mood</td>
</tr>
<tr>
<td>F</td>
<td>Fatigue</td>
</tr>
<tr>
<td>A</td>
<td>Agitation</td>
</tr>
<tr>
<td>C</td>
<td>Concentration</td>
</tr>
<tr>
<td>E</td>
<td>Esteem (sense of worthlessness or poor self-esteem)</td>
</tr>
<tr>
<td>S</td>
<td>Suicidal</td>
</tr>
</tbody>
</table>

Note. Based on information from Montano, 1994; Sharp, 2010.
too few studies validating the PHQ-9 among patients with cancer. The nurse may find that using the short forms of various instruments or the Distress Thermometer is an efficient way to screen for depression within a busy practice. Many cancer centers have these tools on computers or tablets, making them easy for patients to complete.

In the course of caring for patients, nurses develop relationships with their patients and engage in talking with them during care episodes. Thus, it would be normal for nurses to ask screening questions as part of a larger conversation. Using Kroenke, Spitzer, and Williams’ (2003) PHQ-2 scale as a foundation, the nurse could ask two simple questions: “Over the past few weeks, have you been feeling sad, down, depressed, or hopeless?” and “Over the past few weeks, have you had little interest or pleasure in doing your usual activities?” If the patient answers yes to one or both of the questions, the nurse can follow with another simple question about frequency: “How many days of this past week have you felt this way?” If the patient tells the nurse this feeling was present several days of the past week, there is a 37% chance that the patient suffers from a depressive disorder (Kroenke et al., 2003). Although this two-question screening was designed for the general population and is not specific to cancer, it can easily be included in conversations with patients (Lazenby, Dixon, Bai, & McCorkle, 2014) and may serve to cultivate a more in-depth evaluation from other members of the healthcare team. Specifically, nurses can (Lazenby et al., 2014)

- Use simple screening tools to identify the potentially depressed patient.
- Report the findings to the nurse practitioner, physician assistant, or physician for further comprehensive assessment.
- Work with the healthcare team to establish routine screening procedures within their practices.

When assessing patients for depression, nurses must evaluate physical symptoms, as well as emotional, psychological, or behavioral clues. Physical symptoms present in patients with cancer may include fatigue, lack of energy, inability to concentrate, insomnia or drowsiness, subjectively described restlessness, or appetite changes (either loss of appetite or carbohydrate craving). Fatigue is the most commonly reported physical symptom associated with cancer treatment (Donovan & Jacobsen, 2007; Fodeh et al., 2013), with depression increasing feelings of fatigue in patients with cancer (Badger et al., 2005). Furthermore, depression is associated with increased pain and experiencing other cancer symptoms.

The presence of symptom clusters has been identified in patients with cancer and commonly includes symptoms of depression, fatigue, insomnia, anxiety, and pain. In a review

---

**FIGURE 10-4** Links for Depression Screening Tools

- Beck Depression Inventory (BDI) and Beck Depression Inventory—Short Form (BDI-SF): Available online for purchase only; see www.pearsonclinical.com/psychology.html
- Center for Epidemiologic Studies Depression Scale (CESD and CESD-R): http://counsellingresource.com/lib/quizzes/depression-testing/cesd
- Hamilton Rating Scale for Depression: http://healthnet.umassmed.edu/mhealth/HAMD.pdf
- Patient Health Questionnaire (PHQ)-2: www.cmwf.org/usr_doc/phq2.pdf
- PHQ-9: www.phqscreeners.com
- National Comprehensive Cancer Network Distress Thermometer: Requires free online registration; www.nccn.org/professionals/physician_gls/PDF/distress.pdf
of symptom clusters in patients with breast cancer, Nguyen et al. (2011) reported that fatigue was in the cluster of all studies reviewed (N = 5), with depression/distress in the majority (4 out of 5) of studies reviewed. The research has yet to determine the symptom clusters that are present across heterogeneous cancer populations. It is clear, however, that the more symptoms experienced by patients with cancer, the greater the decreases in their QOL.

Diagnosing depression in patients with cancer can be complex, and using the diagnostic criteria can create false positives (i.e., diagnosing depression when it is, in fact, not present). Therefore, the following alternative approaches to assessing depression in patients with cancer are commonly used: inclusive, etiologic, substitutive, exclusive, and increased thresholds (Passik & Lowery, 2011). The inclusive approach uses all the symptoms of depression, regardless of whether they are secondary to medical illness. Most depression screening tools use the inclusive approach. The etiologic approach counts only symptoms that are not the result of physical illness. The advantage of the etiologic approach is fewer false positives, but a major disadvantage is that many depressed patients with cancer may be missed. Furthermore, this approach does not take into account that some groups (e.g., older adults, culturally and racially diverse groups) use somatic symptoms to describe depression (Caplan et al., 2010). The substitutive approach replaces symptoms that may be related to cancer (e.g., fatigue) and includes additional psychological symptoms (e.g., social withdrawal). The advantage to this approach is similar to the inclusive approach; however, it requires use of assessment tools that are not readily available in the literature and with little evidence to support their reliability and validity. The exclusive approach eliminates two common symptoms of depression (fatigue and weight/appetite changes). This approach increases the chances that clinicians will identify potentially depressed patients, but it also increases the chances that clinicians will screen patients who are not depressed. The final approach is to increase the threshold score, such as set a higher score than is typically used to indicate significant depressive symptoms. The issue with this approach is that there have been insufficient studies to determine what the new threshold score should be. Of these approaches, the authors recommend the inclusive method, as it allows for maximum sensitivity in assessing depression in patients with cancer.

**Evidence-Based Interventions**

After a diagnosis of depression, the next step is to determine an evidence-based plan of treatment. In 2008, Fulcher, Badger, Gunter, Marrs, and Reese (2008) reviewed the available literature regarding treatments for depression that were evidence based, and they divided them into three categories: (a) Recommended for Practice, (b) Likely to Be Effective, and (c) Effectiveness Not Established. Interventions supported as beneficial and thus recommended for practice were psychoeducational/psychosocial interventions and pharmacologic interventions. A similar approach was used to evaluate the interventions for this chapter (see Table 10-1).

**Recommended for Practice**

Pharmacologic interventions are recommended for patients with depression and cancer (Fulcher et al., 2014; Hart et al., 2012; Li, Fitzgerald, & Rodin, 2012). Studies of patients with cancer and depression generally support the use of antidepressants and psychotropic medi-
The medications used in patients with cancer and depression should be selected and dosed based on a number of factors, including comorbid conditions, current treatments and medications, side effect profile, potential toxicities, hepatic and renal function, and the effects of the medications in cancer care (Braun & Pirl, 2010). The first antidepressants, which have been available for more than 50 years, were the tricyclics, such as amitriptyline and imipramine, and the monoamine oxidase inhibitors, such as phenelzine. However, the development of newer antidepressants over the past 20 years has substantially changed the approach to depression care in people with cancer. SSRIs such as escitalopram and citalopram, the serotonin-norepinephrine reuptake inhibitor milnacipran, and the atypical antidepressant mirtazapine are preferable over older antidepressants because of their safety profile among patients receiving chemotherapy (Miguel & Albuquerque, 2011). Although the serotonin-norepinephrine reuptake inhibitor venlafaxine has been studied repeatedly for its usefulness in managing hot flashes associated with estrogen blockade, no studies were found that evaluated its effectiveness in treating patients with cancer who had depression. See Table 10-2 for information on medications.

The medications used in patients with cancer and depression should be selected and dosed based on a number of factors, including comorbid conditions, current treatments and medications, side effect profile, potential toxicities, hepatic and renal function, and

<table>
<thead>
<tr>
<th>TABLE 10-1</th>
<th>Interventions for Depression by Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level of Evidence</strong></td>
<td><strong>Interventions</strong></td>
</tr>
</tbody>
</table>
| **Recommended for practice** | • Pharmacologic—Antidepressants  
- Selective serotonin reuptake inhibitors  
- Serotonin-norepinephrine reuptake inhibitors  
- Tricyclic antidepressants  
- Other antidepressants  
• Psychoeducational/psychotherapeutic  
- Behavioral therapy  
- Cognitive behavioral therapy  
- Cognitive therapy  
- Counseling and psychotherapy  
- Mindfulness-based stress reduction  
- Patient education |
| **Likely to be effective** | • Exercise or physical activity  
• Methylphenidate  
• Psychotherapy/counseling  
- Couples or family therapy  
- Interpersonal psychotherapy/counseling  
- Meaning centered group psychotherapy  
• Relaxation therapy |
| **Effectiveness not established** | • Complementary and alternative medicine  
- Acupuncture  
- Guided imagery  
- Herbal preparations  
- Hypnotherapy  
- Massage therapies  
- Music and art therapies  
- Yoga |

*Note. Based on information from Akechi et al., 2008; Carlson, 2010; Cohen et al., 2010; Courneya, 2010; Craft et al., 2012; Cuijpers et al., 2009, 2011; Duijts et al., 2011; Faller et al., 2013; Fulcher et al., 2008, 2014; Grassi et al., 2011; Hart et al., 2012; Kerr et al., 2012; Kissane et al., 2011; Landier & Tse, 2010; Leubbert et al., 2001; Li et al., 2012; Luzzatto & Magill, 2010; Northouse et al., 2010; Rajasekaran et al., 2005; Rodin et al., 2007.*
### Antidepressant Medications Used in Patients With Cancer

#### Selective Serotonin Reuptake Inhibitors (SSRIs)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Comments/Positive Effects</th>
<th>Common Side Effects/Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Low drug-drug interaction potential, few gastrointestinal (GI) side effects; good for older adults, those with agitation depression, and those with GI sensitivity</td>
<td>Headache, diarrhea, constipation, restlessness, sexual side effects, mild CYP2D6 inhibitor. Use with caution in patients with renal impairment.</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Low drug-drug interaction potential, few GI side effects; good for older adults and those with agitation depression</td>
<td>Headache, diarrhea, constipation, restlessness, sexual side effect, mild CYP2D6 inhibitor. Use with caution in patients with renal impairment.</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Activating, good for patients with lack of energy, long half-life; good for forgetful or poorly compliant patients</td>
<td>Very long half-life, potent CYP2D6 inhibitor, sexual side effects; not good for patients on multiple medications or medications that are anticipated to require frequent titration</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Good for patients with comorbid anxiety disorder</td>
<td>Nausea, anticholinergic effects, dizziness, headache, may occasionally increase anxiety, increased half-life in older adults, weight gain, potent CYP2D6 inhibitor, sexual side effects</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Low drug-drug interaction; good for patients with psychomotor retardation</td>
<td>Restlessness, headache, constipation, insomnia, potent CYP2D6 inhibitor, diarrhea, sexual side effects</td>
</tr>
</tbody>
</table>

#### Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Comments/Positive Effects</th>
<th>Common Side Effects/Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desvenlafaxine</td>
<td>Does not interfere with most medications (except ketoconazole, desipramine, monoamine oxidase inhibitors, and midazolam), so is good for patients with polypharmacy</td>
<td>May worsen hypertension; increased risk of bleeding; may activate mania</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Good for comorbid depression and pain</td>
<td>Nausea, dizziness, fatigue, noninhibitor of CYP2D6, sexual side effects. Use extreme caution with use in patients with heavy alcohol use or chronic liver disease.</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Good for comorbid depression and pain</td>
<td>Hypertension at higher doses, constipation, vivid dreams, significant withdrawal syndrome requires slow taper, nausea and vomiting, headache, sexual side effects, noninhibitor of CYP2D6</td>
</tr>
</tbody>
</table>

#### Tricyclic Antidepressants (Use with caution due to side effects.)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Comments/Positive Effects</th>
<th>Common Side Effects/Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline (tertiary amine)</td>
<td>Good for patients with peripheral neuropathy and insomnia</td>
<td>Sedating, dry mouth, constipation, dizziness, weight gain</td>
</tr>
<tr>
<td>Desipramine (secondary amine)</td>
<td>–</td>
<td>Dry mouth, drowsiness, urinary retention, constipation, dizziness. Long-term use may be associated with an increased risk of breast cancer in women.</td>
</tr>
</tbody>
</table>

*(Continued on next page)*
<table>
<thead>
<tr>
<th>Medication</th>
<th>Comments/Positive Effects</th>
<th>Common Side Effects/Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxepin (dibenzoxazepine derivative)</td>
<td>Good for anxious, depressed patients</td>
<td>Dry mouth, drowsiness, urinary retention, constipation, dizziness. Long-term use may be associated with an increased risk of breast cancer in women.</td>
</tr>
<tr>
<td>Imipramine (tertiary amine)</td>
<td>Good for patients with chronic pain and comorbid depression</td>
<td>Hypotension, QT prolongation, drowsiness, dry mouth, dizziness, low blood pressure, thrombocytopenia, leukopenia, nausea, vomiting, weakness, blurred vision, constipation, urinary retention, may increase suicidality. Adjust dose for older adults and patients with hepatic impairment and glaucoma. Long-term use may be associated with an increased risk of breast cancer in women.</td>
</tr>
<tr>
<td>Nortriptyline (secondary amine)</td>
<td>–</td>
<td>Orthostatic hypotension, urinary retention, constipation, dry mouth, drowsiness.</td>
</tr>
<tr>
<td>Protriptyline (secondary amine)</td>
<td>Also used for panic disorder</td>
<td>Dry mouth, drowsiness, urinary retention, constipation, dizziness. Long-term use may be associated with an increased risk of breast cancer in women.</td>
</tr>
</tbody>
</table>

**Monoamine Oxidase Inhibitors**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Comments/Positive Effects</th>
<th>Common Side Effects/Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nefazodone Brand name (Serzone) discontinued in the United States; only available as a generic.</td>
<td>Good for anxious patients with insomnia</td>
<td>Fatigue, dizziness, sedation, weight gain, interactions with many common medications; contraindicated with most statins, sildenafil, and pimozide; increases digoxin level; inhibits CYP3A3 and CYP3A4. Black box warning: May cause hepatic damage/failure.</td>
</tr>
<tr>
<td>Phenelzine</td>
<td>Also used for bulimia</td>
<td>Avoid aged cheese, wine, and pickled meats, which can interact and cause severe hypertension.</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
</tbody>
</table>

**Other Antidepressants**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Comments/Positive Effects</th>
<th>Common Side Effects/Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion (norepinephrine/dopamine reuptake inhibitor)</td>
<td>Good for apathetic, low-energy depression; no sexual side effects; may be used in combination with SSRIs and SNRIs</td>
<td>May increase heart rate and lower seizure threshold; strong CYP2D6 inhibitor. Do not use if patient has history of seizures, substance abuse, bulimia, anorexia, or electrolyte disturbances.</td>
</tr>
<tr>
<td>Mirtazapine (serotonin and alpha-2 receptor blocker)</td>
<td>Good for patients with anorexia, insomnia, nausea; low drug-drug interaction</td>
<td>Weight gain, very sedating. Reduce dose by 50% for hepatic impairment and 25% for renal impairment.</td>
</tr>
</tbody>
</table>
published indications. Selection of antidepressants should be made according to the following general principles (Rodin et al., 2007).

- Patients with neuropathic pain may benefit from tricyclic antidepressants (Grassi, Nanni, Uchitomi, & Riba, 2011).
- Patients with comorbid cardiovascular disease may benefit from medications that cause the least orthostatic hypotension (such as fluoxetine and sertraline).
- Patients with slow intestinal motility may benefit from antidepressants that have the least anticholinergic effects (such as the SSRIs). Patients who cannot swallow pills may use liquid formulations (available for some SSRIs and tricyclic antidepressants).
- Patients with impaired hepatic or renal function may benefit from antidepressants with short half-lives (such as sertraline and paroxetine).

Major depression is a well-known side effect of interferon-alpha, which is used to treat malignant melanoma. One small study by Musselman et al. (2001) found that prophylactic treatment with paroxetine two weeks before starting interferon-alpha treatment significantly reduced the likelihood that interferon would have to be discontinued because of depression. In a subsequent study (Capuron et al., 2002), paroxetine was effective in decreasing depressed mood, anxiety, cognitive dysfunction, and pain but was not helpful with fatigue or anorexia. The lack of randomized controlled trials among patients with cancer on interferon-alpha treatment notwithstanding, a meta-analytic study of seven clinical trials of patients with hepatitis C receiving interferon-alpha showed that prophylactic treatment with an SSRI reduced the incidence of interferon-alpha–induced depression (Jiang et al., 2014).

A major concern in recent years has been that antidepressants may interfere with the effectiveness of tamoxifen, a selective estrogen receptor modulator used as adjuvant therapy for early-stage, estrogen receptor–positive (ER+) breast cancer in premenopausal women. Given that about two-thirds of women with breast cancer are estrogen and/or progesterone receptor positive, use of tamoxifen to prevent recurrence remains high. In a recent review,
Breitbart (2011) concluded that the literature supports that antidepressants that are potent or strong inhibitors of CYP2D6 (active metabolites that cause tamoxifen to work) may reduce the clinical efficacy of tamoxifen when used concurrently with tamoxifen. Breitbart (2011) thus recommended that in clinical practice, clinicians should avoid potent CYP2D6 inhibitors (i.e., fluoxetine, paroxetine, and sertraline) and use those that are either milder inhibitors or noninhibitors of CYP2D6 (also see Danhauer et al., 2013).

Evidence at the highest level supports psychosocial and psychoeducational interventions during and following cancer treatment (Akechi, Okuyama, Onishi, Morita, & Furukawa, 2008; Hart et al., 2012). Interventions with the strongest evidence include cognitive therapy or cognitive behavioral therapy (CBT), mindfulness-based stress reduction (MBSR), patient education, counseling and psychotherapy, behavioral therapy, and social support. Psychotherapeutic interventions vary in the number of sessions, length of treatment (average of 8–12 weeks), method of delivery (face to face, web-based, telephone), target of intervention (individual vs. group, dyad, couple, or family). Yet, despite the variability in type and format, psychosocial interventions have resulted in symptom improvements.

Most intervention studies conducted among patients with cancer, however, have been with patients experiencing psychological distress (e.g., depressive symptoms, stress, anxiety) rather than among patients who have a specific diagnosis of depression (i.e., major depressive disorder). Psychoeducational and psychosocial interventions generally require advanced education and training and usually are performed by professionals other than nurses. These professionals may not always be readily available without referral.

Cognitive therapy or CBT and its derivatives (e.g., problem-solving therapy, acceptance and commitment therapy) are among the most widely used types of counseling among patients with cancer with depressive symptoms over the past several decades (Hart et al., 2012; Kissane, Levin, Hales, Lo, & Rodin, 2011; Li et al., 2012; Mohr et al., 2012). This type of therapy is based on the premise that it is not a specific situation that causes the emotional disturbance but rather how the person perceives the situation (Beck, 2011). For example, one person may feel depressed when participating in routine follow-up cancer screening because he or she believes that this means that the cancer will be found again regardless of treatment, whereas another person may not feel depressed because she or he believes that screening means that all reasonable guidelines are being followed. In the first scenario, the person has developed cognitive distortions that resulted in psychological distress.

CBT is used to help patients recognize and change cognitive distortions (for example, how screening is viewed) that cause or exacerbate psychological distress (depression). CBT is guided by a therapist who works collaboratively with patients to uncover how cognitions (thoughts), emotions, and behavior interrelate and how experiences or other external stimuli influence perceptions (Beck, 2011). The therapist assists patients in evaluating their cognitive distortions and reformulating or changing their thoughts and perceptions to reduce negative outcomes (e.g., depression, stress). CBT is goal oriented and based on the principles of behavior change (Beck, 2011).

Several studies of short-term CBT delivered by nurses have found that CBT was effective for reducing depressive symptoms and general stress/distress. Pitceathly et al. (2009) found that a short CBT intervention delivered by nurses trained in CBT significantly reduced depressive symptoms in patients who were at high risk for depression but were not depressed at baseline. Groarke, Curtis, and Kerin (2013) found that their five-week group CBT stress management intervention was effective in reducing stress and anxiety, but not depression, in women with breast cancer (N = 355). Moorey et al. (2009) taught homecare nurses to use CBT techniques in their practice with patients in palliative care and found that the use of CBT was effective in reducing anxiety.
Another effective cognitively focused intervention is MBSR (Henderson et al., 2013; Hoffman et al., 2012). In this type of intervention, mindfulness is defined as bringing the complete attention of the individual to an experience that occurs in the present moment in a nonjudgmental and accepting way. Typically, patients attend a workshop, have individual sessions, and practice at home to achieve a state of mindfulness. Ledesma and Kuman (2009) reviewed 10 studies and concluded that MBSR was effective in improving the psychosocial adjustment of patients with cancer and alleviating the emotional adverse effects of cancer.

Psychoeducational interventions have been shown to reduce depressive symptoms. The focus of these interventions is education, such as teaching patients about cancer, distress, or specific health-related behaviors (e.g., eating well, staying physically active). Unlike the counseling and psychotherapeutic intervention, psychoeducational interventions generally do not require specialized training. Badger and colleagues, in studies with men with prostate cancer (Badger, Segrin, Figueredo, et al., 2013; Badger et al., 2011) and Latinas with breast cancer (Badger, Segrin, Hepworth, et al., 2013), found that a health education intervention delivered by telephone was effective in reducing depressive symptoms, negative affect, and stress and in increasing QOL. Similar positive results were found with a nurse-led, palliative care–focused intervention (Project ENABLE [Educate, Nurture, Advise, Before Life Ends]) with 322 patients with advanced cancer (Bakitas et al., 2009). Compared to the usual care group, those receiving the ENABLE intervention had improved QOL (p = 0.02) and mood (p = 0.02).

Psychoeducation is often part of a larger intervention package. For example, in the Improving Mood—Promoting Access to Collaborative Treatment (IMPACT) program, education, support of a depression care manager, and a brief, structured problem-solving psycho-social intervention were combined to treat older patients with cancer (N = 215) (Fann, Fan, & Unützer, 2009). At 6 and 12 months, 55% and 39% of intervention patients had at least 50% reduction in depressive symptoms from baseline, versus 34% and 20% of usual care patients (p = 0.003 and p = 0.029). Marcus et al. (2010) had similar positive findings (i.e., 50% reduction in distress and depression) with their 16-session telephone-delivered counseling intervention. Although it was called counseling, this program had a considerable educational component that covered six topics relevant to living with cancer: uncertainty, physical change, self-change, sexuality after breast cancer, relationships, and economic change. In a large clinical trial with 472 Hispanic patients, Ell et al. (2008) found the ADAPt-C (Alleviating Depression Among Patients With Cancer) collaborative care management program to be effective in reducing depression. The program included educational components and problem-solving psychotherapy.

The benefits of education are clear, and nurses routinely teach patients as an integral part of patient care. Nurses can decrease depressive symptoms and distress by talking with patients and families about cancer and its treatments, psychological and physical symptoms, and strategies to deal with the symptoms, such as eating well, staying physically active, and getting sufficient rest, along with other topics relevant to health and well-being. During this teaching, nurses can assess for depression and refer for additional assessment as needed.

**Likely to Be Effective**

Methylphenidate, exercise, relaxation, and certain psychotherapy and counseling interventions are interventions that were supported as likely to be effective (Fulcher et al., 2014; Kerr et al., 2012). These interventions did not have the rigorous supporting data to allow classification in the Recommended for Practice category.
Methylphenidate, a central nervous system stimulant, has been used most often for its mood-elevating properties, to negate the effect of opioid-induced somnolence, and to improve cognitive functioning. It is often used in children with attention-deficit disorder and attention-deficit/hyperactivity disorder and has an extrapyramidal effect in adults. In a review of psychostimulants in the treatment of depression, Sinita and Coghill (2014) reported that, among older adult patients, when added to escitalopram, methylphenidate was found to be useful in treating depression, with 80% of the patients having a favorable response. Kerr et al. (2012) found that methylphenidate reduced symptoms of fatigue and depression when compared to placebo. Patients who presented with clinically significant depression at baseline showed a significant reduction in depressed mood following a trial with methylphenidate. Berger, Yennu, and Million (2013), among others (e.g., Lasheen et al., 2010), found similar results when using methylphenidate in patients with advanced cancer.

Exercise or physical activity may have beneficial effects on QOL, physical functioning, role and social functioning, and fatigue (Courneya, 2010; Courneya et al., 2009; Duijts, Faber, Oldenburg, van Beurden, & Aaronson, 2011; McClellan, 2013; Mishra et al., 2012), but results have been mixed (Courneya et al., 2014; Craft, Vaniterson, Helenowski, Rademaker, & Courneya, 2012). The majority of studies have been conducted in women with breast and colon cancers and in men with colon cancer. Although the preliminary evidence has suggested that exercise reduced cancer risk and depression, more research is needed. More powerful effects have been found for moderate or vigorous intensity versus mild intensity (Mishra et al., 2012). Although exercise does have positive effects, a major limitation often cited is patients’ lack of adherence to programs.

Several psychotherapy and counseling interventions have shown promise among patients with cancer. Preliminary findings have demonstrated that the interventions are effective in decreasing depression. However, the evidence is insufficient to move these to the Recommended for Practice category. Interpersonal psychotherapy (IPT), as well as its derivative, interpersonal counseling (IPC), has been well documented to be effective in populations such as depressed primary care patients and women with breast cancer (Cuijpers et al., 2011; Cuijpers, van Straten, van Schaik, & Andersson, 2009; Donnelly et al., 2000). The focus of IPT is on interpersonal conflicts, life transitions, grief, losses, and social isolation. Badger et al. (Badger, Segrin, Dorros, Meek, & Lopez, 2007; Badger et al., 2005, 2011) found that disruptions in interpersonal functioning were associated with increased symptoms of depression, anxiety, and fatigue in people with cancer. Following telephone-delivered IPC counseling, mood improved (Badger et al., 2007).

The inclusion of family members in interventions yields positive effects on caregiving burden, depression, and anxiety (Northouse, Katapodi, Song, Zhang, & Mood, 2010), and the strongest effects are evident when the intervention targets relationship issues. The psychological distress experiences of family members are linked, and family members can ameliorate or exacerbate depression in the person with cancer (Segrin & Badger, 2013; Zaider & Kissane, 2010). In a study of focused grief therapy among families before and after a family member has died from cancer, Kissane et al. (2006) found that more effective communication, enhanced cohesion, and adaptive resolution of conflict reduced depression and encouraged mourning. Relationship-focused interventions such as IPT, IPC, and couples or family therapy can effectively strengthen family functioning amid illness-related changes, reduce the risk for psychiatric morbidity, and enhance the QOL of both the patients with cancer and their families. For a more detailed discussion of family caregivers, see Chapter 7.

Meaning-centered group psychotherapy (MCGP) (Breitbart et al., 2010) was established to help patients with advanced cancer to sustain or enhance a sense of meaning, peace, and purpose in their lives, even as they approached the end of life. In a randomized clinical trial,
Breitbart et al. (2010) compared MCGP to supportive group psychotherapy. MCGP resulted in significantly greater improvements in spiritual well-being, sense of meaning, anxiety, and desire for death (p < 0.05). No such improvements were seen in the supportive group. For a recent review of nonpharmacologic approaches to treating depression in patients at the end of life, see Stagg and Lazenby (2012).

Relaxation therapy is a technique that focuses on inducing a relaxed physical and mental state using guided imagery, hypnosis, and autogenic training. Although it is the most widely used alternative therapy offered to patients with cancer and has been reported by many clinicians as useful in reducing distress, few recent clinical trials have been conducted (Faller et al., 2013). Leubbert, Dahme, and Hasenbring’s (2001) meta-analysis of 15 studies found that relaxation therapy had a significant effect on reducing cancer treatment–related side effects, including depression. In a more recent review of relaxation therapy, Cohen, Russell, Garcia, Biegler, and Frenkel (2010) found similar results.

**Effectiveness Not Established**

Complementary and alternative therapies in this evidence category consist of massage therapy (Cohen et al., 2010), yoga (Carlson, 2010; Rao et al., 2009), hypnotherapy (Lew, Kravits, Garberoglio, & Williams, 2011), music (Li et al., 2011; Luzzatto & Magill, 2010), guided imagery, and herbal preparations. It is important to note that these interventions may be useful, but insufficient randomized controlled trials have been conducted to support the level of effectiveness.

One of these interventions, hypnotherapy, is a behavior therapy using hypnosis to induce heightened concentration, receptivity, and relaxation. Hypnotherapy is only performed by a trained hypnotherapist, usually a psychologist or psychiatrist, who uses various methods to induce a tranquil state during which the patient can focus on positive behavior changes (Fulcher et al., 2014). A review of 27 studies using hypnotherapy for symptom relief in terminally ill patients with cancer revealed that only one study was a randomized controlled trial. Although one trial showed improvement in depression with hypnosis, the small sample size was not adequate to suggest hypnotherapy as a reliable intervention (Rajasekaran, Edmonds, & Higginson, 2005).

Other complementary interventions noted in the literature include St. John’s wort, S-adenosylmethionine (known as SAMe), dehydroepiandrosterone (known as DHEA), folate and other herbal supplements, yoga (Carlson, 2010), acupuncture (Cohen et al., 2010), music (Li et al., 2011), and meditation (Carlson, 2010). Landier and Tse (2010) completed an integrative review of use of complementary and alternative medical interventions with pediatric oncology populations. Results suggested that mind-body interventions were useful in managing distress, pain, and anxiety in these patients. Nurses must ask about the use of complementary therapies when evaluating patients.

Many complementary and alternative therapies will not interfere with standard treatment (Fulcher et al., 2014) but have insufficient evidence to recommend. One specific complementary and alternative therapy, the Chinese herbal preparation known as PHY906, has been shown in animal studies to have antitumor activity and to mitigate side effects of anticancer therapy (Kummar et al., 2011; Rockwell et al., 2013). However, most over-the-counter herbal preparations have not been tested in rigorous clinical trials, so it cannot be said that they are safe to use in conjunction with prescription medications and chemotherapy (Kummar et al., 2011). It is imperative for nurses to ask specifically about dietary supplements, because some people may be unlikely to think of vitamins or herbal preparations as potentially harmful. Example questions to ask include...
• “Are you taking any type of medicine, vitamins, or herbs that are not prescription?”
• “Do you use any over-the-counter medicines such as laxatives, vitamins, or other supplements such as garlic or ginseng?”
• “Do you see an herbalist or native healer or family member for suggestions or herbal mixtures?”

How Do I Ask About Depression?

A common theme heard in clinical practice is the concern about starting the conversation with patients about depression. Patients with major depressive episodes report experiencing discrimination that prevents them from social participation and successful integration into the workplace (Lasalvia et al., 2013). Although depression is becoming more accepted as a medical illness in society, significant stigma still exists, particularly among older adults and even more acutely among racial/ethnic minority older adults (Jimenez, Bartels, Cardenas, & Alegría, 2013; Rosenzweig et al., 2011).

The following are several examples of ways to open a dialogue with patients when nonverbal behavior (i.e., body language, facial expressions), the nurse’s assessment, or a “sixth sense” indicates that depression is a possibility. For example, if the patient is looking sad or depressed, nurses simply reflecting about what they see and asking for clarification may be enough to start the conversation: “You’re looking a little down to me today. Are you feeling depressed?” Another conversation starter is to talk about normal or usual experiences of patients with cancer: “Many patients undergoing chemotherapy say they feel tired, depressed, or stressed. Are you experiencing any of these feelings?” Yet another conversation starter is for nurses to ask how patients have been doing since they last saw them and if they have had any different side effects or symptoms. A key technique to obtain information from patients is to remain quiet long enough for them to respond after asking the question.

Nurses need to keep an open mind. If the patient replies to a question with “fine” or “OK,” and yet the nurse has a high suspicion of depression, the nurse can follow up with a comment about how he or she is interested in the patient’s well-being and that the nurse is there to help. It is important to convey the sense of presence; a critical part of presence is for the nurse to convey both verbally and nonverbally that he or she really wants to know the answer to that question. In 2002, Karen Stanley wrote about presence in nursing practice in “The Healing Power of Presence: Respite From the Fear of Abandonment” and how nurses can establish presence with their patients. Often, nurses convey through nonverbal behavior that they are too busy or really do not want to know the answer. A common myth is that patients might become upset or annoyed when asked questions about how they are doing. However, that myth has not been supported in the literature or in practice. One way to think about presence is for nurses to be for their patients what they need them to be in the moment they are with them. If the nurse suspects that the patient may be depressed, when the nurse sees the signs of depression, he or she can be what the patient needs at that moment by asking questions and listening for the response. The nurse can be the presence that helps patients to name their feelings and to get help for these feelings—demonstrating the caring art of nursing.

Patient Teaching Points

Multiple resources and websites are available for information about depression and its treatment (see Figure 10-5). It is important to note, however, that not all websites contain
Advise patients to follow recommendations from only well-known sites, such as the American Cancer Society, the National Institutes of Health, NCCN, the Livestrong Foundation, or the American Psychosocial Oncology Society. Nurses should guide patients to information they can retrieve themselves. Many of these websites have downloadable materials that nurses can have on hand to take advantage of “teachable moments.” *Teachable moments* are those times when a patient asks a question or raises a concern. These moments happen multiple times during the nurse-patient interaction, and nurses often miss opportunities to educate patients. Nurses play the primary role in patient education, and the nurse-patient relationship is an integral part of establishing a healing space. When patients feel comfortable and sense that the nurse is present with them in the moment and interested in their health and well-being, positive outcomes ensue. Particularly for those patients who still associate depression with some social or personal stigma, it is critical that nurses normalize the experience and dispel myths, for example, telling patients how common the experience of depression is in patients with cancer and how the brain chemistry in depression is different than it was prior to depression. For patients who may be resistant to taking antidepressants, the analogy of taking insulin for diabetes or chemotherapy for cancer often is effective in helping them to grasp the understanding of depression as a biologic/medical illness. For example, the nurse can say something like, “Depression is a physical illness, resulting, in part, because of the lack of adequate chemicals in the brain. Taking medication for depression is just like taking insulin for diabetes. Treatment for depression is in the form of a pill, taken daily to replace the chemicals in the brain.”

**Conclusion of Case Study**

“Oh, A.B.,” the nurse says while seated in front of her, “I am so thankful you told me how you’re feeling. You look sad to me. Do you feel sad or depressed?” The nurse hands the patient a tissue, and after wiping her eyes, she replies, “Almost all the time. I feel so out of control. I have never felt this out of control before. It’s this chemo. It’s causing it.”
The nurse asks A.B. about her activities over the past two weeks. A.B. leans forward in the infusion chair, getting a bit closer to her nurse, as if to share a secret. “I don’t feel like doing anything. Not a thing. I don’t even feel like seeing my new grandbaby. And, you know, it’s affecting my marriage. My husband wanted to go out to a movie on Friday night. But I couldn’t do it. I just couldn’t. He really wanted to go, though. He loves movies.” The nurse edges her chair a bit closer, and in response, A.B. whispers, “But I got really angry at him. I yelled at him. I said that he just didn’t understand. I told him to just go alone. It was awful. I hate being this sick and fighting with my husband.” She cries a bit more, and the nurse hands her another tissue.

After a few moments of silence, the nurse asks, “Will you please fill out a questionnaire about depression?” The nurse sits quietly while the patient thinks. About 10 or 15 seconds later, A.B. says, somewhat hesitantly, “Sure.” The nurse provides her with a copy of the Hospital Anxiety and Depression Scale. After she finishes it, the nurse scores it and finds that she has a score equivalent with significant depression. “May I share with you the results of the questionnaire you filled out?” “Of course,” A.B. replies, though she fidgets in the chair a bit. “Your score indicates significant depressive symptoms. I am going to have the oncology nurse practitioner come by and talk with you more about it.” The nurse takes the opportunity to teach A.B. that depression is a medical illness that occurs in up to half of patients with cancer; the nurse explains more about the causes and treatment of depression. The nurse gives A.B. some reading material about depression to review before she sees the oncology nurse practitioner.

At the next chemotherapy appointment, the nurse inquires about A.B.’s visit with the oncology nurse practitioner. A.B. reports that the oncology nurse practitioner discussed depression and the symptoms she was experiencing, along with the available treatment options. She agreed to a trial of escitalopram, based on her other medications and health problems. The nurse practitioner also arranged an appointment with a social worker to explore support groups for both A.B. and her husband. A.B. confided that her husband is so relieved that she is getting help and has agreed to participate in a telephone support program with her. Although it has been only three weeks since escitalopram was added, she believes that she is already sleeping better and is not as tired. And she adds, “I’m not as irritable now. I actually took a walk around the block with my husband, and next week, we’re planning on going to a movie together. I really want to go with him, to do something with him that he likes. And I had fun when we baby sat my grandbaby last weekend. I felt like a real grandma.” She reaches out for the nurse’s hand and says, “I’m feeling a lot more hopeful now. Thank you for helping me.”

**Need for Future Research**

What changes in nursing practice must be made to improve treatment for patients with cancer and depression? Little, Dionne, and Eaton (2005) conducted a survey with palliative care nurses who belonged to ONS about depression and their roles and responsibilities. Nurses rated depression as the most important clinical issue of those listed, and 98% of nurses reported feeling adequate to assess and treat depression. However, many of the nurses did not have the advanced training required to prescribe medications or provide psychotherapy. Surprisingly, only 54% indicated they would either like to have more information or would mention the suspected depression to the rest of the healthcare team. The majority reported little familiarity with self-rating depression scales. These findings indicate the urgent need for education re-
garding depression. More studies are needed about optimal methods to educate nurses about depression screening and to incorporate depression screening into clinical practice. This will be especially relevant as depression screening becomes an indicator of quality care.

More studies are also needed to examine antidepressants, psychotherapy, and combinations of medications and psychotherapy to determine the most cost-effective treatment strategies. One question that must be answered is clear: Who will benefit from which intervention at what time during the cancer trajectory? Another important question is whether individually focused or group- or family-focused interventions are more powerful. Much more research is needed about including members of the patient’s social support network in psychosocial treatment. Research is needed to determine the best method of delivering an intervention; for example, are telephone interventions as effective as face-to-face interventions? Preliminary evidence indicates that patients treated with telephone counseling are not only satisfied with its accessibility, but that their symptoms of depression and anxiety remit as early as they do in those treated in person (Mohr et al., 2012). Additional research needs to examine various complementary and alternative treatments. The National Institutes of Health has a list of ongoing studies of depression treatments. Many of these studies are specifically designed to investigate depression in patients with cancer. For a complete list of available clinical trials, visit the National Institutes of Health website at www.nimh.nih.gov/health/trials/depression.shtml.

Since SSRIs were introduced in the 1980s, controversy has existed about the increased risk of suicide ideation. This led to more research about the relationship between suicide ideation and antidepressants, and ultimately a black box warning ensued in the early 2000s. Findings from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (Laje et al., 2007) revealed the presence of two genetic markers in patients with suicide ideation. Both of the genetic markers encode nerve cell receptors for glutamate, a chemical messenger, and their presence suggests a genetic basis underlying suicide ideation. This underscores the need for continued research into potential genetic connections and depression. All research must include comparative effectiveness and cost analyses so that nurses can provide the most cost-effective evidence-based care to patients and their families.

Conclusion

One of the hallmarks of oncology nursing practice is excellent care of the whole patient. Oncology nurses are ideally positioned to recognize, screen, diagnose, and treat depression in patients with cancer. In collaboration with the patient and the rest of the healthcare team, oncology nurses can reduce suffering from depression, improve patients’ and families’ QOL, and facilitate health and healing for the whole patient.

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References


Case Study

P.J. is a 20-year-old unmarried man who was enrolled in a local college full-time until six months ago when unrelenting back pain caused him to seek medical attention. Since then he was evaluated by his primary care provider, who ordered blood work and found elevated alpha-fetoprotein and lactate dehydrogenase levels. Further diagnostic testing was ordered including computed tomography scan, bone scan, and comprehensive blood work, which confirmed the diagnosis of testicular cancer with metastasis to the bone and liver. He has been taking ibuprofen for his back pain, with little relief.

P.J. is scheduled for his initial evaluation with the oncologist and nurse practitioner today. He arrives for this visit alone, is pleasant, and asks very few questions. They discuss his lack of pain control and provide prescriptions for a narcotic-based pain control regimen. After outlining the oncologist’s proposed treatment plan for P.J., the nurse practitioner assesses his comprehension of the plan by asking him to repeat the schedule. P.J. hesitates and states, “Well, I wasn’t going to say anything, but I probably won’t keep that schedule, so you just shouldn’t count on it.” P.J. becomes tearful and stares at the floor. The nurse practitioner leaves the computer station and moves to a chair facing P.J. She begins by saying, “Thank you for sharing this with me. It is important that we work together on the best plan for you, so I want to hear about your concerns. Tell me what concerns you have that will prevent you from keeping this plan so that we can begin to make a plan that works for you.” P.J. describes the problems he anticipates with transportation to treatment, as he has no car, lives alone, and will rely on his family to drive him to all appointments. He states, “My mom and dad both work, and they can’t miss work or they will lose their jobs.” P.J. continues to describe his concern for becoming a burden to his family, his fatigue from being unable to sleep, and his worry about how he will pay for his insurance copayments and gas for his transportation to treatment. He describes his lack of income and the burdens this has already placed on his family and states, “I just don’t want to make this worse for them.” He confides that he has received prescriptions for narcotics to control his pain in the past but has been afraid to take them because he does not want to become addicted.
Overview

Patients with cancer routinely experience distress—an emotional response to a variety of stressors. The National Comprehensive Cancer Network® (NCCN®) defines distress as “a multifactorial, unpleasant emotional experience of a psychological (cognitive, behavioral, emotional), social and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment” (NCCN, 2014, p. DIS-2). The term distress was chosen by a panel of multidisciplinary experts convened by NCCN in 1997 to develop the first evidence-based clinical practice guidelines for the management of cancer-related psychosocial concerns (Holland, Kelly, & Weinberger, 2010). The panel selected the term distress with the belief that it was more acceptable and less stigmatizing than other commonly used terms and included a range of severity from a normal response to one that requires intervention.

Since its description by the panel in 1997, the construct of distress in patients with cancer has received increasing attention in both the research and clinical arenas. In 2008, the Institute of Medicine published a landmark report, Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs, that detailed the breadth of unmet psychosocial needs in the adult cancer population (Adler & Page, 2008). Among the report’s major findings was the conclusion that many patients do not receive psychosocial services, which contributes to negative clinical consequences. The report concluded with recommendations for the adoption of psychosocial services as a standard of quality cancer care. After the publication of the Institute of Medicine report, many oncology professional organizations, including the Oncology Nursing Society (ONS), endorsed distress management as an element of evidence-based professional practice (Eaton & Tipton, 2009), yet translation of this standard into practice has been slow.

Recently, the American College of Surgeons (ACoS) Commission on Cancer (2012) issued new quality care standards required of cancer centers for accreditation beginning in 2015. These standards include a requirement to implement distress management programs by 2015. In 2013, ONS joined the American Psychosocial Oncology Society and the Association of Oncology Social Work in endorsing the new ACoS quality care standards, underscoring the need for oncology nurses to understand the construct of distress and develop competency in its detection and management.

Incidence and Risk Factors

Distress is a form of emotional suffering. It can affect patients in various levels of intensity from mild to extreme throughout the cancer care trajectory from diagnosis onward (Harrison, Young, Price, Butow, & Solomon, 2009). Distress is more common, and often experienced at higher levels, during specific points of cancer care, including transitions in care, times of uncertainty, or changes in care or medical condition (NCCN, 2014) (see Table 11-1). During these times, clinicians need to assess patients more carefully, as patients are more vulnerable to developing distress. This will ensure that interventions to alleviate distress and improve quality of life are instituted in a timely manner for those with clinically significant distress.

Distress arises from a variety of aspects of a patient’s life and cancer experience. These include physical symptoms, emotional and mental health concerns, family issues, and spiritual concerns, as well as information and practical or economic needs (Harrison et al., 2009). The prevalence of these sources of distress varies across patient populations and points of
the cancer trajectory (i.e., diagnosis, treatment, survivorship, end of life). The prevalence rate of distress is estimated at 4 in 10 patients with cancer overall (Carlson, Waller, & Mitchell, 2012; Zabora, BrintzenhofeSzoc, Curbow, Hooker, & Piantadosi, 2001). Prevalence rates of cancer-related distress have been reported as 20%–68% among various populations with cancer (Lee, Katona, De Bono, & Lewis, 2010; Molassiotis, Wilson, Blair, Howe, & Cavet, 2011). No single domain of problems or unmet psychosocial needs has proved to be more prevalent in the cancer population as a whole (Harrison et al., 2009). Table 11-2 provides examples of reported unmet psychosocial needs and potential sources of distress in patients with cancer.

### TABLE 11-1 Points of Care Associated With Increased Vulnerability to Distress

<table>
<thead>
<tr>
<th>Point of Care</th>
<th>Examples in the Cancer Care Continuum</th>
</tr>
</thead>
<tbody>
<tr>
<td>During periods of uncertainty</td>
<td>At the time of initial presentation, diagnosis, surveillance testing and medical follow-up appointments, new onset of symptoms, completion of therapy, and entry into survivorship</td>
</tr>
<tr>
<td>When changes occur in medical condition</td>
<td>When experiencing new symptoms or changes in current symptoms, after treatment failure with recurrence or progression, or upon a change in treatment modality</td>
</tr>
<tr>
<td>During transitions in care</td>
<td>At the end of treatment upon admission to or discharge from the hospital, or upon transfer to hospice or palliative care</td>
</tr>
</tbody>
</table>

*Note. Based on information from National Comprehensive Cancer Network, 2014.*

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### TABLE 11-2 Potential Sources of Distress in Patients With Cancer

<table>
<thead>
<tr>
<th>Domain</th>
<th>Patient Problems and Supportive Care Needs</th>
</tr>
</thead>
</table>
| Physical                | Appearance; body image changes  
|                         | Changes in ability to manage activities of daily living (e.g., mobility, bathing, dressing)  
|                         | Respiratory impairment  
|                         | Changes in urination  
|                         | Gastrointestinal problems such as constipation, diarrhea, nausea, or vomiting  
|                         | Fatigue or lack of energy  
|                         | Problems eating  
|                         | Cognitive problems with memory or concentration  
|                         | Pain, especially if uncontrolled  
|                         | Sexual changes, problems and concerns  
|                         | Issues with skin, hair, or nails  
|                         | Peripheral neuropathies  
|                         | Sleep disturbances  
|                         | Edema, fevers  
|                         | Substance abuse, dependence, or addiction  
|                         | Infertility  
| Practical and economic  | Financial problems  
|                         | Difficulty meeting medical and basic living expenses  
|                         | Insurance (uninsured and underinsured)  
|                         | Transportation and parking availability  
|                         | Employment concerns; returning to work or school  
|                         | Difficulty with preparing meals, food shopping, and other daily needs  

(Continued on next page)
Not all patients who face psychosocial stressors or have unmet supportive care needs will develop distress. A number of risk factors for developing moderate or severe levels of distress, or clinically significant distress have been identified (see Figure 11-1). Undetected and thus unmanaged high levels of distress can adversely affect patients’ medical treatment. Cancer-related distress is associated with lower quality of life, inability to make decisions, decreased patient satisfaction, poor adherence to treatment, and additional visits to the emergency department and has been implicated in reduced overall survival (Adler & Page, 2008; Hamer, Chida, & Molloy, 2009). Each of these contributes comorbidities to the patient and adds preventable costs to the healthcare system. Evidence supports that addressing unmet psychosocial distress may reduce current high costs of care in patients with cancer (Gordon, Beesley, & Scuffham, 2011).

### Measurement and Assessment

Healthcare providers have tools available to assist in the detection of distress. One cancer-specific tool is the NCCN Distress Thermometer (NCCN, 2014). The single-item, patient-reported measure is a visual analog-type scale in which the patient marks the degree of distress experienced in the past week on a scale from 0 (no distress) to 10 (extreme distress). The patient then identifies sources of distress by marking applicable problems from a list.
that includes practical, family, emotional, spiritual/religious, and physical problems (see Figure 11-2). The Distress Thermometer is the focus of numerous studies supporting its reliability and validity and comparing it to other surveys designed to measure psychological issues such as anxiety, depression, and quality of life (Bidstrup et al., 2012; Carlson et al., 2012; Craike, Livingston, & Warne, 2011; Mitchell, 2010; Patel et al., 2011; Ryan, Gallagher, Wright, & Cassidy, 2012; Vodermaier, Linden, & Siu, 2009; Ziegler et al., 2011). Additional cancer-specific distress screening tools are listed in Table 11-3.

Adoption of a valid and reliable measure of distress presents many challenges. The translation of a measure from the research setting to the “real world” clinical setting may present new complexities (Cochrane et al., 2007). Several comprehensive reviews of tools and their reliability, validity, sensitivity, and targeted patient populations exist and can assist clinicians in choosing the best option (Carlson et al., 2012; Mitchell, 2010; Vodermaier et al., 2009; Ziegler et al., 2011).

Physicians (Pirl et al., 2007) and nurses (Tavernier, Beck, & Dudley, 2013) were found to be unaware of routine measures to screen for distress. Clinicians do not value screening or find the results useful (Mitchell, 2013; Tavernier et al., 2013). Clinicians have identified a lack of time, training, or resources as a barrier to successful distress screening implementation (Dudgeon et al., 2012; Mitchell, 2013; Pirl et al., 2007; Tavernier et al., 2013). They have also cited a concern that screening will overwhelm support services or that the support services do not have the breadth of expertise needed for providing patient follow-up, yet the literature does not validate this concern. Moreover, feasibility studies have shown that support services are adequate to respond to high distress scores (Carlson et al., 2012; Mitchell, 2013; Mitchell, Vahabzadeh, & Magruder, 2011).

In the clinical setting, successful screening of distress occurs when a dedicated person or team focuses on the development, implementation, and evaluation of the screening process (Dudgeon et al., 2012). Linking the distress screening process to a quality performance measure can facilitate successful screening programs (Mitchell, 2013). Predictors of using the NCCN Guidelines included lower perceived barriers and higher familiarity with the guidelines (Tavernier et al., 2013). In contrast, with the lack of training being a barrier to implementation, data support the education and training of clinicians as an effective strategy for a successful screening program (Carlson et al., 2012; Dudgeon et al., 2012). Several studies supported using digitized versions of screening and assessment tools that patients complete prior to seeing the oncology clinician (Loscalzo et al., 2010; McCleary et al., 2013; Tari- man, Berry, Halpenny, Wolpin, & Schepp, 2011; Wolpin et al., 2014). Inadequate data exist to support specific implementation and outcome questions such as frequency of assessment, comparative effectiveness of screening tools, and interventions and outcomes.
Rights were not granted to include this figure in electronic media. Please refer to the original source.
The risk for suicide in patients with cancer is twice that of the general public (Misono, Weiss, Fann, Redman, & Yueh, 2008). Nurses must assess for suicidal ideation or thoughts as well as risk factors for suicide in all patients with cancer, including those who have a clinically significant level of distress (Cooke, Gotto, Mayorga, Grant, & Lynn, 2013). These assessments should be incorporated into every clinical assessment for the patient at risk. The NCCN Distress Thermometer tool includes several patient problems that are associated with an increased risk for suicide (NCCN, 2014), including pain, depression, substance abuse, and a loss of interest in usual activities, although combinations of problems and greater numbers of problems also may contribute to suicide risk. Other known risk factors for suicide are reviewed in Chapter 4. Patients who indicate these risk factors either on a screening tool such as the Distress Thermometer or during a clinical assessment require further intervention. The first step is to discuss these findings with the patient.

Oncology nurses must develop confidence in asking patients about potential suicidal thoughts. The following are questions to include in an assessment for suicide risk (Cooke et al., 2013).

- Many patients with cancer have passing thoughts about suicide or consider suicide at some point. Have you ever had thoughts like that?
- Have you been bothered by thoughts that you would be better off dead, or considered hurting yourself in some way?
- Have you had these thoughts in the past few days?

### Evidence-Based Interventions

The screening and detection of distress is futile if no effort is taken to manage a person’s distress. What value is there in assessing patients’ levels of distress if there are no interventions based in evidence to offer to those experiencing distress? Prior to establishing distress

### TABLE 11-3 Cancer-Specific Measures of Distress

<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edmonton Symptom Assessment System (Bruera et al., 1991; Watanabe et al., 2012)</td>
<td>Eight-item visual analog scale. Sum of patient rating scores determines level of pain, activity, nausea, depression, anxiety, drowsiness, appetite, and sensation of well-being.</td>
</tr>
<tr>
<td>Cancer Needs Distress Inventory (Lowery et al., 2012)</td>
<td>39-item self-report measure using 5-point Likert-type scale to measure the severity of problems in 7 areas: depression, anxiety, emotion, social, healthcare, practical, and physical. Each item includes the question of whether the patient would like to speak with a healthcare professional.</td>
</tr>
<tr>
<td>Questionnaire on Stress in Cancer Patients (Herschbach et al., 2004)</td>
<td>23-item self-report measure using a 5-point Likert-type scale to measure if problems in 5 subscales (psychosomatic complaints, fears, information deficits, everyday life restrictions, and social strains) apply to the patient, and if so, the extent to which the problem causes distress.</td>
</tr>
<tr>
<td>Supportive Needs Screening Tool (Pigott et al., 2009)</td>
<td>41-item “yes/no” assessment of self-reported needs in 5 subscales (information, physical, social, psychological, and spiritual).</td>
</tr>
<tr>
<td>Patient Needs Assessment Tool (Coyle et al., 1996)</td>
<td>Interviewer-rated screen for potential problems in physical, psychological, and social functioning.</td>
</tr>
</tbody>
</table>
screening programs, processes must be established for the communication of screening results, differentiation of sources of distress, and the referral to qualified clinicians to begin interventions (Absolom et al., 2011; NCCN, 2014). These aspects of patient care are often the responsibility of nurses—staff nurses, nurse navigators, clinical nurse specialists, and nurse practitioners (Dolbeault, Boistard, Meuric, Copel, & Brédart, 2011; Grassi et al., 2011; ONS et al., 2013; Swanson & Koch, 2010). Despite their integral role in the distress management process, both oncology nurses and physicians describe a lack of knowledge, skill, and clinical confidence in this area (Dolbeault et al., 2011; Tavernier et al., 2013). As cancer programs implement the ACoS Commission on Cancer (2012) standards for distress management processes, the need for professional education in this area will become a priority. Key to implementation success is the presence of competent clinicians who are confident in their distress management skills (ONS et al., 2013). A number of professional education opportunities exist and include the following.

- **ONS (www.ons.org)** offers educational opportunities online and at on-site conferences, as well as evidence-based practice resources online for the management of anxiety, depression, and several physical sources of distress.
- **The American Psychosocial Oncology Society (www.apos-society.org)** is a multidisciplinary professional organization in the United States dedicated to the psychosocial aspects of cancer treatment and offers educational resources including online training and on-site conferences (see www.apos-society.org/professionals/meetings-ed/webcasts/webcasts-ican2.aspx for an online training module in distress management).

A thorough assessment is the cornerstone of care for patients with cancer experiencing distress and guides the nurse in placing referrals to the appropriate providers for care. The referral processes must be well defined prior to detecting distress; this is a major barrier to distress management (Absolom et al., 2011; ONS et al., 2013). NCCN has published referral algorithms for each of the domains of distress sources: practical, emotional, family, spiritual, and physical (NCCN, 2014). Figure 11-3 details this referral process. Oncology nurses can use these referral algorithms to ensure the patient with distress is provided the intervention that will best alleviate the source of distress.

Distress management is needed from not only the oncology and psychosocial team but other sources as well. Oncology nurses may not have access to on-site referrals to qualified practitioners or other resources such as financial counselors or chaplains. In this situation, the resources may be identified in the community or through national supportive care organizations. Oncology nurses should assess patients’ identified support systems, including family, friends, and community support, as well as their current use of these psychosocial supports. Additional resources that provide information and support for people with cancer are available both online and through community organizations. Resources for specific sources of distress such as anxiety or physical side effects can be found within the corresponding chapter. Sample patient resources for cancer-related distress are listed in Figure 11-4.

The evidence supporting psychosocial interventions for distress management is limited and mixed. Results are weakened by a lack of standard terminology and providers. Additionally, most psychosocial intervention studies of patients with cancer fail to include selection criteria in their methodology. Most psychosocial study populations include patients with a variety of cancer diagnoses who are receiving varying treatment modalities and are in varying phases of the cancer trajectory (Faller et al., 2013; Galway et al., 2012; Linden & Girgis, 2012). Despite these methodologic challenges, several conclusions can be drawn. First, psychoeducational interventions, cognitive behavioral therapy (CBT), and group therapy have demonstrated a reduction in distress level and enhanced quality of life in patients with can-
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Intervention outcomes are consistent across the cancer continuum and across patients with varying cancer types and stages. The observed outcome of reduction in distress level has been realized only in the subpopulation of those with a preexisting level of clinically significant distress (Carlson, Waller, Groff, & Bultz, 2013; Faller et al., 2013). However, the lack of reported outcomes on distress level in psychosocial intervention studies may be due to a floor effect; that is, patients without clinically significant distress pre-intervention have no room to improve and therefore dilute the observed response. This lack of selection criteria is common in psychosocial intervention studies of patients with cancer (Linden & Girgis, 2012).

Patients living with cancer and their families experience a multitude of financial stressors. The financial burdens of a cancer diagnosis are well documented and contribute to an overall burden for patients living with cancer to meet financial obligations of daily living (Sharp, Carsin, & Timmons, 2013). From 1996 to 2005, out-of-pocket healthcare expenditures rose disproportionately for people with chronic disease conditions, as shown in the Agency for Healthcare Research and Quality–sponsored Medical Expenditure Panel Survey (Paez, Zhao, & Hwang, 2009). The financial domain of distress management has been identified by patients in several screening studies as a common source of distress (Dolbeault et al., 2011; Kendall, Glaze, Oakland, Hansen, & Parry, 2011). Yet, little evidence supports the recommendations for the types of interventions, their timing and frequency, or the qualifications of the provider. The focus of distress management interventions has been on the emotional component of care with less emphasis on the financial interventions that may reduce emotional distress. This is a high-priority area for future research as healthcare costs and associated out-of-pocket expenses for patients living with a cancer diagnosis continue to rise. NCCN recommends referral to social work and counseling services for interventions to address financial sources of distress and their psychosocial issues (NCCN, 2014). If these re-

### FIGURE 11-4 Patient Resources for Distress Management

- **American Cancer Society**: Provides support resources and an educational brochure about distress available at regional offices or online. [www.cancer.org](http://www.cancer.org)
- **American Society of Clinical Oncology**: Offers resources on the Coping and Emotions page of its patient website. [www.cancer.net/coping](http://www.cancer.net/coping)
- **Cancer Financial Assistance Coalition**: Provides resources from a coalition of organizations to help patients manage their financial challenges. [www.cancerfac.org](http://www.cancerfac.org)
- **Cancer Legal Resource Center**: Provides information and education about cancer-related legal issues to the public through its national telephone assistance line (866-THE-CLRC) and educational resources. [www.disabilityrightslegalcenter.org/cancer-legal-resource-center](http://www.disabilityrightslegalcenter.org/cancer-legal-resource-center)
- **Cancer Support Community**: Provides educational and support resources, as well as distress screening, available online or at local affiliates. [www.cancersupportcommunity.org](http://www.cancersupportcommunity.org)
- **National Cancer Institute**: Offers educational materials for managing sources of distress. [www.cancer.gov](http://www.cancer.gov)
- **National Comprehensive Cancer Network**: Provides NCCN Guidelines for Patients® and other patient and caregiver resources. [www.nccn.org/patients](http://www.nccn.org/patients)
sources are not available on site, they should be sought in the community to establish a referral mechanism.

The spiritual and religious needs of patients living with cancer have been the focus of several qualitative studies, primarily in those with advanced cancer (Balboni et al., 2007; Phelps et al., 2012). In those studies, spiritual support was associated with a higher quality of life and improved satisfaction with medical care. In particular, patients expressed satisfaction with a holistic approach to their care and to the relationship they formed with their physician (Phelps et al., 2012). One report found spiritual growth as an outcome of spiritual support interventions in adult cancer survivors (Allmon, Tallman, & Altmaier, 2013). While these outcomes contribute to the overall quality of care provided, the effect of spiritual interventions on cancer-related distress has received little attention in the literature and should be a priority for future research. NCCN (2014) recommends referral of patients with spiritual sources of distress to spiritual counseling provided by a trained provider such as a chaplain or to a community religious resource person.

A cancer diagnosis burdens patients and their families. The family domain of distress management is a measure of the level of distress these burdens cause for the patient, not the family members themselves. The stress and burden that can be experienced by caregivers is not measured in this domain or by the Distress Thermometer. Rather, the family domain of the Distress Thermometer assesses how distressing this situation is for the patient. There is evidence of enhanced coping resulting from psychoeducational interventions that provide care to the patient and caregiver together as a dyad (Northouse et al., 2013). For patients with a clinically significant distress level that involves the family domain as a source, NCCN (2014) recommends referral to a psychosocially trained clinician or counselor.

It is important to target the limited available treatment resources on those who will best benefit from them. This is a better approach than offering limited resources to all patients with the hope that those who most need them will reach out and benefit from them. There is a lack of support for the routine provision of psychosocial interventions to all patients with cancer (Carlson et al., 2010, 2013; Faller et al., 2013; Galway et al., 2012). Until evidence provides support for routine provision of psychosocial interventions in the prevention of distress to all patients with cancer, oncology nurses and other healthcare providers should design programs for inclusion of those patients with clinically significant distress.

Lastly, there is a reported trend of patient failure to follow through with referrals and refusal to accept referrals to distress management resources. Overall, studies report a 3:1 ratio of those offered help to those who accepted it (Grassi et al., 2011; Lynch, Goodhart, Saunders, & O’Connor, 2010; Merckaert et al., 2010; Tuinman, Gazendam-Donofrio, & Hoekstra-Weebers, 2008). While patients may reject assistance for various reasons, a lack of awareness of available resources or a perception of not needing help were identified as barriers by patients in one historic study (Carlson et al., 2004). Further research is needed to identify other barriers to a successful referral; however, nurses should facilitate the referral process by eliminating those that are known. This includes ensuring that patients have written information regarding the appointment (time, directions, and name of provider), have the necessary support to attend the appointment (transportation, child care), are motivated to follow through, and comprehend the consequences of failure to follow through.

The presence of suicide risk factors or suicidal thoughts or ideation warrants the immediate assessment of safety and an immediate referral of the patient to a mental health professional. Family members should be alerted of the risk for suicidal behavior and engaged in education regarding suicide and its prevention (Cooke et al., 2013). Disclosing suicide risk to family members is not a violation of the patient’s health information privacy; regulations
allow disclosure of private health information if the person is believed to be of harm to self or others (U.S. Department of Health and Human Services, n.d.).

**Patient Teaching Points**

Nurses must present the process of distress management to patients as a part of their routine medical care. In addition to initial education regarding distress management, ongoing teaching and follow-up may be necessary as patients move through vulnerable points in their care. Also, teaching must be done at appropriate times when patients are receptive. Patients experiencing high levels of distress may have an impaired ability to focus or make decisions (NCCN, 2014). Nurses should evaluate patients’ comprehension of teaching points or instructions by asking them to repeat the content (Joint Commission, 2007). Patients must be taught that distress can occur at any point in their treatment trajectory and into survivorship or at the end of life. Just because patients are without significant distress at the beginning of treatment does not mean they will not experience distress at other times throughout their care. Figure 11-5 lists patient teaching points about distress.

**Need for Future Research**

Great strides have been made in the management of cancer-related distress over the past 20 years. These include the development of evidence-based practice guidelines (NCCN, 2014) and their inclusion in oncology clinician practice standards, such as those developed by ONS (Eaton & Tipton, 2009). Distress management is now recognized as an element of quality care and is required by regulatory agencies (ACoS Commission on Cancer, 2012). Screening tools are available for use in the clinical arena, and evidence for successful implementation is developing. Inadequate data exist to support specific implementation details, such as frequency of screening and assessment and the comparative effectiveness of screening tools. The evidence supporting psychosocial interventions is weak at best. It may be strengthened by clinical trials that select patients with clinically significant distress pre-intervention. Lastly, the role of distress screening and outcomes of psychosocial interventions as a method of distress prevention is unknown and should be investigated, as it offers the potential for avoiding negative clinical consequences and costly psychosocial care.

**FIGURE 11-5  Patient Teaching Points About Distress**

Patients should be taught to
- Understand that distress can be managed and symptoms should not be ignored.
- Understand the rationale for screening and the process for responding to results.
- Understand that points of transition in care may lead to vulnerability to distress.
- Identify people in their life who can provide support during difficult and stressful times.
- Talk about their symptoms of distress with their oncology team so that the team can understand their symptoms and plan interventions to help them.
- Follow through with referrals to psychosocial or mental health professionals to manage distress.
- Understand the clinical consequences of unmanaged distress.

*Note. Based on information from Fann et al., 2012; National Comprehensive Cancer Network, 2014; Oncology Nursing Society et al., 2013.*
The ACoS Commission on Cancer will require routine distress screening for all patients with cancer beginning in 2015. Therefore, many nurses and cancer committees are working to implement a psychological distress screening assessment for patients with cancer coupled with a program to offer evidence-based interventions for patients with moderate to severe distress (Brown, 2014). Future research should be conducted to help delineate the best way to assess patients’ distress coupled with interventions that truly make a difference in patient outcomes.

**Conclusion of Case Study**

The nurse practitioner recognized that P.J. is at high risk for distress. The nurse understood the importance of establishing a trusting, therapeutic relationship and employed a number of communication skills to facilitate their communication. These included using open-ended questions, questioning and probing for details, and validating P.J.’s statements. These techniques led to the disclosure of many potential sources of distress, including pain, anxiety, worry, financial concerns, family concerns, and sleep disturbances. P.J. was also at increased risk for suicide. His risk factors include that he has a cancer diagnosis, is male, lives alone, and has unrelenting pain that affects his daily living. Most notably, however, his statement that he does not want to be a burden to his family is considered an expression associated with greater risk for suicide. P.J. had disclosed that he has access to a stockpile of unused narcotics. The nurse practitioner conducted a suicide assessment that included the presence of suicidal thoughts, a suicide plan, and presence of weapons in the house and confirms that P.J. was not stockpiling narcotics. The nurse practitioner reviewed distress with P.J., including its causes and prevalence in patients with a cancer diagnosis, and recommended that P.J. meet with a social worker to develop a plan to address the sources of distress. Once the nurse secured P.J.’s approval for the referral, the nurse called an oncology clinical social worker and they began a full assessment of P.J.’s psychosocial needs. Together they developed a supportive care plan.

This case study highlights the importance of identifying the level and sources of distress and including them in the routine clinical care and treatment planning process of patients with cancer. P.J.’s needs may have been undetected, and remained unmet, had the nurse practitioner not reviewed the treatment schedule. Routine screening for distress with a tool such as the NCCN Distress Thermometer improves distress detection in patients with cancer and should be employed in all areas of cancer care.

**Conclusion**

Psychosocial care of patients with cancer is a critical component of quality oncology nursing care. ONS includes elements of distress management in its evidence-based clinical practice resources (Eaton & Tipton, 2009) for the management of anxiety and depression. ONS endorses distress management as an element of quality cancer care (ONS et al., 2015). The role of the oncology nurse as a care provider is vital in distress management and includes a responsibility to understand the construct of distress, screen for distress, educate patients regarding distress, and navigate patients to appropriate care interventions as their assessments indicate. Successful distress management requires strong collaborations between oncology
nurses and other healthcare professionals in the mental health and psychosocial disciplines, as well as in the community.

A systematic approach to distress screening improves detection and should be accomplished using a screening tool, such as the NCCN Distress Thermometer. NCCN provides an evidence-based approach to cancer-related distress management, and the guidelines are endorsed by ONS, the American Psychosocial Oncology Society, and the Association of Oncology Social Work (ONS et al., 2013). Nurses should become clinically competent and knowledgeable of distress management guidelines, including the use of a screening tool, and must have resources readily available for patient referral.

References


CHAPTER 12

Dyspnea

Catherine Glennon, RN, MHS, OCN®, NE-BC

Case Study

T.J., a 62-year-old Caucasian male, was diagnosed with stage IV non-small cell lung cancer three months ago. His medical history is significant for chronic obstructive pulmonary disease (COPD). He quit smoking cigarettes more than six months ago after smoking a pack per day for 40 years. He is a widower who lives alone but has two supportive daughters who check in on him weekly. Currently, he is being treated with systemic chemotherapy. The ambulatory care nurse is evaluating him today before administering his second cycle of chemotherapy.

He tells the nurse that he has become increasingly short of breath with walking short distances and has decreased his activities accordingly. In addition to the dyspnea, he reports occasional dry cough, increasing fatigue, and anorexia. Upon further assessment by the nurse, he reports occasional constipation. His weight has decreased three pounds since his first cycle of chemotherapy three weeks ago. He is considering acupuncture because his friends told him it worked for others they knew, not just to improve his shortness of breath but also for his weight loss. He denies anxiety or depression but admits to feeling panic during one of his “difficult breathing” episodes. In addition to an anti-nausea regimen, his current medications include a multivitamin, sustained-release morphine sulfate 30 mg every 12 hours for posterior thoracic pain, and two puffs four times a day of an albuterol/ipratropium metered dose inhaler.

The nurse assesses his lung sounds and notes, in general, that the breath sounds are distant bilaterally and are absent one-third of the way up at the base of the left lower lung field. His vital signs include oral temperature of 97.8°F (36.6°C), regular heart rate of 92 beats per minute, respiratory rate of 20 breaths per minute, and blood pressure of 128/77 mm Hg. He denies pain and reports a fatigue rating of 4 and a dyspnea rating of 6 (both out of 10). His oxygen saturation at rest on room air is 94%; however, it desaturates to 88% with exertion on room air.

Overview

This chapter focuses on chronic cancer-related dyspnea. Information and evidence about dyspnea related to noncancer etiologies, especially COPD where much evidence exists, are
presented to facilitate further understanding. However, it is important to note that the theories or interventions for dyspnea as a general symptom may not have been tested in patients with cancer, and the outcomes may be different in cancer-related dyspnea.

Definitions

*Dyspnea* is defined as difficult or labored breathing. *Breathlessness* often is used synonymously with dyspnea, although someone who is breathless may or may not be in distress. Dyspnea should be differentiated from *hyperpnea* (increased depth of ventilation) and *tachypnea* (increased respiratory rate) (U.S. National Library of Medicine, National Institutes of Health, n.d.).

The American Thoracic Society (ATS, 1999), in a consensus statement, broadly defined *dyspnea* as a term used to characterize a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. “The experience derives from interactions among multiple physiologic, psychological, social, and environmental factors and may induce secondary physiologic and behavioral responses” (p. 322). In the updated official statement of ATS, Parshall et al. (2012) endorsed this definition and acknowledged that since that definition was established, substantial evidence has accrued reporting that distinct mechanisms and afferent pathways are reliably associated with different sensory qualities. Distinct sensations most often do not occur in isolation, and dyspnea sensations vary in their unpleasantness and in significance related to emotions and behavior. Sensory qualities are related to work/effort, tightness, and air hunger/unsatisfied inspiration. Dyspnea remains a complex subjective symptom. It can be challenging to manage effectively because it has more than one dimension, can vary in time, and can have multiple causes.

*Acute dyspnea* refers to difficult or distressed breathing with a duration of less than one month. This form of dyspnea frequently causes a person to seek emergency care. Common etiologies of acute dyspnea are airway obstruction, hyperventilation syndrome, pneumothorax (traumatic or spontaneous), pneumonia, pulmonary embolism, pulmonary edema, hemorrhage, congestive heart failure (CHF), and noxious gas inhalation (Lechtzin, 2013b).

On the other hand, the usual onset of *chronic dyspnea* is slow or gradual with a duration of greater than one month. The nature of chronic dyspnea is that it is persistent and can vary in intensity. Common etiologies are obstructive lung disease such as COPD, asthma, CHF, obesity, upper airway conditions, and anemia (Lechtzin, 2013b). Because of its gradual onset, chronic dyspnea is sometimes associated with advancing age and lack of physical fitness. Chronic dyspnea prompts an individual to seek health care when the breathlessness interferes with activities of daily living.

*Hypoxemia* is defined as a condition where arterial oxygen tension is below normal. *Hypoxia* is defined as the failure of oxygenation at the tissue level. They may or may not occur together (Samuel & Franklin, 2008).

Incidence

Dyspnea affects up to half of the patients admitted to acute tertiary care hospitals and 25% of ambulatory patients (Parshall et al., 2012). Prevalence, in population-based studies, was 9%–13% for mild to moderate dyspnea among adults residing in the community, 15%–18% among those age 40–69, and 25%–37% for those age 70 and older (Parshall et al.,
Shortness of breath or dyspnea accounts for three to four million emergency department visits annually (Niska, Bhuiya, & Xu, 2010). Breathlessness is most consistently found in patients with COPD and heart disease with ranges of 90%–95% and 60%–88%, respectively, and in 10%–70% of patients with cancer (Solano, Gomes, & Higginson, 2006). Prevalence of dyspnea in the cancer population ranged from 67% in the outpatient setting to 77% in the terminal phase of illness (Brennan & Mazanec, 2011). Dyspnea is one of the most common and most feared symptoms among patients with cancer and occurs in approximately 20%–40% of individuals at diagnosis of advanced disease. This increases to 70% in the last six weeks of life (Hui, Morgado, et al., 2013).

Studies have shown that 10%–15% of patients with cancer have breathlessness at diagnosis, and 65% will experience breathlessness at some point during their illness. These are predominantly patients with lung cancer but also patients with breast and prostate cancer (Caïns, 2012). In one study of 923 general outpatients with cancer, 46% of the participants reported some shortness of breath. The mean dyspnea scored by diagnostic category was highest in lung cancer (84% incidence) and lowest in sarcoma (33% incidence) (Dudgeon, Kristjanson, Sloan, Lertzman, & Clement, 2001).

Dyspnea has a strong correlation with lung cancer; therefore, lung cancer incidence must be acknowledged. Lung cancer is the leading cause of cancer deaths and poses significant personal and social costs. Worldwide, the annual diagnosis and mortality of lung cancer was reported at 1.6 and 1.3 million, respectively (Jemal et al., 2011). In the United States, predicted incidence of new lung and bronchus cases for 2014 was 224,210, which is 14% in men and 13% in women. Mortality was at 159,260, which was 28% in men and 26% in women (Siegel, Ma, Zou, & Jemal, 2014). In the general cancer population, the prevalence of dyspnea varies according to the setting and the time at which it was measured during the illness trajectory.

Etiology of Dyspnea

Dame Cicely Saunders (as cited in Kamal, Maguire, Wheeler, Currow, & Abernethy, 2011) first described the elements of the biopsychosocial model of “total dyspnea” in the 1960s. This concept included physical, social, psychological, and spiritual elements and captured the full impact of dyspnea on the patient and caregiver. The mnemonic encompassing these biopsychosocial components is

- Depression, sadness
- Yearning
- Social issues
- Physical problems
- Nonacceptance or spiritual distress
- Economic or financial distress
- Anxiety, anger. (Kamal et al., 2011, p. 1169)

Risk and Associated Factors

Dyspnea is particularly common in patients with cancer who have primary or metastatic lung tumors or pleural involvement; however, many patients with cancer without direct lung involvement also report it. Dyspnea can be a primary complaint in numerous medical conditions, including cardiac, pulmonary, and neurologic diseases.
Bowden, To, Abernethy, and Currow (2011) explored the impact of age, gender, social disadvantage, smoking status, levels of physical activity, and obesity on dyspnea using the Health Omnibus Survey. Over the span of two years, 5,331 respondents in southern Australia answered questions regarding health and social issues. Results showed breathlessness to be directly proportional to increasing age, socioeconomic disadvantage, minimal physical activity, and obesity. Participants with severe dyspnea were more likely to be separated or widowed. Breathlessness was more severe as individual body mass index increased and physical activity decreased.

Prevalence of dyspnea is linked to a number of risk factors, such as a history of smoking and environmental exposures. Smoking tobacco is a primary risk factor for lung disease and cancer, and the risk increases with the number of packs smoked and number of years smoking (pack years of smoking history). Low-dose computed tomography (CT) can detect lung cancer at an early, hopefully more curable, stage of disease for high-risk former or current smokers who are asymptomatic. Organizations endorsing low-dose CT screening include the National Comprehensive Cancer Network® (NCCN®), American Cancer Society, American Lung Association, American Society of Clinical Oncology, ATS, and American College of Chest Physicians. An example of screening information for patients can be found at the American Lung Association website (see American Lung Association, 2012).

Primary treatment modalities for cancer, such as surgery, radiation therapy, or chemotherapy, may contribute to the prevalence of cancer-related dyspnea and will be discussed later in the chapter. Breathlessness in patients with cancer usually begins episodically, but it can become continuous in rapid disease progression. Causative factors include infection or pneumonia, tumor obstruction, anemia, and fibrosis following pulmonary embolism and chemotherapy, specifically bleomycin (Cairns, 2012). Risk factors significantly related to dyspnea include history of or currently smoking, asthma, COPD, lung irradiation, and exposure to chemicals and dust (Dudgeon et al., 2001). Table 12-1 summarizes causes of breathlessness in advanced cancer.

Normally, people have no awareness of their own breathing (Thomas & von Gunten, 2003). The respiratory system is designed to maintain homeostasis with respect to gas exchange. Imbalances in oxygenation lead to breathing discomfort. The development of dyspnea is a complex phenomenon that, in many patients, is the result of stimulation of a variety of receptors throughout the upper airway, lungs, and chest wall. Healthy subjects can experience dyspnea in situations such as being at high altitude, breath-holding, stressful situations that may lead to anxiety or panic, and more commonly during strenuous exercise. The physiologic mechanisms underlying dyspnea are the functional status of the respiratory muscles, the role of chemoreceptors and mechanoreceptors, and how the sense of respiratory motor output reaches a level of conscious awareness (Parshall et al., 2012; Romagnoli et al., 2011; Schwartzstein, 2013). Neurophysiologic mechanisms involve sensory information from the respiratory system that activates regions of the cerebral cortex to produce the perception of dyspnea (Parshall et al., 2012). Similar to pain, dyspnea has an affective component. The affective component is an emotional or behavioral response to the physiologic stimulus of respiratory compromise.

Assessment

Dyspnea is subjective and can only be known from the patient’s report about the personal experience, whereas respiratory distress indicates that a clinician has made an observation. Patients experiencing a dyspnea exacerbation will often report feeling “smothered”
<table>
<thead>
<tr>
<th>Causes in Patients With Cancer</th>
<th>Specific Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection/pneumonia</td>
<td>Antibiotics and other standard therapies when appropriate</td>
</tr>
<tr>
<td>Comorbid conditions associated with increased dead space (e.g., pulmonary vascular disease, COPD)</td>
<td>Optimize medical management of preexisting/coincident conditions</td>
</tr>
<tr>
<td>Deconditioning (lack of exercise)</td>
<td>Rehabilitation (see text)</td>
</tr>
<tr>
<td>Anemia</td>
<td>Erythropoietin, blood transfusion where appropriate</td>
</tr>
<tr>
<td>Cachexia possibly leading to breathlessness by an unknown mechanism</td>
<td>Prevention of cachexia: activity plus possibly some dietary supplements</td>
</tr>
<tr>
<td>Comorbidities associated with respiratory muscle weakness (e.g., myasthenia gravis)</td>
<td>Treatment of underlying disease is most effective treatment</td>
</tr>
<tr>
<td>COPD associated with lung (and therefore thoracic) hyperinflation, leading to inefficiency of respiratory muscles</td>
<td>Optimum treatment and palliation of COPD</td>
</tr>
<tr>
<td>Lymphangitis carcinomatosis</td>
<td>Treatment of cancer, often palliative care, although trial of high-dose steroids (60 mg prednisolone then taper) often used</td>
</tr>
<tr>
<td>Tumor obstructing an airway, pleural effusions, pleural disease (e.g., mesothelioma)</td>
<td>Standard oncological/surgical treatment according to patient's condition (e.g., radiotherapy and/or stenting, etc.)</td>
</tr>
<tr>
<td>Fibrosis following pulmonary emboli, radiotherapy, chemotherapy (e.g., bleomycin)</td>
<td>Prevention of fibrosis where possible by early standard intervention in these conditions (e.g., anticoagulation or steroids) or prevention by surveillance during cancer therapy and careful control of chemoradiation dosage</td>
</tr>
<tr>
<td>Conditions affecting the compliance of the chest wall/diaphragm, such as hepatomegaly/ascites splinting diaphragm, pleural disease (e.g., mesothelioma), or chest wall infiltration by tumor</td>
<td>Treat as appropriate</td>
</tr>
<tr>
<td>Comorbid conditions (e.g., asthma, COPD, interstitial lung disease)</td>
<td>Ensure optimum treatment of comorbid conditions</td>
</tr>
<tr>
<td>Pulmonary congestion (e.g., from SVC, heart failure, pulmonary emboli, pericardia effusion)</td>
<td>Standard therapy for underlying cancer or treatment of complication of cancer prevention where possible (e.g., LMWH in high-risk patients)</td>
</tr>
<tr>
<td>Hypoxia is a consequence of many conditions associated with cancer including pulmonary emboli, pleural effusions, lymphangitic carcinomatosis, diaphragmatic splinting (e.g., in ascites or hepatomegaly), infections</td>
<td>Assess contribution of hypoxia to breathlessness in that individual and treat conditions as appropriate</td>
</tr>
</tbody>
</table>

(Continued on next page)
Causes of Breathlessness in Advanced Cancer (Continued)

<table>
<thead>
<tr>
<th>Causes in Patients With Cancer</th>
<th>Specific Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxieties associated with dyspneic episode remind patients they have cancer and are very ill:</td>
<td>Anxiety management using the following alone or in combination:</td>
</tr>
<tr>
<td>• Anxiety of dying gasping for breath</td>
<td>• Nonpharmacologic anxiety management strategies (see text)</td>
</tr>
<tr>
<td>• Fear/anxiety provoked by idea that breathlessness is in itself harmful</td>
<td>• Pharmacological management of fear and anxiety by phenothiazines, butyrophenones, or benzodiazepines</td>
</tr>
<tr>
<td>• Fear/anxiety because breathlessness at some point may be uncontrollable</td>
<td>• Cognitive approaches such as cognitive behavioral therapy or education</td>
</tr>
<tr>
<td>• Fear/anxiety provoked by the feeling of being breathless</td>
<td>• Availability of clinicians skilled in the management of the symptom</td>
</tr>
<tr>
<td>• Memory of relative dying with unrelieved breathlessness</td>
<td></td>
</tr>
</tbody>
</table>

COPD—chronic obstructive pulmonary disease; LMWH—low-molecular-weight heparin; SVCO—superior vena cava obstruction


or “suffocated” (Campbell, 2011). Brennan and Mazanec (2011) referenced descriptors such as suffocating or feeling like “a fish out of water.” Dyspnea profoundly affects the quality of life, and patients often describe themselves as “existing” rather than living (Marciniuk et al., 2011). Dyspnea has physical, psychological, social, and spiritual components; therefore, no one objective measurement method exists. Common descriptors for air hunger include

- Breath does not go in all the way
- Breaths felt too small
- Cannot get enough air
- Feeling of suffocation
- Hunger for air
- Like breath hold
- Need for more air
- Starved for air
- Unsatisfied inspiration
- Urge to breathe. (Parshall et al., 2102, p. 439)

Because of the symptom’s subjective nature, dyspnea assessment is a challenge, complicated by the fact that the sensation often arises from multiple sources or pathophysiologic mechanisms (Parshall et al., 2012). Assessment of the quality and intensity of dyspnea can vary with time; therefore, measuring the patient’s perception of dyspnea is important. Regular and consistent assessment of dyspnea is facilitated by the use of a form or tool that will document the patient’s rating of the symptom and changes over time.

**Assessment Tools**

Dyspnea usually is classified as to the context in which it occurs, such as on exertion, at rest, or nocturnally. The most common method of screening for dyspnea is self-report of the activity level that causes awareness of the symptom. The Medical Research Council (MRC) dyspnea scale (MRC’s Committee on the Aetiology of Chronic Bronchitis, 1960) has been used since 1959 as a discriminate tool to grade the effect of dyspnea or breathlessness on
daily activities; ATS published a similar scale in 1982 (Brooks, 1982). The dyspnea grading is part of a standardized interview guide and respiratory epidemiologic questionnaire. The MRC has established content validity and reliability (Farncombe, 1997; Mahler, Weinberg, Wells, & Feinstein, 1984; Mahler & Wells, 1988) and is easy to administer and useful for general screening and categorizing of individuals (Meek, 2004). The MRC scale is an incremental grading tool that asks questions about activities that precipitate shortness of breath (see Table 12-2). The grade or level of dyspnea is assigned based on the number of questions answered with a “yes,” indicating the most disability experienced by the respondent. These or similar questions help providers in clinical practice to determine and label the extent that dyspnea interferes with function.

Bailey et al. (2013) recommended that the rating of dyspnea be the sixth vital sign for individuals with COPD because dyspnea is a complex and sometimes disabling symptom reported by this group of patients. Nurses have a significant opportunity to influence patient outcomes and quality of life by assessing dyspnea and applying evidence-based interventions. Interventions such as secretion clearance, appropriate administration of medications, vaccination, oxygen, and nutritional strategies could also be applied to the oncology population.

A questionnaire (GlaxoSmithKline, 2009) was developed to help patients with COPD measure the impact the diagnosis had on their well-being and activities of daily life and to guide the healthcare team in the management of the disease. The online questionnaire (see www.catestonline.org/english/indexEN.htm) is available in 63 languages to meet a wide patient population and may be useful in the oncology setting. This quick self-assessment can enlighten professionals on patients’ limitations by rating eight items, such as patients’ level of breathlessness after walking up a hill or one flight of stairs and the impact on their ability to perform activities at home.

Researchers have investigated the use of a proxy in the assessment of dyspnea. Lobchuk, McClement, Daeninck, Shay, and Elands (2007) studied 126 dyads of patients with breast or prostate cancer and their informal caregivers on general symptom measurements. The authors cautioned clinicians to be reflective when prompting proxy responses, as caregivers may overrate symptoms. Hui, Morgado, et al. (2013) conducted a cross-sectional survey of 299 hospitalized patients with advanced cancer and their caregivers and nurses to assess the patients’ dyspnea using a rating of 0 (none) to 10 (worst). Patients’ dyspnea ratings were overestimated by caregivers and underestimated by nurses. Researchers reviewed physiologic measures such as vital signs (heart, respiratory rate, and oxygen level) with patients’ dys-

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**TABLE 12-2 Medical Research Council Breathlessness Scale**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Degree of Breathlessness Related to Activities</th>
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<tbody>
<tr>
<td>1</td>
<td>Not troubled by breathlessness except on strenuous exercise</td>
</tr>
<tr>
<td>2</td>
<td>Short of breath when hurrying on the level or walking up a slight hill</td>
</tr>
<tr>
<td>3</td>
<td>Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace</td>
</tr>
<tr>
<td>4</td>
<td>Stops for breath after walking about 100 yards or after a few minutes on level ground</td>
</tr>
<tr>
<td>5</td>
<td>Too breathless to leave the house, or breathless when undressing</td>
</tr>
</tbody>
</table>

pnea rating and concluded that these physiologic measures were weakly associated to the patients’ subjective rating. Subjective reporting by the patients remains the best assessment; however, caregivers may potentially be a proxy when patients are unable to report.

**Instruments to Measure Dyspnea**

Many tools or instruments are available to measure an individual’s subjective perception of dyspnea; there is not one universally accepted measurement scale. Scale development, definition, validity, use, and responsiveness are not consistently reported, which may impede clinical use and further research. A disciplined assessment of dyspnea includes measurement and documentation terms that allow for longitudinal appraisal of the symptom, as well as response to interventions. The choice of the instrument or tool to measure dyspnea depends on one’s purpose or reason for measuring this symptom, such as for obtaining a clinical baseline, for determining the effect of treatment, or as part of a protocol answering a specific research question. The feasibility of using one tool versus another will depend on the clinical or research situation. Kjellström and van der Wal (2013) provided descriptions and test properties of various dyspnea measurement instruments that can assist clinicians with patient assessment.

A systematic review of 29 measurement scales in palliative care concluded that selection of the most appropriate scale to measure breathlessness depends on the context and purpose (Dorman, Byrne, & Edwards, 2007). A numeric rating scale (NRS) or the modified Borg Scale (Borg, 1982) seems most suited to measure the overall severity of breathlessness. The Cancer Dyspnea Scale assesses the quality of breathlessness, and the Chronic Respiratory Questionnaire dyspnea subscale measures the functional impairment caused by breathlessness. These require further evaluation in a palliative care setting before adoption as a standard (Dorman et al., 2007).

The Baseline Dyspnea Index rates the severity of dyspnea at a single state and is a multidimensional measurement with ratings from 0 (very severe) to 4 (no impairment) (ATS, n.d.). In comparison, the Transition Dyspnea Index measures changes in dyspnea severity from baseline as established by the Baseline Dyspnea Index, with seven grades ranging from –3 (major deterioration) to +3 (major improvement) (ATS, n.d.). Components to consider in the review of tools and questionnaires include (a) test-retest reproducibility, (b) scoring, (c) validity, (d) language, (e) translations, (f) availability, and (g) references.

Only the visual analog scale (VAS) and the Cancer Dyspnea Scale have evidence of either reliability or validity in patients with cancer (Joyce & Beck, 2005). The VAS measures only one dimension of dyspnea (intensity or severity). Figure 12-1 provides an example of a VAS. A common problem in administering the VAS is patient difficulty seeing the line or understanding the orientation of the anchors. The Cancer Dyspnea Scale measures three dimensions of dyspnea (sense of effort, sense of anxiety, and sense of discomfort) and has been tested and used primarily in Asian populations (Dorman et al., 2007).

**History and Physical Examination**

Evaluation of dyspnea includes a complete history and a focused review surrounding the symptom, such as dyspnea intensity and descriptors, respiratory rate and quality, functional assessment, onset and duration, and aggravating and alleviating factors. The stability and circumstances of the patient’s condition will guide the urgency of this evaluation. A rapid initial assessment of airway, breathing, and circulation is appropriate when confronted with acute dyspnea.
Aspects of the medical history pertinent to dyspnea evaluation include assessment of coexisting diagnoses such as cardiac or pulmonary disease; history of current or past tobacco use or exposure to secondhand or environmental tobacco smoke; relevant work history that provides information about toxin exposure, such as asbestos; and current medications and cancer therapy, as well as prior radiation therapy, surgery, or chemotherapy.

A complete examination is indicated for all patients including a clinical assessment based on medical history and physical examination. ATS and the European Respiratory Society (2004) collaborated on standards to improve the quality of care provided to patients with suspected COPD using a disease-oriented approach to ensure a comprehensive clinical assessment. The ATS (2014) COPD clinical assessment outline may be a helpful resource when assessing dyspnea in patients with other diagnoses (see Figure 12-2). The examination includes past and present medical history and review of systems, exposure history, and respiratory and systemic signs. Respiratory review includes inspection, percussion, and auscultation of lungs and heart.

The character and volume of breath sounds are useful in identifying pulmonary disorders. Vesicular breath sounds are the normal sounds heard over most lung fields. Bronchial breath sounds are slightly louder, harsher, and higher pitched; they normally can be heard over the trachea and over areas of lung consolidation, as occurs with pneumonia. Abnormal or adventitious sounds, such as crackles, rhonchi, wheezes, and stridor, should be noted and are described as follows by Lechtzin (2013b).

- **Crackles**, previously called **rales**, are intermittent adventitious breath sounds. Fine crackles are short and high-pitched, whereas coarse crackles are longer-lasting and low-pitched. The sound is similar to that of crinkling plastic wrap and can be simulated by rubbing strands of hair together between two fingers close to one’s ear. They occur most commonly with atelectasis, pulmonary edema, and interstitial lung disease and signify opening of collapsed alveoli.
- **Rhonchi** are low-pitched respiratory sounds. They can be heard during inspiration or expiration and within various conditions (e.g., chronic bronchitis). The mechanism may relate to airway obstruction, as airways distend and narrow with inhalation and exhalation.
- **Wheeze**s are whistling, musical breath sounds. They are worse on expiration compared to inspiration. These sounds can be a physical finding or a symptom and usually are associated with dyspnea.
Clinical Assessment
Clinical assessment is based on medical history and physical examination [1–3]. Although a complete examination is indicated for all patients, these two components are specifically important for patients with suspected COPD.

Medical History
A directed medical history should assess the following issues.

Symptoms
Cough may be intermittent (early morning) at the beginning, progressively becoming present throughout the day, but is seldom entirely nocturnal [4]. Chronic cough is usually productive and is very often discounted as it is considered an expected consequence of smoking. Cough syncope or cough rib fractures may occur.

Sputum initially occurs in the morning but later will be present all day long. It is usually tenacious and mucoid and in small quantities [2]. Production of sputum for \( \geq 3 \) months in 2 consecutive years is the epidemiological definition of chronic bronchitis. A change in sputum colour (purulent) or volume suggests an infectious exacerbation.

Dyspnoea is usually progressive and over time it becomes persistent. At the onset it occurs during exercise (climbing up stairs, walking up hills) and may be avoided entirely by appropriate behavioural changes (e.g., using an elevator). However, as the disease progresses, dyspnoea is elicited even during minimal exertion or at rest. A quantification of dyspnoea using the Medical Research Council scale (see Definition, diagnosis and staging) is indicated since it predicts quality of life and survival.

Past Medical History and Review of Systems
Any of the following should be noted.
- Any history of asthma, allergy, respiratory infections in childhood or any other respiratory diseases such as tuberculosis.
- Any family history of COPD or other respiratory disease.
- Any history of exacerbations of COPD or hospitalisations.
- Any comorbidities, e.g., those associated with the heart or peripheral vasculature, or neurological comorbidities that share the same risk factor (i.e., cigarette smoke exposure). In addition, symptoms of depression and anxiety may indicate the need for appropriate treatment of these conditions.
- Any history of unexplained weight loss is important because, if caused by COPD, it heralds a poor prognosis.
- Other, nonspecific symptoms, such as wheezing and chest tightness or pain, and morning headache.

Exposure History
The history of exposure to risk factors, such as smoking, or occupational or environmental noxious agents, should be noted. A detailed smoking history is essential (pack-years). Pack-years are calculated by multiplying the number of pack equivalent smoked every day by the total number of years.

Physical Examination
A normal physical examination is frequent in early COPD [6]. As the disease progresses some signs become apparent and in the advanced stages many are almost pathognomonic.

As part of the vital signs, all patients should have their respiratory rate measured, weight and height determined, and their body mass index calculated (see Definition, diagnosis and staging). The examination should be aimed at eliciting the presence of the respiratory and systemic effects of COPD.

Respiratory Signs
Inspection: Check for barrel chest deformity, pursed-lips breathing, chest/abdominal wall paradoxical movements and use of accessory respiratory muscles. All these are signs of severe airflow limitation, hyperinflation and impairment of the mechanics of breathing.

Percussion: Check for decreased motion of the diaphragm and tympanic sounds due to hyperinflation or bullae; in addition the liver becomes easily palpable.
• **Stridor** is a high-pitched sound caused by extrathoracic upper airway obstruction. Stridor is usually louder than wheezing, can typically be heard without a stethoscope, is predominantly inspiratory, and can be heard loudly over the larynx. The presence of this sound signals a concern for life-threatening upper airway obstruction.

• **Decreased breath sounds** indicate poor air movement in the airway, such as with asthma and COPD where bronchospasm or other mechanisms impede airflow. A pleural effusion, pneumothorax, or obstructing endobronchial lesion also may cause decreased breath sounds.

• **Friction rubs** are grating or creaking sounds that vary with the respiratory cycle. The sound is similar to that of skin rubbing against wet leather. These signal pleural inflammation and can be heard in patients with pleuritis or empyema and after thoracotomy. Vocal sounds involve auscultation while patients vocalize such as the following.

• **Bronchophony** and **whispered pectoriloquy** are present when the patient’s spoken or whispered voice is transmitted through the chest wall. This voice transmission is the result of alveolar consolidation, such as which occurs with pneumonia.

• **Egophony** (E to A change) occurs when, during auscultation, a patient says the letter “E” and the examiner hears the letter “A”; again, this is present with pneumonia.

To help clinicians discriminate between these important sounds, audio descriptions are available for normal breath sounds, normal bronchial breath sounds, crackles, wheezing, stridor, friction rubs, and egophony (see Lechtzin, 2013b).

Assessment of patients with cancer must include evaluation of cancer and noncancer causes leading to symptoms of dyspnea. Pohl and Gaertner (2009) outlined the classifications of dyspnea in patients with advanced cancer as

- Local or systemic (cardiopulmonary, systemic)
- Causal relationship with tumor (malignant, nonmalignant)
- Lung function pattern (obstructive, restrictive), and
- Oxygen saturation (hypoxic, nonhypoxic).

Hui, Morgado, et al. (2013) reviewed physiologic measures of dyspnea and baseline characteristics such as vital signs, oxygen delivery device, restlessness, paradoxical breathing pattern, accessory muscle use, grunting and nasal flaring, and the look of fear were included. The median intensity of patients’ dyspnea at the time of assessment was 3 (range 0–6). Potential causes of dyspnea were anemia (78%) followed by pleural effusion (56%) and pneu-
monia (48%). The lowest was tamponade (1%). The study concluded that patients’ level of dyspnea was weakly associated with physiologic measures.

Of note, due to the subjective nature of dyspnea and the variability among individuals with apparently similar degrees of impairment, the U.S. Social Security Administration is reluctant to use dyspnea ratings to determine disability (Pohl & Gaertner, 2009).

**Diagnostic Testing**

The choice of appropriate diagnostic tests is guided by the stage of disease, usefulness of the information for possible therapeutic intervention, and patient preference. Basic dyspnea diagnostic testing includes noninvasive pulse oximetry at rest and with exertion and a complete blood count (CBC). Pulse oximetry or oxygen saturation level in a healthy individual is 97%–99%; an oxygen saturation value of 95% is clinically acceptable in a patient with a normal hemoglobin level (Schutz, 2011). The CBC may show a decrease in hemoglobin concentration with a corresponding decline in the oxygen-carrying capacity of the blood, causing dyspnea.

Dyspnea, in addition to cough and weight loss, is a common presenting symptom leading to a lung cancer diagnosis. NCCN (2014a) guidelines recommend that the diagnostic approach be individualized for patient characteristics, tumor size and location, presence of mediastinal or distant disease, and local experience. The least invasive biopsy technique with the highest diagnostic yield should be chosen.

The following diagnostic tests, and their associated focus, are options to assist with diagnosis. A chest radiograph may be indicated to evaluate acute problems, such as pneumothorax, pneumonia, or pleural effusion. CT may provide information such as tumor outline or tumor progression if sequential scans are performed for comparison. Ventilation-perfusion scan can indicate the presence of pulmonary emboli. Pulmonary function tests that measure lung volumes and gas diffusion may be helpful to diagnose a reversible airway obstruction or hypoxemia, which can be improved with therapy. Pulmonary function tests provide measures of airflow, lung volumes, gas exchange, response to bronchodilators, and respiratory muscle function (Lechtzin, 2013a).

Basic pulmonary function tests available in the ambulatory setting include spirometry and pulse oximetry (O’Brien, 2009). These tests provide physiologic measures of pulmonary function and can be used to quickly determine a differential diagnosis and suggest a subsequent strategy of additional testing or therapy. Tests that provide a more detailed description of physiologic abnormalities, and possibly the underlying pathology, include measurement of lung volumes; lung, chest wall, and respiratory system compliance; and complete cardiopulmonary exercise testing. The choice and sequence of testing are guided by the history and physical examination. Extensive diagnostic testing is appropriate only to determine pathophysiologic causes of dyspnea that are potentially reversible with therapy. Patients’ clinical status and wishes should guide clinicians.

Esteban et al. (2008) examined easily available clinical factors associated with mortality in patients with stable COPD and concluded that forced expiratory volume was the main predictor of respiratory mortality and dyspnea for overall mortality. Other variables studied were age, previous hospital admissions and emergency department visits for COPD, pack-years of smoking, comorbidities, body mass index, and health-related quality of life.

**Evidence-Based Interventions**

A synthesis of evidence-based interventions for cancer-related dyspnea (Joyce, Chandracomar, & Shelton, 2014) is available as part of the Oncology Nursing Society (ONS) Put-
ting Evidence Into Practice (PEP) resources. The evidence in the PEP synthesis is ranked and placed into categories such as Recommended for Practice, Likely to Be Effective, Effectiveness Unlikely, and Not Recommended for Practice, among others. Typically, most of the interventions for cancer-related dyspnea, with the exception of immediate-release opioids, lack sufficient evidence to be recommended and thus fall into the category of Effectiveness Not Established. The ONS PEP resource on dyspnea should serve as an evidence-based guide for oncology nurses.

The management of dyspnea can be divided into two categories: therapeutic and palliative. The optimal approach is to treat reversible causes with specific therapies (therapeutic) and to treat irreversible causes with nonspecific or palliative therapies. Dudgeon et al. (2001) organized cancer-related dyspnea into categories related to cause, including (a) directly caused by tumor, (b) indirectly caused by tumor, (c) caused by cancer therapy, and (d) unrelated to cancer (see Figure 12-3). Dyspnea treatment options can be organized accordingly. Cairns (2012) acknowledged the challenge confronting the healthcare team in managing dyspnea and noted that the team must be cognizant of the impact of dyspnea on patients.

**Therapeutic Treatment of Dyspnea**

**Dyspnea Caused by Tumor**

If the etiology of a patient’s dyspnea is the tumor itself, appropriate therapy to treat the underlying cause with surgery, radiation, chemotherapy, or targeted therapy could reduce dyspnea. Even a minor response to cancer treatment can reduce breathlessness. Relief of

<table>
<thead>
<tr>
<th>FIGURE 12-3 Causes of Dyspnea in Patients With Cancer</th>
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<tbody>
<tr>
<td><strong>Dyspnea Directly Due to Cancer</strong></td>
</tr>
<tr>
<td>• Pulmonary parenchymal involvement (primary or metastatic)</td>
</tr>
<tr>
<td>• Lymphangitic carcinomatosis</td>
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<tr>
<td>• Intrinsic or extrinsic airway obstruction by tumor</td>
</tr>
<tr>
<td>• Pleural tumor</td>
</tr>
<tr>
<td>• Pleural effusion</td>
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<tr>
<td>• Pericardial effusion</td>
</tr>
<tr>
<td>• Ascites</td>
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<tr>
<td>• Hepatomegaly</td>
</tr>
<tr>
<td>• Phrenic nerve paralysis</td>
</tr>
<tr>
<td>• Multiple tumor microemboli</td>
</tr>
<tr>
<td>• Pulmonary leukostasis</td>
</tr>
<tr>
<td>• Superior vena cava syndrome</td>
</tr>
<tr>
<td><strong>Dyspnea Indirectly Due to Cancer</strong></td>
</tr>
<tr>
<td>• Cachexia</td>
</tr>
<tr>
<td>• Electrolyte abnormalities</td>
</tr>
<tr>
<td>• Anemia</td>
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<tr>
<td>• Pneumonia</td>
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<tr>
<td>• Pulmonary aspiration</td>
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<tr>
<td>• Pulmonary emboli</td>
</tr>
<tr>
<td>• Neurologic paraneoplastic syndromes</td>
</tr>
<tr>
<td><strong>Dyspnea Due to Cancer Treatment</strong></td>
</tr>
<tr>
<td>• Surgery</td>
</tr>
<tr>
<td>• Radiation pneumonitis/fibrosis</td>
</tr>
<tr>
<td>• Chemotherapy-induced pulmonary disease</td>
</tr>
<tr>
<td>• Chemotherapy-induced cardiomyopathy</td>
</tr>
<tr>
<td>• Radiation-induced pericardial disease</td>
</tr>
<tr>
<td><strong>Dyspnea Unrelated to Cancer</strong></td>
</tr>
<tr>
<td>• Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>• Asthma</td>
</tr>
<tr>
<td>• Congestive heart failure</td>
</tr>
<tr>
<td>• Interstitial lung disease</td>
</tr>
<tr>
<td>• Pneumothorax</td>
</tr>
<tr>
<td>• Anxiety</td>
</tr>
<tr>
<td>• Chest wall deformity</td>
</tr>
<tr>
<td>• Obesity</td>
</tr>
<tr>
<td>• Neuromuscular disorders</td>
</tr>
<tr>
<td>• Pulmonary vascular disease</td>
</tr>
</tbody>
</table>

airway obstruction either through external beam radiation therapy, brachytherapy, or airway stenting with or without laser ablation can palliate respiratory symptoms (Dalal, Palat, & Bruera, 2007; Dudgeon, 2002; Joyce, 2014).

Respiratory compromise from pleural effusions or ascites can be relieved temporarily with thoracentesis or paracentesis. In most instances, the fluid reaccumulates shortly after removal. Generally, 10–20 ml of pleural fluid is spread thinly over visceral and parietal pleurae, facilitating movement between the lungs and chest wall. When excess fluid enters or minimal amount of fluid escapes the pleural space, pleural fluid accumulates (Light, 2012). If relief is obtained with pleural fluid drainage, pleurodesis with a sclerosing agent can obliterate the pleural space and prevent further accumulation of pleural fluid. Pleurodesis is created by instilling a substance, such as talc, via a chest tube or by insufflation during thoracoscopy into the pleural space to fuse the visceral and parietal pleura (Light, 2012). Talc causes inflammation that results in fibrosis and adherence of the serosal surfaces, which eliminates the pleural space. However, subsequent dyspnea described as a sense of lung restriction sometimes results from the pleurodesis procedure.

The frequency of local and systemic symptoms such as cough, dyspnea, hemoptysis, and chest discomfort in patients with lung cancer was calculated by Beckles, Spiro, Colice, and Rudd (2003). Dyspnea developed early in approximately 60% of patients and was usually associated with increasing cough and sputum. If the tumor was occluding a main airway, it caused breathlessness, which could be associated with a unilateral wheeze (Beckles et al., 2003). Signs and symptoms may be the result of intrathoracic spread of lung cancer either by direct extension or lymphatic spread to the nerves, such as the laryngeal nerve, phrenic nerve, brachial plexus, and sympathetic nerve trunks. Other structural involvement included the chest wall and pleura and vascular involvement such as the superior vena cava, pericardium, and heart. Visceral involvement, including the esophagus, was also noted. Distant metastases occurred in approximately one-third of patients, with the most common extrathoracic sites being bone, liver, adrenal glands and intra-abdominal lymph nodes, brain and spinal cord, lymph nodes, and skin (Beckles et al., 2003). Substantial evidence supports that all patients with known or suspected lung cancer should undergo a thorough history, physical examination, and standard laboratory tests as a screen for metastatic disease (Beckles et al., 2003).

**Dyspnea Indirectly Caused by Cancer**

Two common complications of cancer as a chronic illness that may contribute to dyspnea are pneumonia and anemia (Joyce & Camporeale, 2012). Chronic illness, as well as certain cancer therapies, can predispose individuals to these secondary conditions, which may result in increased respiratory effort or discomfort. Pneumonia, an acute inflammation of the lung, can be treated with adequate antibiotic therapy, which can lead to a degree of dyspnea relief. Anemia, a decrease from the normal baseline of oxygen-carrying hemoglobin, may precipitate a feeling of breathing discomfort. If appropriate to the patient’s condition, anemia can be relieved with red cell transfusion or erythropoietin therapy. Correcting anemia may lessen dyspnea. Erythropoiesis-stimulating therapy has been shown to increase hematocrit and decrease transfusion requirements for several months following chemotherapy (U.S. Food and Drug Administration, 2011). Other conditions seen in chronic illness, including malnutrition, electrolyte and mineral imbalance, and overall deconditioning, can lead to dyspnea as well (Joyce & Camporeale, 2012). Correction of these conditions may alleviate dyspnea, depending on the patient’s state of health (Joyce & Camporeale, 2012).
Chapter 12  

Dyspnea Caused by Cancer Treatment

Dyspnea may be the result of cancer treatment modalities, including radiation therapy, chemotherapy, and surgery (Dudgeon et al., 2001). Because lung tissue is radiosensitive, radiation pneumonitis may occur after completion of radiation treatment, with dyspnea as a classic sign (Williams, Johnston, & Finkelstein, 2010). Having a large volume of lung included in the treatment field or concomitant chemotherapy can increase the severity and incidence of pneumonitis and fibrosis and, thus, the degree of dyspnea. Dyspnea is a primary presenting symptom of pneumonitis and pulmonary fibrosis. Resolution of acute radiation pneumonitis is feasible, but some degree of permanent lung fibrosis may result (Ghafoori, Marks, Vujaskovic, & Kelsey, 2008). Acute or chronic pneumonitis may be a consequence of radiation and some chemotherapy agents. An oral corticosteroid, usually prednisone, starting at 40–60 mg daily for one to two weeks followed by a slow taper, such as reducing by 10 mg every one to two weeks, is the mainstay of therapy (Ghafoori et al., 2008).

Chemotherapy drug classifications associated with pulmonary toxicity include alkylating agents, anticancer cytokines, antimetabolites, antibiotics, monoclonal antibodies, nitrosoureas, plant alkaloids, and targeted therapies. Additional chemotherapy agents not in these classifications that affect respiratory function include arsenic trioxide, bevacizumab, bortezomib, lenalidomide, and thalidomide (Polovich, Olsen, & LeFebvre, 2014). Pharmaceutical companies’ drug information or inserts, which include prescribing and important safety information, outline pulmonary adverse drug reactions in newer agents such as crizotinib (Pfizer Inc., 2012), pertuzumab (Genentech, Inc., 2012), and ipilimumab (Bristol-Myers Squibb Co., 2011). Chemotherapy drugs related to acute pneumonitis include bleomycin, carbustine, gemcitabine, methotrexate, mitomycin, procarbazine, and the vinca alkaloids, and those known to cause pulmonary fibrosis include bleomycin, carbustine, cyclophosphamide, methotrexate, and mitomycin (Polovich et al., 2014). Anthracycline chemotherapy agents are associated with cardiac toxicity, most commonly cardiomyopathy, which may progress to heart failure that produces dyspnea (Lechtzin, 2013b; Polovich et al., 2014). Table 12-3 outlines the incidence of dyspnea with specific chemotherapy agents.

Cardiomyopathy with risk of CHF and shortness of breath can result from certain chemotherapy agents, such as doxorubicin. The risk of developing significant cardiomyopathy with doxorubicin is greatest when the total (cumulative) dose exceeds 550 mg/m² (Fischer, Knobf, Durivage, & Beaulieu, 2003; Polovich et al., 2014). Prevention of cardiac toxicity is key and is accomplished by frequent patient assessment. Once cardiac toxicity develops, conventional therapy for CHF is indicated (Polovich et al., 2014).

Park et al. (2013) evaluated the outcome and prognostic factors of 51 patients requiring invasive mechanical ventilation for acute respiratory failure within one month of receiving chemotherapy for a solid tumor in an ambulatory setting. Seven had drug-induced pneumonitis. The cause of acute respiratory failure, requiring mechanical ventilation, in the majority of the patients (n = 24, or 47.1%) was pneumonia followed by acute respiratory failure due to extrapulmonary infection, drug-induced pneumonitis, alveolar hemorrhage, and cancer progression. The intensive care unit mortality rate was 68.6%. Clinically diagnosed pneumonia was defined as a new infiltrate on chest radiography plus one of the following: dyspnea, fever or hypothermia, new cough with or without sputum, or altered breath sounds on auscultation. The authors concluded that prechemotherapy evaluation with a tool such as the Eastern Cooperative Oncology Group (ECOG) Performance Scale should be incorporated into the discussion of treatment options and is an independent predictor of mortality.

Chemotherapy toxicity management in first-line non-small cell lung cancer standard treatment has economic significance as well. Dyspnea was one of the 11 nonhematologic adverse drug reactions included in the review of grade 3 and 4 toxicities of 130 chemotherapy
TABLE 12-3  Pulmonary Toxicity of Chemotherapeutic Drugs: Dyspnea

<table>
<thead>
<tr>
<th>Classification</th>
<th>Drug</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agents</td>
<td>Ifosfamide</td>
<td>Acute dyspnea with hypoxemia may occur due to transient methemoglobinemia.</td>
</tr>
<tr>
<td></td>
<td>Oxaliplatin</td>
<td>The combined incidence of cough, dyspnea, and hypoxia was 43% (any grade) and 7% (grades 3 and 4) in the oxaliplatin plus 5-FU/LV arm compared to 32% (any grade) and 5% (grades 3 and 4) in the irinotecan plus 5-FU/LV arm for patients with previously untreated colorectal cancer.</td>
</tr>
<tr>
<td></td>
<td>Temozolomide</td>
<td>Dyspnea: 5%–8%</td>
</tr>
<tr>
<td>Anticancer cytokines</td>
<td>Aldesleukin (IL-2)</td>
<td>Dyspnea: 43%</td>
</tr>
<tr>
<td></td>
<td>Oprelvekin (IL-11)</td>
<td>Dyspnea: 48%</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Capecitabine</td>
<td>Dyspnea: 14%</td>
</tr>
<tr>
<td></td>
<td>Fludarabine phosphate</td>
<td>Dyspnea: 9%*; 22%**</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine hydrochloride</td>
<td>Dyspnea: 23%; severe: 3%</td>
</tr>
<tr>
<td>Antitumor antibiotic</td>
<td>Bleomycin sulfate</td>
<td>Pulmonary toxicity: 10%</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Arsenic trioxide</td>
<td>Dyspnea: 53%; grades 3 and 4: 10%</td>
</tr>
<tr>
<td></td>
<td>Lenalidomide</td>
<td>Dyspnea: 15%–23%; severe: 4%</td>
</tr>
<tr>
<td></td>
<td>Thalidomide</td>
<td>Dyspnea: 50%; severe: 4%</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>Alemtuzumab</td>
<td>Infusion rate–related dyspnea: 17% Dyspnea: 26% (first week of therapy)</td>
</tr>
<tr>
<td></td>
<td>Trastuzumab</td>
<td>Dyspnea: 22%</td>
</tr>
<tr>
<td>Plant alkaloids</td>
<td>Etoposide</td>
<td>Dyspnea: 0.7%–2% of patients receiving IV etoposide and less than 1% of patients treated with the oral capsules</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>Dyspnea: 2%</td>
</tr>
<tr>
<td>Targeted therapies</td>
<td>Imatinib</td>
<td>Dyspnea: 14%–15%</td>
</tr>
<tr>
<td>• Tyrosine kinase inhibitor</td>
<td>Topotecan hydrochloride</td>
<td>All grades, dyspnea: 22%</td>
</tr>
<tr>
<td>• Topoisomerase inhibitor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*N = 101; ** N = 32

5-FU—5-fluorouracil; IL—interleukin; LV—leucovorin

Note. Based on information from Polovich et al., 2014.

plans in 120 patients in Germany. The researchers concluded that improved supportive care measures and attention to toxicity profiles could reduce patients’ clinical burden as well as have substantial economic impact (Ihbe-Heffinger et al., 2013).

The degree of breathlessness may be affected by surgery, such as a pneumonectomy, lobectomy, and video-assisted thoracic surgery for resection of lung cancer (Dudgeon et al., 2001). Compromised breathing technique and reduced pulmonary function may result in chronic dyspnea. Dyspnea could be related to a surgical complication as well, such as
a pneumothorax or infection. Patients with underlying respiratory conditions may not be able to compensate for reduction in lung capacity. Coats et al. (2013) investigated the feasibility of a short, home-based exercise program with 16 patients with non-small cell lung cancer being evaluated for potential lung resection surgery. Thirteen patients completed the four-week prescribed exercise program. Although exercise improved physiologic parameters, no statistically significant or clinically meaningful changes in quality of life were observed, with the exception of a reduction in depression score. Perceived benefits of the program reported by patients were that it helped them to start performing physical activities \((n = 6)\) and that it improved dyspnea \((n = 5)\). The researchers concluded the program was feasible and improved exercise tolerance and muscle strength, which may be clinically pertinent because poor exercise capacity and muscle weakness are predictors of postoperative complications.

**Palliative Treatment of Dyspnea**

Symptom management of cancer-related dyspnea usually is based on a combination of pharmacologic therapy and supportive measures in the cancer population. Despite advances in cancer treatments, dyspnea remains difficult to manage because of its multifactorial nature.

Tanaka, Hayashi, Ohtakara, and Hoshi (2012) evaluated palliative outcomes of 13 patients, median age of 60 years, with extrinsic malignant tracheobronchial or esophageal stenosis treated with radiation therapy and presenting with dyspnea. Palliative methods included stent placement, dilation, neodymium-doped yttrium aluminum garnet (known as Nd:YAG) laser treatment, argon plasma coagulation, photodynamic therapy, brachytherapy, and external beam radiation therapy. Palliation of the dyspnea occurred in seven \((53.8\%)\) patients within 6–12 days \((median 11\ days)\). Combined radiation and chemotherapy demonstrated greater improvement in scores than radiation therapy alone. This study concluded that external beam radiation therapy, using doses greater than 35 Gy, should be considered for patients with tracheobronchial or esophageal stenosis before symptoms worsen.

A Cochrane review of randomized controlled trials involving 953 participants concluded that endobronchial brachytherapy plus external beam radiation therapy improved symptom relief of dyspnea over external beam radiation therapy alone. Findings from one trial suggested that a twice-weekly dose of 7.4 Gy was superior to the four-times-per-week dose of 3.8 Gy, influencing the mean time for local control and fatal hemoptysis (Reveiz, Rueda, & Cardona, 2012).

NCCN (2014b) outlined interventions and reassessment based on estimated life expectancy. Measures to relieve symptoms include oxygen therapy for symptomatic hypoxia; educational, psychosocial, and emotional support; nonpharmacologic therapies; morphine if the patient is opioid naïve; benzodiazepines if the dyspnea is associated with anxiety and opioids do not provide relief; and noninvasive positive-pressure ventilation support.

**Pharmacologic Interventions**

**Opioids**

The opioid mechanism of action to relieve dyspnea is presumably a respiratory depressive effect. Opioids likely depress spontaneous respiratory drive and modulate cortical activity
(as they do in pain), thus reducing dyspnea (Parshall et al., 2012). Sufficient evidence exists to recommend the use of immediate-release morphine administered by the oral or parenteral route to manage dyspnea in patients with cancer (Cairns, 2012; DiSalvo, Joyce, Tyson, Culkin, & Mackay, 2008; Viola et al., 2008) and in patients with any advanced disease (Cancer Care Ontario, 2010). Toxicity was minimal, and significant relief of dyspnea was experienced. Effectiveness of morphine plus midazolam or extended-release morphine was not established.

Currow et al. (2011) performed a phase II dose-increment study of 85 patients to determine a minimum effective daily dose of opioids for dyspnea improvement and evaluation of clinical benefit over time. Patients were given escalating doses of sustained-release oral morphine starting at 10 mg per day and increasing by 10 mg to a maximum of 30 mg per day if they experienced less than a 10% reduction over their baseline. Seventy percent of the patients sustained benefit for three months at 10 mg per day. This study concluded that 10 mg of sustained-release oral morphine once daily is safe and effective for most patients with chronic dyspnea. This is supported by an earlier study demonstrating significant benefits in dyspnea and insomnia using 10–20 mg sustained-release morphine in divided doses daily (Abernethy et al., 2003). The Canadian Thoracic Society Respiratory Guideline Committee concluded that opioids reduce dyspnea in stable patients with advanced COPD and should be titrated for the individual patient. The recommendation was for oral opioids only, not nebulized opioids (Marciniuk et al., 2011). Nebulized morphine was not effective in controlling dyspnea in any study or meta-analysis and warrants further research.

The use of opioids to relieve dyspnea capitalizes upon the respiratory depressive action of the opioids. Although altered respiratory drive is the desired action to relieve dyspnea, severe decreases in respiratory rate (less than 8 breaths per minute) with unanticipated sedation or hypoxia may be an unexpected untoward outcome. Cautious and slow titration of naloxone is available to treat severe respiratory depression associated with opioid use, along with monitoring the patient’s level of consciousness and respiratory rate. Naloxone is an opiate antagonist, and standard doses cause abrupt opioid reversal precipitating severe pain and symptoms of opioid withdrawal (Hospira, Inc., 2007).

Additional evidence is needed to recommend the addition of midazolam, a benzodiazepine, to morphine for patients with advanced cancer experiencing severe dyspnea during the last week of life, but it appeared promising as an intervention to relieve terminal dyspnea (Navigante, Cerchietti, Castro, Lutteral, & Cabalar, 2006).

Numerous publications have validated opioids’ ability to relieve cancer dyspnea; however, questions concerning opioid choice, including modified or normal release formulation, route, optimum starting dose, and regimen, remained unanswered (Booth, Moosavi, & Higginson, 2008). Excess mortality resulting from opioid use has never been demonstrated in studies to date. In a qualitative study of family physicians and respiratory therapists’ attitudes toward the use of opioids for dyspnea in advanced COPD, clinicians described discomfort prescribing opioids because of insufficient knowledge, lack of education and guidelines, and fear of censure (Young, Donahue, Farquhar, Simpson, & Rocker, 2012). Limited evidence supports the use of opioids over longer terms, such as three to six months (Young et al., 2012). Further investigation continues to assess the value of using low-dose opioids in advanced COPD in addition to conventional treatment (Rocker, 2013).

**Benzodiazepines**

The use of benzodiazepines and selective serotonin reuptake inhibitors (SSRIs) is based on the rationale that individuals with anxiety disorders not only report dyspnea more fre-
ently, but their dyspnea also is usually clustered with the presence of anxiety or depression. Therefore, treating the anxiety and depression may improve dyspnea (Cairns, 2012; NCCN, 2014b). SSRIs may have a direct effect on centers that control the perception of breathlessness (Kamal, Maguire, Wheeler, Currow, & Abernethy, 2012). Scano, Gigliotti, Stendardi, and Gagliardi (2013) noted that emotional states may shape the quality and intensity of dyspnea. Anxiety and depression can increase the intensity of dyspnea disproportionately to cardiorespiratory function and may contribute to the degree of disability associated with dyspnea. The exact relationship between dyspnea and anxiety or depression remains unclear. A trial of anxiolytic treatment may be reasonable for some patients, particularly in those with morbid anxiety or history of respiratory panic attacks (ATS, 1999).

However, expert opinion regarding the use of benzodiazepines is conflicting. Anxiolytics, antidepressants, phenothiazines, indomethacin, inhaled topical anesthetics, nitrous oxide, and sodium bicarbonate have been found to be ineffective or lack sufficient data to recommend their use (Parshall et al., 2012). Based on evidence from 13 studies and consensus of the Canadian Thoracic Society COPD Committee Dyspnea Expert Working Group, it was recommended that anxiolytic and antidepressant medications not be routinely used for management of dyspnea in patients with advanced COPD (Marciniuk et al., 2011). Simon, Higginson, Booth, Harding, and Bausewein (2010) reviewed seven studies in the Cochrane Database that included 200 analyzed participants with advanced cancer and COPD. They found a slight but nonsignificant trend toward a beneficial effect of benzodiazepines for the relief of breathlessness in this patient group. Results justified considering benzodiazepines as second- or third-line treatment within an individual therapeutic trial, when opioids and nonpharmacologic measures have failed to control breathlessness. However, well-conducted and adequately powered studies are still needed.

No randomized controlled trials examined systemic corticosteroids in the treatment of dyspnea in patients with cancer. Studies varied in methodologic quality. Of the other non-opioid drugs examined, only oral promethazine, a phenothiazine, showed some benefit in the relief of dyspnea as a second-line agent if systemic opioids cannot be used or when used in addition to systemic opioids (Viola et al., 2008).

Nebulized Therapy

The nebulized route of different pharmacologic agents (e.g., morphine, fentanyl, furosemide, lidocaine) has been studied to relieve dyspnea. Inhalation deposits a fine mist of aerosolized medication on the respiratory tract with the potential for modification of dyspnea by local action. Bronchodilators are effective because of their direct relaxation effect on smooth muscle cells in the airway (Hanania & Cazzola, 2010). Formoterol and salbutamol have a rapid onset of action, whereas the effect of salmeterol is gradual (van der Woude, Postma, Politiek, Winter, & Aalbers, 2004). With respect to opioids, local binding to pulmonary sensory receptors in the lung is thought to augment pulmonary effect and minimize systemic toxicity. DiSalvo et al. (2008) noted that scientific data are lacking regarding nebulized opioids in the treatment of dyspnea because of inefficient design of studies and limited sample sizes. An integrated synthesis of 20 studies including experimental trials, chart reviews, and case studies that examined the efficacy of nebulized opioids concluded that further rigorous research stratifying patients into opioid-tolerant and opioid-naïve groups is needed before recommending that nebulized opioids be adopted into practice (Joyce, McMenemy, Carriere-Kohlman, & Hawkins, 2004).

Nebulized morphine is not recommended for dyspnea, particularly because of the potential adverse effects such as unexpected respiratory depression (Cairns, 2012), and is not sug-
gested for dyspnea in patients with advanced COPD (Marciniuk et al., 2011). The varied dosing and delivery methods limited cross-report comparison, and most reports of benefit were limited to case reports and case series (Kamal et al., 2012). Nebulized opioids have not been associated with fewer side effects than oral or parenteral opioids in randomized controlled trials (Viola et al., 2008). Nebulized furosemide warrants further study, as insufficient data exist to support its use in dyspnea to date (Parshall et al., 2012).

Parone et al. (2013) compared the breath-actuated nebulizer to the handheld nebulizer to administer ipratropium bromide and/or albuterol sulfate in 54 subjects presenting to a university hospital emergency department with a chief complaint of wheezing and dyspnea. This comparative design study found no significant differences between the breath-actuated nebulizer and handheld nebulizer in respect to respiratory rate, peak flow measurement, and modified Borg scores (Parone et al., 2013).

**Oxygen**

Researchers have postulated that supplemental oxygen may provide dyspnea relief through changes in chemoreceptor stimulation, affecting breathing pattern and/or stimulation of receptors related to gas flow through the upper airway (Parshall et al., 2012). Reduced chemoreceptor activation and associated reduced ventilation effort is thought to be oxygen’s primary mechanism to relieve dyspnea either at rest or during exercise (Parshall et al., 2012). However, other factors are thought to contribute to reduce dyspnea and may explain the variability in response to supplemental oxygen. Oxygen may be useful for patients with advanced heart or lung disease, especially if hypoxemic at rest or with minimal activity (Parshall et al., 2012). Continuous oxygen therapy for patients with COPD, including advanced disease, who were hypoxemic at rest was shown to reduce mortality and dyspnea (Baily et al., 2013; Marciniuk et al., 2011).

Although oxygen therapy is useful in correcting hypoxia, dyspnea and breathlessness are not always related to hypoxia. Evidence supporting the use of supplemental oxygen in nonhypoxic patients is inconclusive (Bailey et al., 2013; DiSalvo et al., 2008; Marciniuk et al., 2011). In a study of 51 patients with cancer where the majority were nonhypoxic, the use of oxygen and air for the relief of dyspnea demonstrated no significant difference (Philip et al., 2006). In the hypoxic subgroup, the mean oxygen saturation levels increased significantly with oxygen, but the mean change in VAS dyspnea scores did not differ significantly when oxygen or air was administered. This supports the multidimensional concept of dyspnea, in that correction of the physiologic oxygen deficit alone may not be sufficient to relieve the symptom sensation. Subjectively, some patients reported benefit from oxygen and used it intermittently, such as at night during sleep or during activities that involved exertion (Philip et al., 2006).

The Centers for Medicare and Medicaid Services (CMS, n.d.) allows payment coverage of oxygen therapy for

- A severe lung disease, such as COPD, diffuse interstitial lung disease, whether of known or unknown etiology; cystic fibrosis, bronchiectasis; or widespread pulmonary neoplasm
- Hypoxia-related symptoms or findings that might be expected to improve with oxygen therapy, such as pulmonary hypertension, recurring CHF, erythrocytosis, impairment of the cognitive process, nocturnal restlessness, and morning headache.

Medical documentation, in the patient’s record, must support the need for oxygen. If electronic billing is used, separate documentation is required. A prescription written by the patient’s attending physician who has examined the patient within a month of the start of therapy will meet the documentation requirement but must specify “(a) diagnosis of the disease requiring home use of oxygen; (b) oxygen flow rate; and (c) an estimate of the frequen-
cy, duration of use (e.g., 2 L/min, 10 min/hr, 12 hr/day), and duration of need (e.g., six months or lifetime)” (CMS, n.d.).

The prescription of oxygen in the absence of documented hypoxemia is problematic from a reimbursement perspective. The National Coverage Determination (NCD) for Home Use of Oxygen (240.2), released by CMS in October 1993, concluded that evidence to identify the optimal daily use and long-term duration of oxygen therapy for Medicare beneficiaries is lacking. Consequently, CMS had determined that additional clinical research is appropriate under its Coverage with Evidence Development policy. The NCD specifies that the home use of oxygen is covered for Medicare beneficiaries who have arterial oxygen partial pressure measurements of 56–65 mm Hg or oxygen saturation at or above 89% when enrolled in clinical trials approved by CMS and sponsored by the National Heart, Lung, and Blood Institute (NHLBI). NHLBI and CMS have launched the largest randomized controlled clinical trial to study the effectiveness and safety of long-term home oxygen therapy for people with COPD. Patient recruitment for the Long-term Oxygen Treatment Trial began in late 2007, and the estimated completion date is 2015; no results have been reported to date (CMS, 2014). Patients are randomly selected to receive supplemental oxygen for approximately three years. All participants are periodically monitored; those who were not initially selected to receive oxygen were prescribed oxygen if their blood oxygen levels worsened during the trial (CMS, 2014).

Because oxygen frequently makes patients feel better and report less dyspnea, practitioners should appreciate the subjective benefit of this intervention regardless of the physiologic findings, such as oxygen saturation, and seek alternative reimbursement. Supplemental oxygen without a specific hypoxic requirement is usually provided under the umbrella of a hospice homecare program. Parshall et al. (2012) suggested symptomatic benefit may not be restricted to patients who meet Medicare guidelines for supplemental oxygen and may be useful for patients with advanced heart or lung disease.

One small study evaluated the use of Heliox28 (72% helium and 28% oxygen) compared to oxygen-enriched air (either 28% or 21.1% oxygen combined with nitrogen) to palliate dyspnea and improve exercise capacity in 12 patients with lung cancer (Ahmedzai, Laude, Robertson, Troy, & Vora, 2004). Helium has a low density with the potential to reduce the work of breathing and improve alveolar ventilation when replacing nitrogen in the air. The side effects of breathing helium-enriched air are a characteristic increase in the pitch of the voice and reduction of the core body temperature because helium is a better conductor of heat than nitrogen. Heliox28 improved distances walked compared to both oxygen groups and significantly reduced dyspnea scores compared to the 21.1% oxygen group. A slight fall in the study participants’ body temperature was noted, which was statistically significant but not clinically significant. Current evidence is not established for the use of Heliox28 in practice (DiSalvo et al., 2008); however, potential benefit needs to be confirmed in a larger randomized controlled trial (Parshall et al., 2012).

**Ambient Airflow**

Anecdotally, patients who are short of breath frequently ask to sit near a fan or open window. It is thought that cold air directed across the cheek and through the nose can alter ventilation and reduce the perception of breathlessness, perhaps by affecting sensory receptors in the distribution of the trigeminal (fifth) cranial nerve that respond to both thermal and mechanical stimuli (Dudgeon, 2002). This is a low-cost and low-risk intervention that can be easily tried and recommended if it makes the patient feel better. One small randomized crossover trial demonstrated a small, statistically significant reduction in breathlessness with facial stimulation. The authors concluded that this low cost, convenient, and internationally available intervention should be considered for palliative man-
agement for reducing breathlessness associated with advanced disease (Galbraith, Fagan, Perkins, Lynch, & Booth, 2010). Fresh air or a fan directed on the face used as cold facial stimulation decreased dyspnea induced in healthy individuals. However, no large clinical trial has examined the use of fans or cool airflow for the relief of dyspnea (ATS, n.d.; Bailey et al., 2013).

**Supportive Care Measures**

Evidence from a Cochrane systematic review (Lacasse, Goldstein, Lasserson, & Martin, 2006) supported the use of pulmonary rehabilitation in the care of patients with COPD. Pulmonary rehabilitation is defined as exercise training for at least four weeks with or without education and/or psychological support. The analysis included 31 randomized controlled trials and found statistically significant improvements in exercise capacity and quality of life, including the domains of dyspnea, fatigue, and the patient’s control over disease, in individuals with COPD who completed pulmonary rehabilitation.

Evidence from one multicenter randomized controlled study and two smaller studies supported breathlessness clinics for individuals with cancer-related dyspnea. The intervention, described as a nurse-led program, used a structured weekly approach that included assessment, education, and instruction in breathing control and coping techniques (Thomas, Bausewein, Higginson, & Booth, 2011). Because the intervention contained many components, the exact contribution of each component remains unclear. A researchable question is whether all components of the breathing rehabilitation program are needed to achieve the same outcome or if one aspect of the intervention is more significant.

A Cochrane Database review by Rueda, Solà, Pascual, and Casacuberta (2011) consisted of 15 trials. Three trials of a nursing intervention to manage breathlessness demonstrated benefit in symptom management, performance status, and emotional function. Four trials assessed structured nursing programs and established a positive impact on delay in clinical deterioration, dependency, and symptom distress, as well as improvement in emotional status and care satisfaction. Three trials assessed different psychotherapeutic, psychosocial, and education interventions in patients with lung cancer, which demonstrated improvement in patients’ quality of life. They posited that counseling may improve coping ability, but the evidence was not conclusive. Two trials assessed exercise, and one trial assessed nutritional interventions; however, relevance and lasting improvements in quality of life have not been established. Two small trials of reflexology demonstrated short-term benefits only. Another review of nine trials of nursing interventions and programs to manage breathlessness revealed that these approaches may improve patient coping but reinforced the need for increased training and education of healthcare professionals providing the interventions (Rueda et al., 2011). Higher methodologic research is needed to explain the mechanisms (Rueda et al., 2011).

Strategies of the nurse-led clinic described by Corner, Plant, A’Hern, and Bailey (1996) included:
- Detailed assessment of breathlessness and factors that improve or worsen it
- Advice and support for patients and families on ways to manage breathlessness
- Explorations of the meaning of breathlessness, their disease, and feelings about the future
- Training in breathing control techniques, progressive muscle relaxation, and distraction exercises
- Goal setting to complement breathing and relaxation techniques
- Early recognition of problems warranting pharmacologic or medical intervention.
Johnson and Moore (2003) countered that these strategies have not always proved to be straightforward in clinical practice and strongly suggested that the management of breathlessness not be secured by a unique group of nurses but rather that aspects of it be incorporated into everyday clinical practice. Difficulties that may be encountered in incorporating this into practice included (Johnson & Moore, 2003)

- Acknowledgment of the difference between research and clinical practice
- Organizational and practical issues or barriers
- Confidence in using the interventions
- Nurses’ awareness of their own roles and limitations.

Some alternative measures have shown success in the treatment of dyspnea. A review of 2,151 publications was screened for symptom management in cancer care using alternative measures (Garcia et al., 2013). Of those, 41 randomized controlled trial analyses concluded that acupuncture is an appropriate adjunctive treatment for chemotherapy-induced nausea and vomiting, but additional studies are needed for other symptoms because efficacy remains undetermined. Williams (2006) reported that acupuncture and acupressure have been studied successfully in three trials and suggested this complementary therapy can be used to improve dyspnea in patients with COPD. However, this analysis also cited other reports that did not display a positive effect on dyspnea associated with advanced cancer and other nonmalignant causes.

Acupuncture has not been accepted as a standard adjunct to medical treatment, partly because of the use of different techniques, such as electrical or manual, outcome measures, needle protocols, and duration of treatment (Kasymjanova et al., 2013). A pilot randomized controlled trial with 47 patients with lung or breast cancer indicated the need for further study (Wang & Bao, 2013). The role of both acupuncture and acupressure for relief of dyspnea requires further study (Marciniuk et al., 2011; Parshall et al., 2012).

In relation to dyspnea in patients with advanced COPD, Marciniuk et al. (2011) summarized the evidence supporting the benefits of neuromuscular electrical stimulation, chest wall vibration, walking aids, and pursed-lip breathing in the management of dyspnea in individuals with advanced COPD. Minimal data exist to support the relief of dyspnea or breathlessness with the use of alternative and complementary medicine measures such as yoga and mindfulness treatment (Parshall et al., 2012) in addition to music and relaxation (Brennan & Mazanec, 2011). Although insufficient evidence exists to support the routine use of distractive auditory stimuli (music), relaxation, handheld fans, counseling programs, and psychotherapy, this does not imply these interventions cannot be beneficial for many individuals.

A Cochrane Database review by Bausewein, Booth, Gysels, and Higginson (2013) focused on nonpharmacologic interventions for breathlessness in advanced stages of malignant and nonmalignant diseases. More than 40 studies were included (2,532 participants) and categorized as follows: walking aids (n = 7), music (n = 6), chest wall vibration (n = 5), acupuncture/acupressure (n = 5), relaxation (n = 4), neuroelectrical muscle stimulation (n = 3), and use of a fan (n = 2). Multicomponent interventions were categorized as counseling and support (n = 5), breathing training (n = 3), counseling and support with breathing and relaxation training (n = 2), case management (n = 2), and psychotherapy (n = 2). The authors concluded that breathing training, walking aids, neuroelectrical muscle stimulation, and chest wall vibration appeared to be effective nonpharmacologic interventions for relieving breathlessness in advanced stages of disease. Low-level evidence supported the helpfulness of acupuncture/acupressure. Insufficient evidence exists in support of music, relaxation, fan use, counseling and support, counseling and support with breathing and relaxation training, case management, and psychotherapy. Most studies have been
conducted in patients with COPD, with only a few studies including participants with other conditions.

**Expected Patient Outcomes**

Because dyspnea is a subjective symptom, similar to pain, patient report is the gold standard with respect to assessment of symptom intensity and relief from any intervention (Hui, Morgado, et al., 2013). The exertional or paroxysmal nature of dyspnea needs to be accounted for when evaluating outcomes. For example, many research assessments of dyspnea ask about its presence on average, or in the past 24 hours, or during the past week in addition to the current state of dyspnea to capture the symptom’s variability. One clinical recommendation is that dyspnea should be measured with a quantitative measure such as a VAS, NRS, or another reliable tool in a longitudinal manner so that the symptom can be monitored and addressed. One research recommendation is to publish reports of the use of specific tools to measure cancer-related dyspnea and associated psychometric data to build evidence about the reliability and validity of the instrument in the cancer population.

Correction of abnormal physiologic parameters such as tachypnea, use of accessory muscles, cyanosis, or oxygen saturation will help providers to assess resolution of clinical status with an understanding that the symptom of dyspnea may or may not resolve with return to normal parameters. The expectation of an intervention for dyspnea is that initial attempts to correct reversible causes will be made and attempts to palliate irreversible causes will be pursued with the goal that patients will report relief or comfort. However, given the refractory nature of dyspnea, NCCN (2014b) recommends selection of an appropriate sedative treatment plan based on response to recent and current medications as a potential intervention in terminal settings.

**Patient Teaching Points**

Education about disease and treatment is thought to provide patients with information and skills to understand and control symptoms. One randomized controlled study of 30 participants suggested a positive effect on the perception of breathlessness when adults were taught techniques as part of their physiotherapy management plan in pulmonary rehabilitation (Hochstetter, Lewis, & Soares-Smith, 2005).

Education and relaxation training are important components in the management of breathlessness in patients with dyspnea (Disalvo et al., 2008; Hochstetter et al., 2005; Thomas et al., 2011). It is reasonable to think the combined benefit of interventions would be advantageous for patients with cancer. Psychoeducational care, which combines education, counseling, and supportive interventions conveyed individually or in groups, has enhanced learning, especially for caregivers (Honea et al., 2008).

The main components of dyspnea education are knowledge of the signs and symptoms to report to healthcare providers, including accessing the closest emergency department; medication regimens; and self-care strategies. Self-care strategies include recognizing maneuvers that precipitate dyspnea and maximizing body positions and breathing techniques to decrease breathlessness (Campbell, 2011).

The symptom of dyspnea can change rapidly or insidiously. With an understanding that some causes of acute dyspnea are treatable or reversible even in the context of chronic dyspnea, patients should be informed and instructed to report changes in baseline dyspnea,
particularly increased shortness of breath, fever, pain, and change in sputum production. Patients should be taught to avoid respiratory irritants, such as primary or secondary tobacco smoke and exposure to individuals with respiratory infections. Nurses can advise about the preventive benefit of immunizations if not contraindicated, such as the pneumococcal vaccine and an annual influenza vaccine.

Teaching patients and caregivers about medication regimens for dyspnea should include expected actions and side effects of the medications and administration techniques. If administration of medication or treatment by patients or caregivers is included in symptom management, instruction and practice to gain confidence in proper technique would be required. Proper and safe use of equipment, such as oxygen, would be critical information to relay to patients as well.

Use of specific breathing techniques may be helpful and require teaching; however, many people who experience dyspnea discover by trial and error body positions and a variety of breathing techniques that improve their dyspnea. Nonetheless, reinforcement of proper technique and encouragement to use breathing techniques in times of anxiety or distress are important teaching goals. Breathlessness management techniques commonly are taught in a rehabilitation program for people with chronic pulmonary disease and could be included in individualized teaching. These include positioning, pursed-lip breathing, diaphragmatic breathing, activity modification or energy conservation, and relaxation training such as progressive muscle relaxation.

A prospective randomized controlled trial of 94 patients with COPD investigated the effects of a diaphragmatic breathing training program on thoracoabdominal motion and functional capacity (Yamaguti et al., 2012). A new contribution from this study was that the diaphragmatic breathing training program not only improved respiratory mechanics with natural breathing but also influenced functional outcomes. This strategy is inexpensive and could be applicable for group therapy and home-based pulmonary rehabilitation (Yamaguti et al., 2012).

Kim et al. (2012) studied 12 men to determine the influence of breathing maneuver and sitting posture on tidal volume (TV), respiratory rate (RR), and muscle activity of the inspiratory accessory muscles in patients with COPD. The results suggested that in COPD, pursed-lip breathing induced a favorable breathing pattern (increased TV and reduced RR) compared to quiet natural breathing. Positions with arm support and with arm and head support increased muscle activity of the inspiratory accessory muscles during inspiration versus a neutral position. Differential involvement of accessory respiratory muscles can be readily studied in patients with COPD, allowing for monitoring of respiratory load during pulmonary rehabilitation.

The leaning-forward position enhances dyspnea relief by reducing rib cage and neck muscle activation and promoting maximum static inspiratory pressure. This is the preferred posture in the majority of the patients with COPD in the acute phase. Posture has no effect on maximum static inspiratory or expiratory pressures in healthy individuals (Jolley & Moxham, 2009). Common forward-leaning positions are shown in Figure 12-4.

Pursed-lip breathing is thought to decrease rate of breaths, maintain an open airway longer, and allow more air to flow in and out of the lungs. To do pursed-lip breathing, a person takes breaths through the nostrils followed by slowly breathing out through pursed lips, similar to blowing out a candle. Exhaling is two to three times longer than inhaling; counting to two while inhaling and to four or six while exhaling may be helpful (National Institutes of Health, 2010). If a person cannot exhale through pursed lips, an alternative is to exhale through a fist held up to the mouth. Patients need to avoid exhaling too forcefully or hyperventilating. Chronic hyperventilation or dysfunctional breathing leads to increased
oxygen and decreased carbon dioxide levels in blood gases, which leads to respiratory alkalosis. Chronic hyperventilation causes fatigue and symptoms related to chest pain or palpitations, paresthesia in the feet and hands, and acid reflux (Henderson, 2008).

Abdominal or diaphragmatic breathing actively uses the diaphragm rather than accessory muscles during inspiration. This technique can encourage a sensation of relaxation, stress reduction, and overall well-being (American Medical Student Association, n.d.). Dependent on the methodology to best meet patients’ educational needs, diaphragmatic breathing instructions are available in a step-by-step printed format in addition to pictures (Cleveland Clinic Foundation, 2011) or video (Lung Cancer Alliance, n.d.). A common diaphragmatic breathing exercise is as follows (American Medical Student Association, n.d.).

- Put one hand on your chest and one on your abdomen.
- Inhale slowly through your nose.
- As you inhale, feel your stomach expand with your hand.
- Slowly exhale through your mouth for a count of eight.
- Rest and repeat for a total of five deep breaths.
- It is important to remember that you deepen respirations not by inhaling more air but by completely exhaling it.

Pulmonary rehabilitation and improved exercise routines have been shown to relieve fatigue and dyspnea and also to enhance patients’ sense of control over their disease. The benefit of pacing activities to conserve energy is thought to regulate exertional dyspnea.
Most people with dyspnea learn these regulatory mechanisms on their own, but educational interventions can support individuals in their ability to cope with lifestyle changes. Education about assistive devices or compensatory techniques to complete activities of daily living can teach patients how to perform activities more efficiently and to function more independently. Referral to occupational therapy may be helpful, as this discipline specializes in educating patients in the performance of efficient and productive activities of daily living.

Relaxation training is another recommended educational point that may be helpful in cancer-related dyspnea, as it has been shown to have utility in cardiopulmonary-related dyspnea (Hochstetter et al., 2005). Many different approaches exist for relaxation training, including progressive muscle relaxation, visual imagery, biofeedback, and meditation. Relaxation is a behavioral self-care strategy that can enhance a sense of control during periods of increased breathlessness by aiming one’s breath toward the abdomen with the desired outcome of having the abdomen rise on inhalation and fall with exhalation (Glennon & Seskevich, 2008). A case study of relaxation breathing exercise over a six-month period demonstrated steadily improved pulse oximetry readings as indicated by month, beginning with month one: 74%, 79%, 85%, 89%, 92%, and 94% (Glennon & Seskevich, 2008). Healthcare providers can work closely with patients and families to tailor a relaxation strategy to their situation. Instructional methods vary from live demonstrations to technologically delivered sessions. Mind-body-spirit interventions are useful adjunctive treatments for the reduction of stress, and with practice, individuals can master the relaxation skill. Given their relatively low cost and limited potential for adverse effects, these interventions merit further study as therapeutic adjuncts (Seskevich, Crater, Lane, & Krucof, 2004).

The goals of patient and caregiver education are to inform them about the symptom of dyspnea and empower them to perform self-care strategies to promote symptom reduction. This approach is reinforced in multiple areas of oncology care. Nurses are important in the care of patients with dyspnea because symptom management education is an integral component of nurses’ dialogue with patients and caregivers. Tools and strategies conducive to adult learning, especially during problematic or symptomatic periods, need to be used. A variety of instructional formats should be considered to meet patients’ unique learning needs.

An interactive website is available that illustrates each step of the pursed-lip breathing technique (see National Institutes of Health, 2010). Another interactive tool assists patients to comprehend the respiratory system by clarifying the oxygen requirement for cellular life and its circulation through the bloodstream. Functions of the nose, mouth, throat, alveoli, diaphragm, and trachea are demonstrated (American Lung Association, n.d.). If dyspnea is related to lung cancer, NCCN provides patient guidelines that outline various treatment modalities and the patients’ role in the treatment plan, in addition to a dictionary and other pertinent information (NCCN, 2014c). Macmillan Cancer Support (2013a) has outlined patients’ tips to conserve and reduce energy spent on everyday activities such as dressing, bathing, toileting, and household duties, in addition to a tool for self-guided relaxation for breathlessness (Macmillan Cancer Support, 2013b).

Along with education focused on the patient, education and support also needs to be provided to caregivers throughout the illness trajectory of the dyspneic patient. Their contribution to patients’ treatment and quality of life should not be underestimated. Malik, Gysels, and Higginson (2013) performed a cross-sectional, descriptive, comparative survey of caregivers and their care recipients to determine how caregivers experience breathlessness and the differences in caring for an individual with malignant versus nonmalignant disease. The researchers analyzed levels of caregiver burden, sleep, mood, and other concerns among a total of 101 caregivers: 50 caregivers of patients with lung cancer and 51 caregivers of pa-
tients with heart failure. Of these, 72% were spouses and 80% were female caregivers for male patients. Levels of caregiver burden, sleep, and mood, in addition to caregiver reports of patient needs and other concerns, were compared between the two groups. Caregivers used, on average, eight different coping strategies; the most common employed was “acceptance” with greater than 90% of caregivers reporting use of this strategy from both groups. High levels of unmet needs and burden were equally severe for heart failure and lung cancer caregivers. The authors concluded that support and additional interventions for caregivers, such as direction on symptom management, need to be considered. Support should be tailored according to breathlessness severity and caregiver need rather than the patient’s primary diagnosis.

Need for Future Research

The symptom of dyspnea is a fertile area for research but, as noted in many research studies, is a difficult symptom to study in a controlled manner because of the fragile clinical status of patients that often accompanies the symptom. Also, recruitment of patients to cancer-related dyspnea clinical trials is difficult because of patients’ potentially unstable clinical status; thus, studies typically have small sample sizes. These recruitment and research design issues challenge researchers to collaborate or conduct multicenter trials to increase sample sizes and strengthen findings.

Implications for future clinical trial design, including sample size and eligibility criteria, need to be considered in light of a high attrition rate in supportive care and palliative oncology clinical trials. A key reason for withdrawal from palliative care studies is increasing symptom distress, but it has not been determined whether this is attributable to natural progression of disease, adverse effects from the study intervention, or the inability of the study intervention to control the targeted symptom. Predictors of attrition were high levels of fatigue, dyspnea, and a poor ECOG performance status. Despite this high expected attrition rate, it is essential to conduct studies with frail and symptomatic patients, particularly those with dyspnea and fatigue. For completion of vital research, it is recommended to keep studies as short as possible, minimize the study burden, and incorporate close monitoring and support for the patients (Hui, Glitza, Chisholm, Yennu, & Bruera, 2013). Based on patient characteristics and high baseline symptom burden, end-of-study attrition was associated with higher baseline levels of dyspnea, fatigue, Hispanic race, and higher level of education, as well as longer study duration and outpatient studies (Hui et al., 2013).

All areas of cancer-related dyspnea (description, assessment, measurement, and intervention) need further research. Qualitative description of the experience of general dyspnea exists, but description of cancer-related dyspnea and the affective dimension of dyspnea is particularly lacking. Further testing of the reliability and validity of dyspnea measurement tools in the cancer population is needed, and the impact of cancer-related dyspnea on function and quality of life needs to be explored.

Intervention research is needed most. Replication of many studies that demonstrated a positive effect of dyspnea interventions in the COPD population should be conducted in the cancer population.

Nurse-led and cognitive behavioral interventions for dyspnea need further testing so that specific recommendations for practice can be made. Cognitive behavioral therapy is an area where nursing-sensitive patient outcomes are abundant and recommended interventions could be integrated. Once research confirms the evidence, nurses could educate patients in complementary or alternative dyspnea management techniques.
Parshall et al. (2012) suggested the following research priorities for dyspnea, regardless of the underlying disease process.

- New treatments and larger clinical trials aimed at underlying mechanisms of dyspnea and funding made available to support multi-institutional studies
- Dyspnea measures to be adequately validated as patient-reported outcomes for use as endpoints in clinical trials and effort toward validating translations of existing measures
- Rigorous design and evaluation of clinical translation studies in neuromodulation, neuroimaging, and central processing of unpleasantness, dyspneic sensations, and affective distress
- Interdisciplinary approaches into dyspnea mechanisms and treatments that will accelerate translation of findings into clinical practice, including clinicians and researchers across specialties and disciplines

Large randomized controlled trials are needed to confirm benefit of interventions on this challenging symptom. Review of the literature revealed the challenge in enrolling patients experiencing dyspnea in studies when they present in a compromised and fragile state. Instead, researchers could consider obtaining informed consent prior to tenuous clinical situations when symptoms are not yet severe but the course of disease most likely may lead to dyspnea.

**Conclusion of Case Study**

T.J. had been instructed to report breathing-related changes to his healthcare team, and because previous dyspnea rating scores were documented, the nurse assessing him was alerted to the increase in his dyspnea. A chest x-ray was obtained, which revealed a new left pleural effusion. Because this is a potentially reversible cause of dyspnea, an ultrasound-guided thoracentesis was arranged to drain the pleural fluid. More than 1 L of pleural fluid was removed, which significantly improved his breathing. Unfortunately, the fluid rapidly reaccumulated over one week, and his dyspnea returned. While arrangements were being made for a pleurodesis procedure, he was given a prescription for a short-acting, immediate-release opioid to relieve the shortness of breath. Because he is taking 30 mg of sustained-release morphine, a 2.5 mg dose of immediate-release morphine (25% of his four-hour dose) was ordered to relieve his dyspnea on an as-needed basis. A stool softener was ordered at his last visit, but now constipation is present. The nurse instructed him on an over-the-counter laxative to take.

At T.J.’s next visit to the cancer center, assessment parameters showed a hypoxic oxygen saturation of 87% obtained on room air at rest. In addition to this physiologic parameter, the patient rated his breathlessness as a 7 out of 10 on the assessment NRS. His oxygen saturation improved to 94% with the use of supplemental oxygen at 2 L/min by nasal cannula. In addition to correcting the hypoxia, 15 minutes after the oxygen was applied, he reported a lower dyspnea score of 4. His ambulatory nurse arranged for home delivery of portable oxygen to be used both at rest and with exertion.

With T.J.’s history of COPD, in addition to the newly diagnosed lung cancer, the treatment team thinks a referral to a pulmonary rehabilitation program might be of benefit to control his dyspnea. When asked if interested in such a program, he says the idea sounded appealing and helpful, but he is concerned about his ability to participate because of fatigue and his debilitated state and “relying too much on my daughters lately.” Instead, he asked for education about breathing techniques that he could practice on his own. Not wanting to overwhelm him with information, his nurse chooses initially to teach him
the forward-leaning position and the pursed-lip breathing technique. He was given written step-by-step instructions with pictures in addition to a video that demonstrated relaxation training. The nurse advised him to practice relaxation as a self-care strategy for times of dyspnea exacerbation. She included his daughters in the education, ensuring they were aware of how they can support their father. They both remarked about their fatigue as their father needed more support with meals, housekeeping, and routine activities. They now try to check on him daily. The nurse informed them of a weekly caregiver support group that the American Lung Association sponsors and encouraged their consideration to ensure they do not neglect their own health and self-care.

These measures were successful in keeping the patient’s dyspnea under control for several weeks. His disease did not respond to the systemic chemotherapy, and he was referred to a hospice homecare program with his daughters actively participating in his care. He maintained good symptom control until the last week of his life, when dyspnea again became a prominent symptom. A trial of nebulized morphine did not improve his breathing, as he was too weak to participate in the breathing treatment. Successive increases in the dose of immediate-release morphine were employed to palliate his dyspnea.

Conclusion

Because of the potential multiple causes of dyspnea and its physiologic and reactive dimensions, it remains a complex symptom that requires thorough assessment and attention. A guiding principle is to treat reversible causes of dyspnea with specific therapies and to use nonspecific or palliative therapy to manage irreversible causes. Although evidence is limited, the use of the evidence-based interventions described in this chapter is essential, while research continues to discover the best methods to care for individuals with dyspnea. The ONS PEP dyspnea resource (see www.ons.org/practice-resources/pep/dyspnea) should serve as the foundation for oncology nurses in the treatment of patients with dyspnea.

Dyspnea can lead to physical distress, emotional suffering, reduced quality of life, and social isolation. Cairns (2012) asserted that healthcare professionals must have an in-depth understanding of breathlessness and the available treatments. “Those who do not consider breathlessness and its significance are failing their patients” (Cairns, 2012, p. 46).

Dyspnea is one of the most distressing symptoms experienced by patients with cancer. It often is a symptom that appeals for intervention because of the distress it evokes in both the person experiencing it and the caregiver witnessing it. Current evidence must be employed by nurses, in collaboration with the healthcare team, as the quest for best practice continues.

The author would like to acknowledge Margaret M. Joyce, PhD, APRN-BC, AOCN®, for her contribution to this chapter that remains unchanged from the first edition of this book.

References


Electrolyte Imbalances, Syndrome of Inappropriate Antidiuretic Hormone, and Tumor Lysis Syndrome

Amanda Fredericks Pace, RN, BSN, OCN®

Case Study

T.C. is a 58-year-old man recently diagnosed with acute myeloid leukemia who has been admitted to the hospital to begin induction chemotherapy. Prior to diagnosis, he exhibited a recent history of nausea, anorexia, fatigue, night sweats, and weight loss. He states that he has not been able to tolerate eating or drinking lately and has only been voiding once or twice daily. His prechemotherapy laboratory tests indicate white blood cell count of 107,000/mm$^3$ with 82% blasts, hemoglobin of 7.9 g/dl, and platelet count of 145,000/mm$^3$. Electrolytes reveal sodium level of 135 mEq/L, potassium level of 5.2 mEq/L, and chloride level of 111 mEq/L. Additional studies reveal a blood urea nitrogen (BUN) of 48 mg/dl, creatinine of 2 mg/dl, lactate dehydrogenase (LDH) of 1,099 IU/L, and a uric acid level of 13.9 mg/dl.

T.C. appears to be at risk for developing potentially life-threatening electrolyte imbalances. The goal of this chapter is to help oncology nurses assess, identify, manage, monitor, and educate patients regarding clinically significant laboratory abnormalities such as those T.C. is demonstrating. Understanding electrolyte imbalances is critical in oncology nursing. Proficiency in this area helps oncology nurses to deliver high-quality, holistic, and patient-centered care, which can greatly affect patients’ experience and clinical outcomes through their cancer journey.

Overview

Electrolytes, including sodium, chloride, potassium, magnesium, phosphorus, and calcium, are chemicals that regulate important physiologic functions within the body. They are
primarily responsible for the movement of nutrients into cells and the movement of wastes out of cells. Electrolytes, when dissolved in water, break up into positively and negatively charged ions. Nerve and muscle function and metabolic and fluid balances are dependent upon the proper exchange of these ions into and out of the cells. Electrolytes have a narrow range of normal functionality and are located primarily within one of two cellular compartments (Kamel, 2014; Kee, Paulanka, & Polek, 2010; Kurtin, 2014b, 2014c, 2014d; Moore & Rosh, 2012), which are

- Extracellular: sodium, chloride, and bicarbonate
- Intracellular: potassium, magnesium, and phosphorus.

A membrane-bound sodium-potassium adenosine triphosphatase (ATPase) pump maintains the differentials between these cellular compartments. The balance of fluid and electrolytes is maintained by their constant movement between the body’s fluid compartments (McLafferty, Johnstone, Hendry, & Farley, 2014).

Electrolytes are usually measured per liter of blood, and the normal ranges and functions are listed in Table 13-1. Imbalances in these electrolytes, especially in patients with cancer, can be very serious if not prevented or promptly treated. For example, patients with breast cancer and metastasis to the bone are at increased risk for hypercalcemia, which could have significant cardiac, neuromuscular, and renal effects if left untreated (Kaplan, 2011).

Electrolyte imbalances occur for numerous reasons, including treatment side effects, disturbance in fluid balances, malignancies with high tumor burdens, alterations in kidney or liver functions, hormone secretion from tumors, and side effects of concomitant drugs (Kee et al., 2010). The systemic effects of these imbalances cause symptoms that can significantly affect the quality of life of patients with cancer. Oncology nurses need to understand the function of electrolytes, identify patients who are at risk for imbalances, recognize symptoms promptly, and provide appropriate and timely interventions. Although many electrolyte and metabolic imbalances can occur in patients with cancer, this chapter will focus primarily on the clinical presentation and management of high and low levels of calcium, sodium, potassium, and magnesium. Also reviewed will be the conditions of syndrome of inappropriate antidiuretic hormone (SIADH) and tumor lysis syndrome (TLS).

### TABLE 13-1 Normal Values and Functions of Electrolytes

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Normal Adult Range*</th>
<th>Roles in Body Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (Na⁺)</td>
<td>135–145 mEq/L</td>
<td>Fluid balance, muscle contraction and nerve function</td>
</tr>
<tr>
<td>Chloride (Cl⁻)</td>
<td>96–106 mmol/L</td>
<td>Fluid balance</td>
</tr>
<tr>
<td>Potassium (K⁺)</td>
<td>3.5–5 mEq/L</td>
<td>Regulation of heart contraction, fluid balance</td>
</tr>
<tr>
<td>Magnesium (Mg²⁺)</td>
<td>1.8–3 mg/dl</td>
<td>Muscle and nerve function, heart rhythm, bone strength, regulation of blood pressure,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>support for immune system, aid in control of blood sugar levels</td>
</tr>
<tr>
<td>Calcium (Ca²⁺)</td>
<td>4.5–5.5 mEq/L; ionized: 2.2–2.5 mEq/L (8.5–10.5 mg/dl; ionized: 4.6–5.3 mg/dl)</td>
<td>Bone formation, nerve and brain function, muscle contraction, hormone secretion, kidney</td>
</tr>
<tr>
<td></td>
<td></td>
<td>regulation</td>
</tr>
</tbody>
</table>

* Ranges may vary slightly from different laboratories.

Note. Based on information from Berendt & D’Agostino, 2005; Kee et al., 2010; Kurtin, 2014c; MedlinePlus, 2013a.
Calcium Imbalances

Pathophysiology

Calcium is essential to the formation and maintenance of bones and teeth, muscle contractility, nerve impulse transmission, and normal clotting mechanisms (Kee et al., 2010; Kurtin, 2014a). It plays an important role in cardiac automaticity, enzyme reactions, white blood cell chemotaxis, and cell membrane permeability. Normal calcium levels are 4.5–5.5 mEq/L (8.5–10.5 mg/dl) (Kaplan, 2011). When levels decrease below the normal range, hypocalcemia develops; when levels increase above the normal range, hypercalcemia occurs.

Ninety-nine percent of the body’s calcium is distributed and stored in the skeletal tissue, or bones, in the form of insoluble crystals, providing strength and durability (Kee et al., 2010; Kurtin, 2014a). Bone tissue is constantly changing through a process known as bone remodeling. Bone remodeling involves bone formation, which is controlled by cells called osteoblasts, and bone resorption, or breakdown, which involves cells called osteoclasts. A number of hormones also are involved in the balance of bone remodeling. During normal bone remodeling, very little exchange of calcium actually occurs between bone and plasma (Gobel, 2005).

The remaining 1% of calcium is located in the serum. Nearly half of the serum calcium is ionized (physiologic active form, or free, iCa\(^{2+}\)); 40% is bound to protein, primarily albumin; and the remaining 12% is bound to anions such as phosphate, carbonate, citrate, lactate, and sulfate (Kurtin, 2014a). Ionized calcium is necessary for excitation of nerves and the function of cardiac muscle, voluntary skeletal muscles, and involuntary muscles of the gut (Gobel, 2005; Kurtin, 2014a). Under normal conditions, the ionized calcium is in equilibrium with the protein-bound calcium. However, changes in serum protein levels (serum albumin) that are common in the very ill, malnourished, or elderly have a direct impact on serum calcium levels. Therefore, serum calcium levels need to be corrected based on albumin levels to accurately represent the active free calcium present in the serum (Kurtin, 2014a; Myers, 2007). A formula for correction is included in Table 13-2.

Mechanisms for regulating calcium include bone formation and resorption, gastrointestinal (GI) absorption, and urinary excretion or absorption. These mechanisms are controlled by a complex balance of the following three hormones: the parathyroid hormone (PTH), calcitriol (1,25-dihydroxyvitamin D), and calcitonin (Kurtin, 2014a). Extracellular calcium levels are balanced by the actions of these hormones in the kidneys (which filter and reabsorb ionized calcium), in the gut (which absorbs dietary calcium and excretes it in feces), and in the bone (which acts as the storage depot for the body’s supply of calcium). The balance of these hormones is controlled through a negative feedback loop in which individual hormones respond as needed to increases or decreases in the serum calcium concentration by altering the renal, GI, or bone absorption or release of calcium (Green, 2014; Kurtin, 2014a).

Hypercalcemia

Overview

Hypercalcemia is a metabolic disorder defined by a serum calcium level greater than 10.5 mg/dl (Kaplan, 2011). Hypercalcemia is commonly caused by primary hyperparathyroidism or malignancy (Green, 2014; Kee et al., 2010; Kurtin, 2014a). Other causes include immobility, granulomatous disorders, renal disease, infectious diseases, medication side effects, various endocrine disorders, and dietary disorders (Green, 2014; Kaplan, 2011; Kee et al., 2010;
Hypercalcemia is a potentially life-threatening disorder with a variable onset and often may go undetected until it is severe. Left untreated, it can lead to renal failure, coma, or cardiac arrest (Myers, 2007).

For hypercalcemia to develop, the normal calcium homeostasis between stored, ionized, and protein-bound calcium must be overwhelmed by an excess in PTH, calcitriol, some other serum factor that mimics these hormones, or an increased calcium load. The increased calcium load is the result of the kidneys’ decreased ability to clear calcium from the blood, increased calcium absorption from the gut, or increased bone resorption (Kaplan, 2011). Excessive calcium in the serum, or hypercalcemia, depresses neuromuscular function, causes increased contractility and irritability of the heart, and interferes with antidiuretic hormone (ADH) action. It also can result in calcium deposits outside the skeletal system, especially in the kidneys (Kaplan, 2011).

The two primary causes of hypercalcemia are PTH-mediated, or primary hypercalcemia, and non-PTH-mediated, or malignant hypercalcemia, disorders.

### TABLE 13-2 Diagnostic Tests for Calcium Imbalances

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Indications/Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium, ionized if possible</td>
<td>May need to calculate corrected (ionized) calcium: Corrected (ionized) calcium = total serum calcium (mg/dl) + [0.8 x (4.0 – serum albumin level [g/dl])]</td>
</tr>
<tr>
<td>Albumin</td>
<td>If albumin level is low and no ionized calcium levels were obtained, calculate corrected calcium. Hypoalbuminemia is the most common cause of hypocalcemia (Kurtin, 2014a).</td>
</tr>
<tr>
<td>Serum magnesium (Mg²⁺)</td>
<td>May be low to normal Hypomagnesemia inhibits parathyroid hormone secretion, leading to decreased calcium release from bones and decreased renal reabsorption (Kurtin, 2014a).</td>
</tr>
<tr>
<td>Serum phosphorus (PO₄⁻)</td>
<td>Has inverse relationship with calcium Phosphorus binds free calcium.</td>
</tr>
<tr>
<td>Blood urea nitrogen/creatinine</td>
<td>Assesses kidney function Renal failure leads to retention of calcium and phosphorus (Kurtin, 2014a).</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>Elevated if related to primary hyperparathyroidism; decreased or normal if malignant cause Increased parathyroid hormone leads to increased serum calcium.</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Will be elevated with bone metastasis and breast cancer</td>
</tr>
<tr>
<td>Urine calcium (Ca²⁺) and PO₄⁻</td>
<td>Increased; may be present in urine before serum calcium levels are elevated</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>Performed to rule out tumor, sarcoidosis, and any bony changes associated with hyperparathyroidism</td>
</tr>
<tr>
<td>Plain x-ray/bone scan</td>
<td>Performed to determine bone metastasis or multiple myeloma</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>Performed to look for changes such as increased PR segment, shortened QT interval, or widening T wave</td>
</tr>
</tbody>
</table>

Note. Based on information from Green, 2014; Kurtin, 2014a; Myers, 2007.
Primary Hypercalcemia

Primary (PTH-mediated) hyperparathyroidism, the most common cause of hypercalcemia in the general population, is often asymptomatic and is seen mostly in the outpatient setting (Green, 2014; Kee et al., 2010; Kurtin, 2014a). Primary hypercalcemia is generally less severe and lasts longer than hypercalcemia associated with malignancy, or non–PTH-mediated hypercalcemia (Agraharkar, Dellinger, & Gangakhedkar, 2012; Green, 2014). Because the parathyroid glands are the primary regulators of calcium homeostasis, calcium elevations from hyperparathyroidism are directly related to the inappropriate or excess secretion of PTH by the parathyroid glands.

Malignant Hypercalcemia

Malignant hypercalcemia is the most commonly occurring, and potentially fatal, metabolic complication of cancer and is reported in 10%–20% of patients with cancer (Kaplan, 2011; Kee et al., 2010). Hypercalcemia presents most frequently in patients with breast cancer, multiple myeloma, squamous cell cancers, and renal cell carcinoma (Kaplan, 2011; Kurtin, 2014a). Hypercalcemia is often seen in patients with advanced-stage disease and at the end of life (Kurtin, 2014a).

Hypercalcemia associated with malignancy results from paracrine or endocrine secretion of humoral factors, high tumor burden in the bone, or absorptive changes stimulated by excess vitamin D activation by the cancer (Kaplan, 2011; Rosner & Dalkin, 2012). As a result, the calcium concentration in the extracellular fluid overwhelms the kidneys’ ability to adequately clear excess calcium, and hypercalcemia results. Inadequate renal calcium clearance can lead to polyuria, dehydration, decreased renal blood flow and glomerular filtration, and ultimately calcium precipitation into the renal tubules (Kaplan, 2011). Hypercalcemia of malignancy can occur through several different mechanisms depending on the action and location of the cancer cells. However, two primary mechanisms exist: humoral hypercalcemia of malignancy (HHM) and local osteolytic hypercalcemia (LOH).

HHM, which is responsible for 80% of cases of malignant hypercalcemia, is caused by the presence of humoral factors (e.g., hormones, cytokines), which are released or regulated ectopically by malignant cells (Kurtin, 2014a). These humoral agents are not controlled by the same mechanisms as those present in normal cells. HHM develops as a result of humoral agents inhibiting bone formation, stimulating bone resorption and osteoclastic activity, and increasing renal tubular reabsorption of calcium (Kurtin, 2014a; Myers, 2007).

The most common malignancy-related humoral agent is PTH-related peptide (PTHrP). Overproduction of PTHrP may be stimulated by several cancer-related factors, including ectopic production by the malignant tumor cells themselves. PTHrP mimics the activity of PTH at the associated receptors, causing increased bone resorption, decreased osteoclast bone formation, and altered renal clearance, all of which result in the extracellular transfer and buildup of calcium (Fojo, 2011; Kaplan, 2011; McClelland, 2010). PTHrP-mediated hypercalcemia has been found in patients with solid tumors and is most common in squamous cell cancers (e.g., lung, cervix, esophagus); some lymphomas; renal cell carcinoma; and adenocarcinoma of the breast, prostate, and ovary (Rosner & Dalkin, 2012). Patients with HHM often have little or no bone metastases. Other humoral factors associated with HHM are cytokines (interleukin-1), transforming growth factors, tumor necrosis factors, osteoclast activation factors, colony-stimulating factors, and 1,25-dihydroxyvitamin D (Fojo, 2011).

LOH, which accounts for approximately 20% of patients with malignant hypercalcemia, is a result of direct bone destruction caused by the osteolytic activity of tumor cells either by direct tumor invasion or metastasis (Kaplan, 2011; Kurtin, 2014a; Rosner & Dalkin, 2012). As an imbalance occurs in bone remodeling, osteoclastic activity increases, more destruction
from metastatic disease occurs, and an excess of calcium is released into the serum. LOH often is associated with the formation of lytic lesions on the bone and occurs most frequently in breast cancers and multiple myeloma with bone metastases (Kaplan, 2011).

A variety of factors contribute to the perpetuation or worsening of hypercalcemia. These can include prolonged immobilization, dehydration, excessive use of certain vitamin supplements or calcium-containing drugs, renal failure, nephrotoxic medications, and prolonged use of thiazide diuretics (Kaplan, 2011; Myers, 2007).

Clinical Assessment

Conducting a thorough diagnostic workup including a history, physical examination, and laboratory tests is critical in early identification of hypercalcemia and differentiation of the cause, type, and severity. Table 13-2 reviews the relevant laboratory and diagnostic tests for diagnosis of imbalances in calcium.

Nurses should obtain information about the onset, duration, and description of the patient’s symptoms, cancer diagnosis, and any known sites of metastases. Current chemotherapy or hormonal treatments and a list of all medications, including diuretics, vitamins, and supplements, should be obtained. A thorough review of systems and physical assessment should be performed. Pain and neurologic status should be assessed, and any mental status changes identified. A cardiac examination should include heart rate and rhythm, orthostatic blood pressures, and electrocardiogram. Nurses should assess for nausea, vomiting, and constipation and should evaluate abdominal sounds and assess for signs or symptoms of dehydration. Nurses should inquire about changes in fluid intake or urinary function and signs or symptoms of kidney stones (e.g., flank pain). A neuromuscular examination should include assessment of speech, reflexes, muscle tone, and strength (Kurtin, 2014a).

Clinical Manifestations

The signs and symptoms associated with hypercalcemia are nonspecific and vary according to severity, rate of onset, and underlying causes of the imbalance. They may often be misinterpreted as manifestations of terminal cancer or side effects from chemotherapy, radiation, or medications (Kaplan, 2011). Patients may be asymptomatic or may exhibit mild, moderate, or severe degrees of symptoms. Signs and symptoms are directly related to the underlying cause and the destruction of the involved body systems. In severe cases, changes in mental status, cardiac arrhythmia, seizure, coma, and even death may result (Fojo, 2011; Kaplan, 2011; Kurtin, 2014a). See Table 13-3 for signs and symptoms according to body system and degree of hypercalcemia.

Evidence-Based Interventions

Treatment for hypercalcemia is based on the severity, presenting symptoms, renal and cardiac function, and underlying cause or prognosis of the disease. Treating the malignancy is the most effective and only long-term treatment strategy for hypercalcemia of malignancy. For example, initiating chemotherapy in a patient with multiple myeloma may produce a remission of the cancer cells, thereby decreasing the release of cytokines from tumors and resultant hypercalcemia. If left untreated, cancer-induced hypercalcemia is progressive, and death is usually inevitable. In many cases, control of the malignancy may not be possible. A thorough evaluation of the patient’s disease status should be performed with the patient, family, and medical team prior to the initiation of treatment. Treatment options, in the case of advanced disease, should be directed at palliation and enhancing quality of life (Kaplan, 2011; Myers, 2007).
Acute medical management of hypercalcemia has three main goals: (a) to correct any dehydration, (b) to increase renal excretion of calcium, and (c) to inhibit calcium resorption from bone, usually with antiresorptive agents (Kaplan, 2011). In patients with mild, asymptomatic hypercalcemia (10.5–11.9 mg/dl), outpatient management with oral rehydration and frequent laboratory monitoring is the primary intervention while the underlying cause is treated. Increasing oral fluid intake to 3–4 L/day may be sufficient to rehydrate the patient and correct calcium levels (Kaplan, 2011). Close monitoring of electrolytes and renal function tests should be continued, as well as monitoring of intake and output (I&O) and cardiac function. Mobilization, with the goal of ambulation at least three times daily and low-weight–bearing exercises, may help decrease resorption of calcium from the bones and should be encouraged and reinforced (Kaplan, 2011; Myers, 2007). Nurses should implement nonpharmacologic and pharmacologic pain management strategies, as well as antiemetic therapy, as indicated.

Patients with symptomatic or moderate hypercalcemia (12–13.9 mg/dl), who are often unable to tolerate oral fluids, require hospital admission for aggressive IV hydration with 0.9% normal saline to promote sodium diuresis and induce calcium excretion. The amount and rate of fluid administration depend on the severity of hypercalcemia, degree of dehydration, and renal and cardiac status. IV fluid should be initiated at a rate of 100–300 ml/hr over the first 24 hours and can then be decreased to 2.5–4 L daily until the patient is stabilized (Kaplan, 2011).

Loop diuretics, such as furosemide, may be used to accelerate the elimination of calcium once rehydration has been achieved. Loop diuretics aid in blocking the reabsorption of calcium and sodium and preventing fluid overload from vigorous hydration; this is especially important in patients at risk for cardiac toxicity from IV hydration. Loop diuretics should be used cautiously, as excess extracellular fluid losses can actually promote calcium resorption and the depletion of potassium and magnesium. Therefore, these electrolytes should be monitored frequently (Myers, 2007). Thiazide diuretics, such as hydrochlorothiazide, should be avoided completely because of their potential to worsen hypercalcemia (Kaplan, 2011).

### TABLE 13-3

<table>
<thead>
<tr>
<th>Signs and Symptoms of Hypercalcemia by Degree and Systemic Effect</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Systemic Effect</th>
<th>Mild (&lt; 12 mg/dl)</th>
<th>Moderate (12–15 mg/dl)</th>
<th>Severe (&gt; 15 mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Possible hypertension, orthostatic hypotension</td>
<td>Electrocardiogram changes, cardiac dysrhythmias</td>
<td>Heart block, cardiac arrest, death</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Anorexia, nausea, vomiting, vague abdominal pain</td>
<td>Constipation, increased pain, abdominal distention, bloating</td>
<td>Obstipation, ileus</td>
</tr>
<tr>
<td>Muscular</td>
<td>Fatigue, generalized muscle weakness, hyporeflexia</td>
<td>Bone pain, increased muscle weakness</td>
<td>Pathologic fractures, ataxia, severe muscle weakness</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Restlessness, irritability, indifference, difficulty concentrating, lethargy</td>
<td>Confusion, apathy, drowsiness, somnolence</td>
<td>Coma, seizures, stupor, death</td>
</tr>
<tr>
<td>Renal</td>
<td>Polyuria, nocturia, polydipsia, pruritus</td>
<td>Renal tubular acidosis, dehydration, renal calculi</td>
<td>Renal insufficiency, oliguric renal failure, azotemia</td>
</tr>
</tbody>
</table>

*Note. Based on information from Kaplan, 2011; Myers, 2007; Shuey & Brant, 2004.*
Antiresorptive therapy is the next step in the restoration of calcium balance. In conjunction with hydration, the use of antiresorptive drugs, such as pamidronate or zoledronic acid, is the mainstay of treatment for hypercalcemia of malignancy (Fojo, 2011). These bisphosphonates, which are given IV, selectively concentrate in bone where they inhibit tumor cell binding and decrease bone resorption. They may help to strengthen and stabilize bone. Antiresorptive therapy should start promptly after initial rehydration, particularly for patients whose corrected calcium is greater than 13 mg/dl; IV hydration should continue during bisphosphonate therapy and patients should sustain a urine output of at least 2 L daily (Kaplan, 2011). Nurses should monitor for side effects and toxicities of bisphosphonates, which may include fever, flu-like symptoms, bone pain, hypocalcemia, renal function impairment, and osteonecrosis of the jaw (with long-term therapy) (Kaplan, 2011; Kurtin, 2014a). Research has shown zoledronic acid to be significantly more effective than pamidronate in normalizing calcium levels within 4–10 days, lasting up to six weeks in the majority of patients (Fojo, 2011; Kaplan, 2011). Table 13-4 describes the mechanism of action, recommended doses, and important considerations for antiresorptive treatment and other pharmacologic management strategies for hypercalcemia, including oral phosphates and corticosteroids.

Denosumab is a fully humanized monoclonal antibody that interferes with bone resorption by binding receptor activator of nuclear factor kappa-B ligand (referred to as RANKL), known to play an integral role in osteoclast-mediated bone metabolism (Hu et al., 2013; Kaplan, 2011). Early studies show effectiveness in reducing calcium levels in patients with hypercalcemia.

### TABLE 13-4 Antiresorptive Agents and Other Medications Used to Treat Hypercalcemia

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Mode of Action</th>
<th>Adverse Reactions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid (third generation)</td>
<td>4 mg IV over 15 minutes; retreat with 4 mg IV for relapsed or refractory cases after 7 days</td>
<td>Inhibits action of osteoclasts</td>
<td><strong>Renal toxicity:</strong> skeletal pain, fever, flu-like syndrome, nausea/vomiting, fatigue, constipation; hypophosphatemia; hypocalcemia Do not give with calcitonin. Use caution with diuretics. Monitor for osteonecrosis of the jaw (ONJ).</td>
<td>First-line treatment; superior efficacy and short infusion time; rapid results May repeat in 7 days, then every 4 weeks for ongoing management <strong>Monitor serum creatinine before each dose.</strong></td>
</tr>
<tr>
<td>Pamidronate (second generation)</td>
<td>60–90 mg IV over 2–24 hours</td>
<td>Inhibits action of osteoclasts</td>
<td>Fever, flu-like syndrome, phlebitis, nausea Monitor for ONJ.</td>
<td>First-line therapy; highly effective and still used widely May be used with calcitonin Onset of action in 24 hours. May repeat weekly until normal calcium level is achieved, then every 4 weeks for chronic management <strong>Monitor serum creatinine before each dose.</strong></td>
</tr>
</tbody>
</table>

(Continued on next page)
### TABLE 13-4
**Antiresorptive Agents and Other Medications Used to Treat Hypercalcemia (Continued)**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Mode of Action</th>
<th>Adverse Reactions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallium nitrate</td>
<td>200 mg/m²/day IV over 24 hours for up to 5 days</td>
<td>Antineoplastic; inhibits osteoclastic bone resorption without toxicity to bone cells; stabilizes bone crystals</td>
<td>Nephrotoxicity, anemia, nausea/vomiting</td>
<td>Must be hospitalized; highly effective but slow onset; saline hydration must be maintained during use with urinary output at least 2 L/day; duration of response is about 6 days. Not generally used because of expense, toxicities, and inconvenience. Monitor renal function.</td>
</tr>
<tr>
<td>Plicamycin (mithramycin)</td>
<td>25 mcg/kg/day IV over 4–6 hours for 3–8 doses</td>
<td>Neoplastic agent; inhibits RNA synthesis in osteoclasts</td>
<td>Nausea/vomiting, cumulative nephrotoxicity, hepatotoxicity, bone marrow toxicity</td>
<td>Onset in 1–2 days Duration of 2 weeks; third-line treatment; not recommended and rarely used Agent is a vascular irritant.</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>4 U/kg subcutaneously every 12 hours; 8 U/kg every 6 hours PRN if no response</td>
<td>Inhibits action of osteoclasts; decreases renal absorption of Ca²⁺</td>
<td>Allergic reaction, nausea/vomiting, flushing of face and hands, polyuria</td>
<td>Most rapid onset and short duration; resistance develops Check serum Ca²⁺ every 5–6 hours. Continue with hydration and use of furosemide PRN; intradermal test dose recommended. May be given with pamidronate if serum Ca²⁺ &gt; 13 mg/dl.</td>
</tr>
</tbody>
</table>

### Oral Phosphates

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Mode of Action</th>
<th>Adverse Reactions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple agents</td>
<td>250–375 mg PO 4 times daily</td>
<td>Prevent gastrointestinal absorption; inhibit bone resorption</td>
<td>Diarrhea; contraindicated with renal failure</td>
<td>Used to correct hypophosphatemia and in chronic hypercalcemia</td>
</tr>
</tbody>
</table>

### Corticosteroids

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Mode of Action</th>
<th>Adverse Reactions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>100–300 mg/day IV for 3–7 days</td>
<td>Inhibits lymphoid tissue growth</td>
<td>Hyperglycemia, sodium and water retention, immunosuppression, Cushingoid symptoms, gastritis, osteoporosis, muscle wasting</td>
<td>Used with steroid-sensitive tumors (e.g., hematologic, breast). May enhance and prolong effect of calcitonin. Never used alone or as primary treatment, and not for long-term use because of adverse effects</td>
</tr>
<tr>
<td>Prednisone</td>
<td>40–100 mg/day PO</td>
<td>Inhibits regulation of steroid receptors; promotes urinary excretion of Ca²⁺</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
</tbody>
</table>

*Note. Based on information from Green, 2014; Kaplan, 2011; Myers, 2007; Novartis Pharmaceuticals Corp., 2013.*
percalcemia refractory to bisphosphonates, suggesting that this agent may offer a novel approach to HHM in patients with cancer (Hu et al., 2013).

For severe hypercalcemia (greater than 14–16 mg/dl), the rate of hydration should be increased, if tolerated, in the first 24 hours, and loop diuretics (e.g., furosemide) up to 80–100 mg every two hours should be initiated once rehydration has been obtained (Kaplan, 2011). Intensive care unit admission may be indicated to closely monitor hemodynamics and fluid volume status during this aggressive therapy. Antiresorptive agents should be started as soon as possible (see Table 13-4).

For life-threatening hypercalcemia (greater than 16 mg/dl), the use of IV calcitonin may be necessary. Calcitonin aids in reducing the calcium levels quickly, usually within four to six hours, by decreasing renal tubular reabsorption of calcium and by blocking osteoclast resorption. It reaches maximum efficacy within 12–24 hours; however, the effect is short term and drug resistance may develop (Kaplan, 2011). Therefore, calcitonin should be given for acute management, before transitioning to longer-acting bisphosphonate therapy. Dialysis, although rarely used in the treatment of hypercalcemia, may be a viable option for people who have preexisting renal insufficiency and cannot tolerate saline diuresis (Kaplan, 2011).

Expected Patient Outcomes

Hypercalcemia of malignancy is the most common complication of malignancy and is reversible in 80% of episodes if it is recognized promptly and aggressive treatment is initiated. However, the mortality rate is 50% in those not treated quickly (Myers, 2007). Most patients presenting with hypercalcemia of malignancy will require ongoing management while receiving treatment for their underlying malignancy. Hypercalcemia often occurs as a late complication of advanced cancer. Treatment in this instance is palliative, and the focus remains on enhancing quality of life (Kaplan, 2011).

Patient Teaching Points

Figure 13-1 reviews teaching points for patients and family members on the management of hypercalcemia.

Hypocalcemia

Overview

Hypocalcemia is defined by a calcium level less than 8.5 mg/dl or an ionized calcium level less than 4.5 mg/dl (Berendt & D’Agostino, 2005; Kaplan, 2011). The regulation of calcium
levels is maintained through a complex balance of feedback loops between PTH, vitamin D, and calcitonin that act primarily on the bone and renal and GI systems. Magnesium, phosphorus, and albumin levels also affect calcium levels. Oncology nurses need to be aware of both the general and the cancer-related mechanisms that can lead to hypocalcemia.

Numerous cancer-related causes of hypocalcemia exist. Pharmacologic causes include chemotherapy agents (e.g., high-dose cisplatin, fluorouracil/leucovorin combination therapies, cetuximab, doxorubicin); hormone-modulating drugs (e.g., tamoxifen); certain anti-infectives (e.g., aminoglycosides, amphotericin B, ketoconazole); loop diuretics; high doses of fluorides, glucose, insulin, and anticonvulsants (e.g., phenobarbital, phenytoin); proton pump inhibitors; corticosteroids; and foscarnet used to treat cytomegalovirus or herpes infections (Hanamura, Iwamoto, Soga, Sugimura, & Okuda, 2010; Suneja & Muster, 2014).

A myriad of cancer-related factors pose a risk for hypocalcemia as well. Osteoblastic bone metastases and bisphosphonate therapy may lead to hypocalcemia. TLS, which will be discussed in detail later in this chapter, is associated with hypocalcemia and other electrolyte imbalances. Radiation therapy or surgery involving the thyroid gland or head and neck may contribute to hypocalcemia. Nonspecific electrolyte or serum chemistry abnormalities can cause or worsen hypocalcemia. These may include hypoalbuminemia; hypoparathyroidism; hyperphosphatemia; malabsorption or deficiencies of vitamin D, magnesium, or dietary calcium; and chronic renal failure (Suneja & Muster, 2014). Chelating agents, hungry bone syndrome (significant and prolonged hypocalcemia due to significant skeletal calcium utilization after parathyroidectomy [Witteveen, van Thiel, Romijn, & Hamdy, 2013]), blood citrates (conferred by multiple transfusions), plasmapheresis, and acute pancreatitis also may lead to hypocalcemia (Kurtin, 2014a).

Clinical Assessment

Oncology nurses should collect a thorough history in assessing for hypocalcemia, paying special attention to any history of pancreatitis or liver or renal failure. Nurses need to assess for recent thyroid, parathyroid, bowel, or head and neck surgery, trauma, or infection; radiation therapy to the neck; and any recent blood or plasma transfusions, chemotherapy, or bisphosphonate therapy. They should inquire about current medications, including antibiotics, diuretics, estrogen therapies, anticonvulsants, and any type of supplements. A nutritional assessment should be performed, including questions about intake of calcium, vitamin D, magnesium, and phosphorus-containing foods or drinks. Assessment should include alcohol intake and sun exposure. Table 13-5 identifies important indicators in the physical assessment for the diagnosis and determination of causes for hypocalcemia.

Table 13-6 describes the appropriate diagnostic tests to identify hypocalcemia and assess its severity and underlying cause (Khosla, 2012). Again, the goal is to provide supportive care to prevent serious sequelae while identifying and treating the underlying cause of the imbalance (Kurtin, 2014a).

Clinical Manifestations

Signs and symptoms of hypocalcemia vary according to the underlying cause, onset, and acuity. They are primarily related to the neurologic, muscular, and cardiac functions of calcium (Suneja & Muster, 2014). The most common early sign of hypocalcemia is neuromuscular “irritability” exhibited by twitching muscles and spasms, leg or arm muscle cramps, and numbness or tingling in the perioral area or in the fingers and toes (Berendt & D’Agostino, 2005; Khosla, 2012).

Mild or chronic hypocalcemia can be asymptomatic; however, patients with chronic hypocalcemia may exhibit signs of chronic pruritus, cataracts, coarse hair, brittle nails, psoria-
There are two classic findings in patients with chronic hypocalcemia: Chvostek sign and Trousseau sign. Chvostek sign is characterized by twitching of the muscles around the mouth, elicited by tapping the facial nerve in front of the ear. Note, however, that approximately 10% of normocalcemic individuals may have a positive Chvostek sign; therefore, it is neither sensitive nor specific (Khosla, 2012). Trousseau sign, on the other hand, is more sensitive and specific to hypocalcemia. It is elicited by applying a blood pressure cuff to the patient’s arm and leaving it inflated to a pressure 20 mm Hg above the individual’s systolic blood pressure for approximately three minutes; a positive sign is characterized by carpal spasms induced by the resultant ischemia (Jesus & Landry, 2012; Khosla, 2012).

Severe hypocalcemia may lead to acute seizures, hallucinations, tetany, hypotension, QT prolongation and cardiac arrhythmias, laryngospasm and bronchospasm, and ultimately heart failure and death (Berendt & D’Agostino, 2005; Khosla, 2012). Therefore, rapid identification and correction of hypocalcemia are critical.

### Evidence-Based Interventions

Treatment for hypocalcemia depends on the exact cause, the presence of symptoms, and the severity of the condition. Mild, asymptomatic hypocalcemia may be managed on an out-
patient basis with oral supplementation and correction of any underlying hypomagnesemia. Calcium supplements should be initiated at doses of 1,000–3,000 mg/day in divided doses two to four times a day (Suneja & Muster, 2014). Calcium in any form needs vitamin D in order to be absorbed by the GI tract, and many calcium supplements include vitamin D in their preparations. A general guideline for vitamin D supplementation is 400–800 IU/day to ensure that the calcium taken is absorbed. The least expensive and most common form of supplemental calcium is calcium carbonate; this requires stomach acid for absorption and therefore must be separated from antacid medications and taken with a meal (Kurtin, 2014a). Oral calcium gluconate, calcium citrate, or calcium lactate also may be used. Special attention should be paid to the actual amount of elemental calcium in each preparation. Calcium carbonate contains 40% elemental Ca\(^{2+}\), so 650 mg tablets actually contain approximately 250 mg of elemental calcium (Kurtin, 2014a; Skugor, 2009). If calcium supplements alone do not improve the hypocalcemia, thiazide diuretics may be used cautiously because of their potential to increase renal absorption of calcium; serum calcium levels should be monitored closely.

The determination of additional supplement requirements will be partially dependent on the reason for hypocalcemia. Additional vitamin D supplements may be necessary if hypocalcemia is related to vitamin D deficiencies. Determining the cause of vitamin D deficiencies (i.e., chronic renal failure, hypoparathyroidism, or dietary deficiency) will direct the appropriate dosing of vitamin D supplementation (Kurtin, 2014a; Suneja & Muster, 2014).

Imbalances in magnesium and phosphorus levels may affect serum calcium levels and thus must be identified and corrected. Hypomagnesemia often renders calcium and vitamin D supplementation ineffective; therefore, oral or IV magnesium repletion may be required before serum calcium levels can improve. Prophylactic supplementation may also be considered in patients at risk for hypomagnesemia (e.g., patients receiving cisplatin) to prevent decreases in serum magnesium levels and resultant hypocalcemia. The recommended treatment for hypomagnesemia will be discussed later in this chapter.

Phosphorus and calcium have an inverse relationship; if hyperphosphatemia is present, the reason (e.g., TLS, rhabdomyolysis) will need to be identified and corrected for the hypo-

### TABLE 13-6 Physical Assessment Indicators for Hypocalcemia

<table>
<thead>
<tr>
<th>System</th>
<th>Assessment Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Evaluate blood pressure and heart rate and rhythm, looking for evidence of hypotension, arrhythmias, or congestive heart failure.</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Assess for hyperactive bowel sounds, intestinal colic, or recent diarrhea.</td>
</tr>
<tr>
<td>Integumentary</td>
<td>Assess for coarse hair, brittle nails, dry skin, pruritus, or psoriasis.</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Assess for depression, irritability, personality changes, confusion, hallucinations, dementia, or extrapyramidal symptoms.</td>
</tr>
<tr>
<td>Neuromuscular</td>
<td>Assess for muscle irritability, numbness, tingling, muscle spasms, or cramps. Assess for positive Chvostek or Trousseau signs with severe hypocalcemia.</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Auscultate breath sounds for evidence of stridor; wheezing caused by bronchospasms; rales; voice changes because of laryngospasms; or any dysphagia.</td>
</tr>
</tbody>
</table>

*Note. Based on information from Kurtin, 2014a; Suneja & Muster, 2013.*
calcemia to resolve (Kaplan, 2011). Phosphate-binding antacids, such as calcium carbonate or aluminum hydroxide, may be given to decrease the GI absorption of phosphate. Dietary restrictions of foods containing phosphate may be instituted. In acute cases of hyperphosphatemia, hydration with IV saline and acetazolamide diuresis may be used while monitoring for worsened hypocalcemia (Skugor, 2009). If renal failure is present with hyperphosphatemia and hypocalcemia, dialysis may be required.

Severe, acutely symptomatic cases of hypocalcemia (ionized calcium level less than 3 mg/dl) require immediate evaluation and treatment in the inpatient setting. IV calcium gluconate is the preferred formulation; 1–2 g should be administered in 50 ml of 5% dextrose in water over 20–30 minutes (Kurtin, 2014a). Calcium chloride is an alternative and has a higher percentage of ionized calcium (272 mg elemental calcium/10 ml), but it must be infused via a central line because of the risk for venous irritation and tissue injury with extravasation. The action is immediate but short lived, and a continuous calcium infusion often is recommended at 0.5–2 mg elemental calcium/kg/hr until the patient is stabilized. Frequent measuring of ionized calcium via arterial line will be necessary (Suneja & Muster, 2014), and seizure precautions should be instituted (Berendt & D’Agostino, 2005). In patients with cardiac arrhythmias or on digoxin therapy, continuous electrocardiogram (ECG) monitoring is indicated during calcium infusions because calcium potentiates digitalis toxicities (Suneja & Muster, 2014).

**Expected Patient Outcomes**

The prognosis for correcting acute hypocalcemia is excellent once the cause has been determined and it is treated promptly. Patients should be monitored closely for recurring hypocalcemia. Long-term (chronic) hypocalcemia can lead to irreversible eye damage, such as cataracts (Kurtin, 2014a; Suneja & Muster, 2014). Some patients, such as those with resistance to PTH or with chronic renal failure, may require long-term use of vitamin D, phosphorus, or calcium supplements. Occasionally, hemodialysis is required.

**Patient Teaching Points**

Figure 13-2 describes teaching points that should be used to instruct patients on the management of hypocalcemia.

<table>
<thead>
<tr>
<th>FIGURE 13-2</th>
<th>Teaching Points for Hypocalcemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Signs and symptoms of hypocalcemia include depression, irritability, muscle cramps in legs or arms, and numbness or tingling in fingers and toes.</td>
<td></td>
</tr>
<tr>
<td>• Identify patients who are at high risk for hypocalcemia; use preventive measures (i.e., IV magnesium sulfate prior to treatment) and frequent laboratory monitoring as necessary, especially in patients receiving cisplatin, cetuximab, zoledronic acid, or pamidronate and patients with bone metastasis from breast cancer or those who are at risk for tumor lysis syndrome.</td>
<td></td>
</tr>
<tr>
<td>• Provide patients with a list of foods high in calcium and vitamin D. Dairy products contain the most calcium; however, leafy greens, fish such as sardines and salmon, soy products, red beans, and some calcium-fortified foods such as cereals and orange juice are good sources. Teach patients the importance of reading labels and taking in proper nutrition.</td>
<td></td>
</tr>
<tr>
<td>• Advise patients to take calcium carbonate supplements with meals to improve absorption.</td>
<td></td>
</tr>
<tr>
<td>• Teach management techniques for constipation (i.e., stool softeners, fiber), as it commonly occurs with calcium supplements.</td>
<td></td>
</tr>
<tr>
<td>• Discuss increased risk for brittle bones and fractures because of the risk of bone thinning resulting from chronic low calcium levels.</td>
<td></td>
</tr>
</tbody>
</table>

Note. Based on information from Kurtin, 2014a; Suneja & Muster, 2014.
Sodium Imbalances

Pathophysiology

Sodium is the major cation (positive ion) in the extracellular fluid. It has a principal role in the maintenance of serum osmolarity and fluid balance (Kurtin, 2014d). Maintenance of this homeostasis relies on the complex interactions between renal activity of arginine vasopressin (AVP), or ADH, the renin-angiotensin-aldosterone system, the sympathetic nervous system, and the thirst response to balance water intake and losses (Aditya & Rattan, 2012; Semenovskaya, Sinert, & Stephanides, 2014). It is indirectly regulated by sensory receptors (osmoreceptors), which promote either the uptake of water or the excretion of urine (Berendt & D’Agostino, 2005). Serum sodium concentration is ultimately regulated by a complex coordination of sodium intake, central thirst mechanism, and hormone-mediated alterations in the retention or excretion of sodium and water (Berendt & D’Agostino, 2005; Kurtin, 2014d). This balance is often dysregulated in patients with cancer (Fojo, 2011). It is important to closely monitor electrolytes, especially sodium, magnesium, and potassium, and replete as needed to prevent cardiac dysrhythmias.

Hypernatremia

Overview

The normal range for sodium is 135–145 mEq/L (Kurtin, 2014d). Hypernatremia is defined as a high serum sodium level, greater than 145 mEq/L. The most common cause is from inadequate free water intake to balance net losses, leading to hypovolemia and increased plasma osmolarity. This hyperosmolarity draws fluids from the intracellular to the extracellular compartments, leading to depletion of intracellular fluids and cell volume contraction. This dehydration, namely in the cells of the central nervous system (CNS), is responsible for most of the symptoms of hypernatremia (Semenovskaya et al., 2014).

People with hypernatremia have either too much salt, too little water, or a combination of the two related to their total volume status. Proper treatment depends upon the patient’s fluid volume status; therefore, the type of hypernatremia must be determined: hypovolemic, euvoletic, or hypervolemic. Table 13-7 describes the various causes of hypernatremia based on volume status.

Semenovskaya et al. (2014) estimated that hypernatremia occurs in approximately 1% of hospitalized patients and up to 2% of debilitated older adults and breast-fed infants. When severe hypernatremia occurs in hospitalized patients, it is associated with a high mortality rate—greater than 50% in some studies (Vanderghynst et al., 2013). Cancer rarely is a direct cause of hypernatremia. It most commonly is seen secondary to cancer symptoms or treatment-related toxicities such as dehydration caused by inadequate water intake, or in patients with severe diarrhea, vomiting, or high fever (Berendt & D’Agostino, 2005; Kurtin, 2014d). In patients with cancer, hypernatremia is primarily hypovolemic in nature as a result of GI losses or increased sensible water loss (Berk & Rana, 2006).

Other causes of hypernatremia include diabetes insipidus resulting from CNS or nephrogenic causes, impaired renal function, burns, profuse sweating, CNS disorders or malignancies, excessive diuresis, and respiratory infections (Berendt & D’Agostino, 2005; Kurtin, 2014d). The following medications also may cause hypernatremia: administration of hypertonic saline, sodium bicarbonate, or high-sodium parenteral nutrition and long-term use of amphotericin B, corticosteroids, antihypertensives, hydralazine, reserpine, lactulose, and lithium (Berendt & D’Agostino, 2005; Kurtin, 2014d; Semenovskaya et al., 2014).
As with all electrolyte imbalances, a thorough history and physical examination are critical in the identification of imbalances and assessment of cause. Laboratory assessments should include serum sodium and osmolality, as well as urine sodium and osmolality (Kurtin, 2014d). Additional tests may be indicated if diabetes insipidus or adrenal insufficiency is suspected. Table 13-8 displays important diagnostic tests related to hypernatremia.

**TABLE 13-7** Volemic States of Hypernatremia

<table>
<thead>
<tr>
<th>Volemic State</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Hypovolemic (water deficit > sodium deficit) | Extrarenal—diarrhea, vomiting, burns, sweating, fever  
|                               | Renal—osmotic diuresis, renal disease, diuretics, hyperglycosuria  
|                               | Hypodipsic—lack of or inability to respond to thirst  
|                               | • Primary—destruction of thirst center in hypothalamus (tumors, central nervous system disorders, trauma)  
|                               | • Secondary—inability to respond to thirst signals (older adults, infants, physically or mentally debilitated)  
| Hypervolemic (sodium gain > water gain) | Sodium bicarbonate or hypertonic solution administration  
|                               | Accidental salt ingestion  
|                               | Hyperaldosteronism  
| Euvolemic (increased pure water loss) | Extrarenal—increased insensible loss (hyperventilation, dermal or respiratory causes)  
|                               | Renal—diabetes insipidus  
|                               | Central—lack of central stimulus (antidiuretic hormone) to concentrate urine  
|                               | Nephrogenic—lack of renal response to stimulus of antidiuretic hormone secretion  

*Note.* Based on information from Berk & Rana, 2006; Semenovskaya et al., 2014.

**Clinical Assessment**

As with all electrolyte imbalances, a thorough history and physical examination are critical in the identification of imbalances and assessment of cause. Laboratory assessments should include serum sodium and osmolality, as well as urine sodium and osmolality (Kurtin, 2014d). Additional tests may be indicated if diabetes insipidus or adrenal insufficiency is suspected. Table 13-8 displays important diagnostic tests related to hypernatremia.

**History and Physical Assessment**

In collecting the history, nurses should first identify presenting symptoms and gather information about their onset, duration, severity, and precipitating factors (Kurtin, 2014d). They should identify any recent fluid losses (e.g., vomiting, diarrhea, fever, burns, profuse sweating) and inquire about patients’ thirst response (i.e., excessive versus no thirst), fluid intake and urine output (polydipsia, polyuria, oliguria), and behavioral/physical tolerance of oral fluids. Nurses should elicit information about recent intake of high-sodium products and use of tap water enemas. A review of current medications and treatments is important to determine whether any pharmacologic factors may be contributing to sodium overload, fluid restriction, or renal impairment (Berendt & D’Agostino, 2005; Kurtin, 2014d).

A full set of vital signs and complete physical examination should be performed, including assessment of overall fluid status. A thorough neurologic examination should be performed to facilitate early identification of deficits and aid in determining the severity and underlying cause of the hypernatremia, as neurologic changes are common in hypernatremia because of the cell dehydration (Berk & Rana, 2006; Semenovskaya et al., 2014).

**Clinical Manifestations**

Physical findings associated with hypernatremia can be nonspecific and depend upon the cause and severity of the sodium imbalance. As hypernatremia progresses, cell dehydration and cell volume contraction occur as water leaves the intracellular compartment. This cell
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dehydertion leads to many of the signs and symptoms of hypernatremia. Common symptoms of hypernatremia include lethargy, restlessness, irritability, muscle twitching, hyperreflexia, ataxia, tremors, seizures, and coma. Patients with hypotonic fluid losses will present with signs and symptoms of dehydration: tachycardia, hypotension, decreased skin turgor, dry mucous membranes, and thick, “doughy”-like skin (Kurtin, 2014d).

**Evidence-Based Interventions**

Managing hypernatremia consists of a two-pronged approach: (a) restoring the serum sodium to normal and (b) diagnosing and treating the underlying cause. Correction of hypernatremia generally begins with the calculation of total free water deficits to include predicted insensible water losses and other ongoing losses. Rapid correction of hypernatremia should be avoided because of the risk of CNS swelling and subsequent neurologic effects, including cerebral edema and subdural hemorrhaging (Semenovskaya et al., 2014). The general recommendation is to correct half the total free water deficit in the first 24–36 hours; however, correction of hypovolemia should occur at a rate no faster than a 1 mEq/L/hr decrease in serum sodium, up to a maximum decrease of 12 mEq/L in 24 hours (Kurtin, 2014d; Semenovskaya et al., 2014). It may take two to three days to correct the total free water deficit and restore sodium balance (Berendt & D’Agostino, 2005). In patients with chronic hypernatremia, correction may take longer in order to prevent any subsequent neurologic sequelae.

Sodium-containing medications should be minimized or eliminated, dietary sodium should be restricted, and free water intake should be encouraged, if possible. Serum electrolyte values should be checked frequently (every one to two hours initially) to monitor so-

<table>
<thead>
<tr>
<th>TABLE 13-8</th>
<th>Diagnostic Tests for Hypernatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test</strong></td>
<td><strong>Rationale and Findings</strong></td>
</tr>
<tr>
<td>Serum electrolytes (K⁺, Cl⁻, CO₂, Na⁺)</td>
<td>To determine hydration status and acid-base balance. Na⁺ = 150–170 mEq/L indicates dehydration. Na⁺ &gt; 170 mEq/L may indicate diabetes insipidus. Na⁺ &gt; 190 mEq/L may indicate long-term salt ingestion.</td>
</tr>
<tr>
<td>Blood urea nitrogen and creatinine</td>
<td>To determine kidney function and volume status. Increased in renal insufficiency and dehydration.</td>
</tr>
<tr>
<td>Urine: Na⁺, specific gravity, OsM</td>
<td>To help to determine volemic state and whether associated with renal or nonrenal losses, diabetes insipidus, or insensible free water losses. Urine Na⁺ &gt; 20 mEq/L and U/P OsM &gt; 0.7 = renal loss Urine Na⁺ &gt; 20 mEq/L and U/P OsM &lt; 0.7 = excessive water intake Urine Na⁺ &lt; 10 mEq/L and U/P OsM &gt; 0.7 = extrarenal loss Urine Na⁺ variable and U/P OsM &lt; 0.7 = CNS disease, AVP disorder</td>
</tr>
<tr>
<td>Serum glucose</td>
<td>To rule out hyperglycemia and diabetic ketoacidosis. Serum glucose may be elevated.</td>
</tr>
<tr>
<td>Computed tomography scan or magnetic resonance imaging (severe hypernatremia)</td>
<td>To rule out intracranial hemorrhaging or dural sinus thrombosis, or to identify a CNS cause for hypernatremia. CNS lesions, tumors, infection, or trauma may affect fluid regulation mechanisms.</td>
</tr>
</tbody>
</table>

AVP—arginine vasopressin; Cl⁻—chloride; CNS—central nervous system; CO₂—carbon dioxide; K⁺—potassium; mEq—milli-equivalent; Na⁺—sodium; OsM—osmolality; U/P—urine/plasma

*Note.* Based on information from Kurtin, 2014d; Semenovskaya et al., 2014.
diurn levels. Potassium may need to be added to the IV solutions to prevent potassium depletion. Strict monitoring of fluid I&O is critical (Berk & Rana, 2006).

The treatment for hypernatremia depends on the type of fluid volume state that accompanies the sodium imbalance. Treatment guidelines based on the three volume states are described in Figure 13-3.

**Expected Patient Outcomes**

Most patients survive an episode of hypernatremia. However, residual neurologic deficits have been reported in up to 30% of patients with acute hypernatremia (Semenovskaya et al., 2014). Patients with a serum sodium level greater than 180 mEq/L or who have too-rapid correction of hypernatremia often have residual CNS damage (Semenovskaya et al., 2014). Therefore, the goals of therapy are to detect hypernatremia quickly before sodium levels become greater than 160–170 mEq/L and to slowly correct elevated sodium levels to help prevent any residual neurologic sequelae.

**Patient Teaching Points**

Figure 13-4 describes teaching points that may be used to instruct patients on the management of hypernatremia.

**Hyponatremia**

**Overview**

*Hyponatremia* is defined as a serum sodium level less than 130 mEq/L and is the most common electrolyte imbalance among patients with cancer (Berendt & D’Agostino, 2005). It can occur as a result of diuretic therapies, abrupt withdrawal of steroids, development of SIADH or as a side effect of some chemotherapy drugs including cyclophosphamide and vincristine (Berendt & D’Agostino, 2005).

<table>
<thead>
<tr>
<th>FIGURE 13-3 Treatment Guidelines for Hypernatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypovolemic (water loss &gt; sodium loss)</strong></td>
</tr>
<tr>
<td>1. Treat dehydration:</td>
</tr>
<tr>
<td>Volume expansion with 0.9% NS until hemodynamically</td>
</tr>
<tr>
<td>stable (normal blood pressure and heart rate and</td>
</tr>
<tr>
<td>urine output &gt; 25 ml/hr).</td>
</tr>
<tr>
<td>2. Then, correct free water deficits orally or</td>
</tr>
<tr>
<td>by IV with hypotonic NS (0.45% in adults, 0.2% in</td>
</tr>
<tr>
<td>children) or with D$_5$W.</td>
</tr>
<tr>
<td><strong>Hypovolemic (excess sodium)</strong></td>
</tr>
<tr>
<td>1. Remove excess sodium: Use loop diuretics</td>
</tr>
<tr>
<td>(furosemide) combined with IV D$_5$W to replace</td>
</tr>
<tr>
<td>free water losses.</td>
</tr>
<tr>
<td>2. Avoid sodium in foods, medications, and fluids.</td>
</tr>
<tr>
<td>3. If the patient is in acute renal failure, may</td>
</tr>
<tr>
<td>need hemodialysis.</td>
</tr>
<tr>
<td><strong>Euvolemic (pure water loss)</strong></td>
</tr>
<tr>
<td>Correct free water deficits and excrete excess so-</td>
</tr>
<tr>
<td>dium by</td>
</tr>
<tr>
<td>1. Instructing the patient to drink increased</td>
</tr>
<tr>
<td>amount of water (preferred method), or</td>
</tr>
<tr>
<td>2. Administering IV fluids of D$_5$W.</td>
</tr>
<tr>
<td><strong>Central DI</strong></td>
</tr>
<tr>
<td>Replace ADH: Reduces free water loss and con-</td>
</tr>
<tr>
<td>centrates urine.</td>
</tr>
<tr>
<td>Medications:</td>
</tr>
<tr>
<td>1. Vasopressin (short-term use)</td>
</tr>
<tr>
<td>2. Desmopressin (long-term use)</td>
</tr>
<tr>
<td><strong>Nephrogenic DI</strong></td>
</tr>
<tr>
<td>Decrease urine volume:</td>
</tr>
<tr>
<td>1. Salt restrictions</td>
</tr>
<tr>
<td>2. Thiazide diuretics</td>
</tr>
<tr>
<td>3. Prostaglandin inhibitors</td>
</tr>
</tbody>
</table>

ADH—antidiuretic hormone; D$_5$W—dextrose 5% in water; DI—diabetes insipidus; NS—normal saline

Note. Based on information from Berendt & D’Agostino, 2005; Berk & Rana, 2006; Kurtin, 2014d; Semenovskaya et al., 2014.
Pathophysiology

When sodium levels drop in the fluid outside the cells, water shifts into the cells in an attempt to balance the intracellular and extracellular salt concentration. The result is cellular swelling and cerebral edema, which cause most of the symptoms of hyponatremia (MedlinePlus, 2013b; Schrier & Bansal, 2008; Simon, Hamrahian, & Teran, 2014). These CNS effects demonstrate the potential severity of this imbalance. Hyponatremia occurs in one of four volemic states (see Figure 13-5).

Clinical Assessment

Hyponatremia is confirmed by the history, physical examination, and baseline diagnostic laboratory studies. Initial laboratory studies are identified in Figure 13-6. Additional testing may be necessary to elucidate the underlying cause or rule out alternative issues. It is critical to determine serum sodium and osmolality and urine sodium and osmolality and to assess laboratory and clinical indicators of volume status to determine the nature of the sodium imbalance (Castillo, Vincent, & Justice, 2012).
A complete cancer history should be obtained, including any history of cancer or cancer therapy (e.g., surgery, radiation therapy, chemotherapy), supportive or concomitant medications, and the doses and dates of such therapies (Berendt & D’Agostino, 2005; Kurtin, 2014d). Other past medical history and comorbidities are important to note, as they may help distinguish the etiology of the sodium imbalance (Fojo, 2011). Presenting symptoms should be identified, along with any changes in the patient’s routines and abilities to perform activities of daily living. The underlying cause and onset of hyponatremia are the most important treatment indicators.

A thorough physical examination should be completed with special attention paid to (a) alterations in behavior and mental status, (b) hydration status, (c) vital signs, and (d) assessment of skin, cardiac, GI, and neurologic systems. Determining patients’ fluid volume status will help to distinguish the underlying cause and guide the appropriate intervention. For instance, hypovolemic patients with hyponatremia will present with dry mucous membranes, diminished skin turgor, tachycardia, orthostatic hypotension, and decreased weight because of increased loss of body fluids, whereas hypervolemic patients could present with signs and symptoms of fluid overload, including peripheral edema or ascites because of excess retention of sodium and free water (Schrier & Bansal, 2008; Simon et al., 2014).

### Clinical Manifestations

Signs and symptoms of hyponatremia range from mild or vague to severe and can vary according to degree and onset. Slow decreases in serum sodium may cause relatively few symptoms, whereas an acute decrease of the same magnitude can cause significant cerebral edema, coma, or even herniation of the brain stem and cardiopulmonary arrest (Schrier & Bansal, 2008). Sodium balance is critical to the maintenance of blood pressure, muscle function, and peripheral and central nervous function. Therefore, these systems are affected first in hyponatremia, causing early symptoms such as lethargy, confusion, headache, anorexia, nausea, and vomiting (Berendt & D’Agostino, 2005). As hyponatremia becomes more severe, muscle twitching, loss of reflexes, ataxia, delirium, and seizures may occur, which can lead to coma and death if not treated promptly (Kurtin, 2014d; Schrier & Bansal, 2008). Signs and symptoms are grouped according to severity in Figure 13-7.

### Evidence-Based Interventions

The interventions used to treat hyponatremia depend on the onset, duration, and severity of the imbalance. The focus of treatment is on the underlying cause of hyponatremia,
such as in cases of malignancy and SIADH, hypothyroidism, adrenal insufficiency, excessive fluid loss, or hyperglycemia.

Initial interventions are based on stabilizing patients’ sodium and water imbalance without adverse effects on the neurologic system. Sodium replacement must be done very carefully and slowly. If sodium levels rise too rapidly, osmotic demyelination syndrome could occur as a result of brain cell dehydration (Keenan, 2011). Corrections in serum sodium levels should proceed no faster than 0.5 mmol/L/hr or 8–10 mmol/L over 24 hours (Gross, 2012; Keenan, 2011; Spasovski et al., 2014). Restrictions of free water intake may be necessary. The administration of hypertonic IV saline (3% sodium) with diuresis may be indicated if severe or acute hyponatremia is present but should not exceed 1 ml/kg/hr (Kurtin, 2014d). Table 13-9 describes treatment recommendations based on the severity and type of hyponatremia.

Given the limitations and challenges of fluid restriction and the aforementioned pharmacologic interventions, a targeted approach at vasopressin antagonism is potentially beneficial in the treatment of hyponatremia. Few such drugs have been studied and approved by the U.S. Food and Drug Administration (FDA). Two vasopressin receptor antagonists, conivaptan and tolvaptan, have been FDA-approved for the treatment of euvolemic or hypervolemic hyponatremia (Castillo et al., 2012). They forgo the need for fluid restriction and typically do not deplete other electrolytes. However, they are only appropriate or effective for patients who are not volume depleted, and they have limited clinical evidence to support their use in the oncology population at this time (Aditya & Rattan, 2012). These drugs will be revisited later in this chapter in the section on SIADH.

With all cases of hyponatremia, nurses should monitor serial sodium levels, neurologic status, fluid I&O, and daily weights. They also should provide comfort measures secondary to restricted water intake (e.g., routine mouth care, lip care, ice chips as directed) and provide supportive care for patients who have an altered mental status or risk of seizures (Kurtin, 2014d; Myers, 2007).

**Expected Patient Outcomes**

The goal of treatment is to correct the sodium and fluid imbalance and treat any underlying causes. Patients will require frequent laboratory studies until the electrolyte balance is stable. Acute-onset hyponatremia, occurring in 48 hours or less, is less common but more dangerous than chronic or slowly developing hyponatremia, as this condition may overwhelm the body’s compensatory mechanisms and result in clinically significant sequelae (Simon et al., 2014).
### Treatment Recommendations for Hyponatremia

<table>
<thead>
<tr>
<th>Degree of Hyponatremia</th>
<th>Treatment Indications</th>
</tr>
</thead>
</table>
| **Mild/asymptomatic (hypervolemic)** | Maintain outpatient status, if possible.  
Restrict water intake (500–1,000 ml/day).  
Provide minimum level of sodium from 1–3 g/day.  
If imbalance is related to congestive heart failure, loop diuretics and an angiotensin-converting enzyme inhibitor may be used. |
| **Mild to moderate (hypovolemic)** | Correct or treat underlying cause (diarrhea, administration of chemotherapy).  
Restore fluid loss, usually with isotonic saline (0.9%) at recommended rate of 0.5–1 mEq Na⁺/L/hr until serum Na⁺ = 120 mEq/L, then reduce to 0.5 mEq/L/hr. |
| **Moderate** | Restrict fluids (500–1,000 ml/day).  
Discontinue medications, except chemotherapy, that may contribute to hyponatremia (e.g., diuretics).  
Give demeclocycline (600–1,200 mg/day) if not responsive to fluid restrictions. Acts by stimulating diuresis. Used mostly with chronic syndrome of inappropriate antidiuretic hormone (SIADH). Do NOT restrict fluids while on demeclocycline.  
Monitor renal and hepatic function.  
Consider other agents to treat chronic SIADH such as lithium, urea, and fludrocortisones. |
| **Severe/acute** | Continue water restrictions.  
Place patient in intensive care setting.  
Administer IV hypertonic saline (3% normal saline) at rate to increase Na⁺ level by 4–6 mEq/L over the first 1–2 hours; 8–10 mEq/L in the first 24 hours. Goal is to stop seizures, severe confusion, coma, and other serious conditions  
Give IV diuretics to increase water loss.  
Perform frequent urine and serum Na⁺ levels, electrolytes, and neurologic assessments.  
Give supplemental oxygen.  
Implement seizure precautions. |


### Patient Teaching Points

Figure 13-8 includes patient teaching points related to hyponatremia.

#### FIGURE 13-8 Teaching Points for Hyponatremia

- Patients should be able to identify and report the following.  
  - Signs and symptoms of hyponatremia, from mild to severe  
  - Any changes in weight, including loss or gain of more than 5% of body weight  
  - Any critical or sudden changes in their condition, including severe vomiting or diarrhea, presence of any mental status changes, and sudden changes in their urinary output or fluid intake  
- Nurses should be aware of specific cancers and chemotherapy treatments that may predispose patients to hyponatremia.  
- Patients may be on fluid restrictions or sodium dietary requirements. They should be able to read food and drink labels, identify the amount of sodium in each, and decide if the food is appropriate for them.

Note. Based on information from Berk & Rana, 2006; Myers, 2007.
Potassium Imbalances

Pathophysiology

Potassium is the most abundant intracellular cation. Very little potassium (2%–3%) is found in the extracellular fluids, where sodium is the major cation (Kurtin, 2014b). Potassium plays an integral role in cell membrane potential through the maintenance of sodium and potassium equilibrium via the sodium-potassium ATPase pump. The sodium-potassium pump, which is controlled by activation of insulin and beta-2 receptors, controls the intracellular to extracellular exchanges of potassium (Garth, 2014). This potassium balance is critical for nerve impulse transmission, muscle contraction, and cardiac function.

Imbalances in potassium are potentially life threatening and require immediate investigation and treatment. Long-term potassium balance is achieved through matching dietary intake and GI absorption with renal and nonrenal potassium losses (Garth, 2014; Kurtin, 2014b). The body is unable to store potassium; therefore, a minimum intake of 40–60 mEq/day of potassium must be acquired from nutrition. Foods rich in potassium include fruits (e.g., dates, cantaloupe, bananas), vegetables (e.g., avocados, potatoes, tomatoes), orange juice, nuts, whole grains, dairy products, and meats (Berendt & D’Agostino, 2005). Potassium excretion occurs primarily via the kidneys with a small amount eliminated by the gut and skin (Kurtin, 2014b). The regulation of renal elimination occurs at the collecting ducts of the kidneys where excretion is modulated by aldosterone receptors, changes in sodium or potassium levels, acid-base balances, rate of urine flow, and renal function (Lederer, Alsauskas, Mackelaite, & Nayak, 2014b).

Cellular balance of potassium is maintained constantly as a result of transmembrane shifts, which are regulated by several different factors. Serum potassium concentration reflects the amount of potassium that has moved between the intracellular and extracellular compartments but does not necessarily reflect the total body potassium stores. Therefore, an imbalance in cellular potassium levels can exist without a true change in absolute potassium stores. False imbalances in serum potassium level, termed pseudohyperkalemia or pseudohypokalemia, should be ruled out prior to initiating treatment to correct imbalances (Garth, 2014).

Hypokalemia

Overview

Hypokalemia is defined as a serum potassium level less than 3 mEq/L. (Berendt & D’Agostino, 2005). Although severe hypokalemia (less than 2.5 mEq/L) is relatively uncommon, up to 21% of hospitalized patients have potassium levels less than 3.5 mEq/L, and 5% have potassium levels less than 3 mEq/L (Lederer et al., 2014b). Up to 20%–50% of patients taking non–potassium-sparing diuretics become hypokalemic (Lederer et al., 2014b).

Hypokalemia usually results from multiple factors. Symptoms may be nonspecific and are predominantly related to cardiac or muscular dysfunction. Weakness and fatigue are the most common initial complaints. Patients who have hypertension or congestive heart failure, or take diuretics, are at increased risk for hypokalemia (Berendt & D’Agostino, 2005). Hypokalemia most often results from increased excretion of potassium. Increased renal potassium losses may occur as a result of drugs (e.g., potassium-wasting diuretics, some antibiotics), imbalances in other electrolytes (e.g., hypomagnesemia), renal tubular dysfunction, or other pathophysiologic disorders (Kurtin, 2014b). Hypokalemia also may occur as a result of poor intake or intracellular shifts of potassium (Kurtin, 2014b). If unidentified or un-
treated, severe hypokalemia can lead to paralysis, cardiac arrhythmias, and death. Specific causes of hypokalemia are described in Figure 13-9.

**Clinical Assessment**

Obtaining a thorough history and physical examination is important, as it often aids in identifying the most likely cause of the hypokalemia. Nurses should collect a history of any cancer diagnoses and all cancer treatments, a list of current prescribed and over-the-counter medications (i.e., diuretics, laxatives, digoxin, calcineurin inhibitors, nonsteroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme [ACE] inhibitors, antibiotics, dietary/herbal supplements), and past medical history including diabetes, kidney disease, GI disorders, congenital disorders, or hypertension. Any presenting symptoms should be identified, such as nausea, vomiting, polyuria, constipation, abdominal distension, muscle

<table>
<thead>
<tr>
<th>Decreased Intake</th>
<th>Renal and Nonrenal Losses</th>
<th>Redistribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Poor oral intake</td>
<td>• Increased excretion</td>
<td>• Cellular shifts</td>
</tr>
<tr>
<td>• Eating disorders such as bulimia or anorexia</td>
<td>• Renal losses</td>
<td>• Release of insulin—can cause a shift of K⁺ back into the cells, especially in diabetic ketoacidosis</td>
</tr>
<tr>
<td>• Alcoholism</td>
<td>– Renal tubular acidosis</td>
<td>• Acidosis—K⁺ moves out of cell in exchange for hydrogen, creating total body depletion of K⁺ as the kidneys continue to excrete K⁺</td>
</tr>
<tr>
<td>• Inability to chew or swallow</td>
<td>– Osmotic diuresis</td>
<td>• Metabolic or respiratory alkalosis—K⁺ loss caused by an increase in absorption of bicarbonate</td>
</tr>
<tr>
<td>• Poor nutritional intake</td>
<td>– Hyperaldosteronism</td>
<td></td>
</tr>
<tr>
<td>• Use of potassium (K⁺)-poor total parenteral nutrition or K⁺-free IV fluids</td>
<td>– Hypomagnesemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Hypovolemia</td>
<td></td>
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<tr>
<td></td>
<td>– Congenital disorders</td>
<td></td>
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<tr>
<td></td>
<td>– Adrenal disorders or adenomas</td>
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</tr>
<tr>
<td></td>
<td>– Leukemia—nonlymphocytic type</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Drug-related losses</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Diuretics (most common cause)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Insulin or glucose administration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Antibiotics—gentamicin, amphotericin B, carbenicillin</td>
<td></td>
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<tr>
<td></td>
<td>– Bicarbonate ingestion, infusions</td>
<td></td>
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<td></td>
<td>– Steroids</td>
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<td></td>
<td>– Aminoglycosides</td>
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<td></td>
<td>– Theophylline</td>
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</tr>
<tr>
<td></td>
<td>– Chemotherapy—cisplatin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Severe vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Diarrhea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Laxative abuse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Long-term use of suctioning or intestinal drainage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Positive for <em>Clostridium difficile</em> or GI candidiasis</td>
<td></td>
</tr>
</tbody>
</table>

Note. Based on information from Berendt & D’Agostino, 2005; Kurtin, 2014b; Lederer et al., 2014b.
weakness, leg cramps, palpitations, or fatigue (Kurtin, 2014b). Table 13-10 describes the tests to diagnose and identify the etiology of a low potassium level.

The physical examination should include assessment for changes in mental status or concentration, lethargy, fatigue, or confusion. Neuromuscular assessment should be done to identify paresthesias, myalgias, muscle weakness, hyporeflexia, tremor, or seizure (Berendt & D’Agostino, 2005; Kurtin, 2014b; Lederer et al., 2014b). In cases of severe hypokalemia, flaccid paralysis can occur. Cardiopulmonary examination should be performed, noting heart rate and rhythm. Initially, vital signs may be normal except for occasional tachycardia or tachypnea secondary to muscle weakness. The pulse may become weak and irregular, and hypotension (indicating diuretic or laxative use, bulimia, or tubular disorders) or hypertension (indicating primary aldosteronism, renal stenosis, or congenital or genetic hypertensive syndromes) can be present (Lederer et al., 2014b). If hypokalemia is severe, patients may develop ventricular fibrillation, respiratory paralysis, and cardiac arrest (Berendt & D’Agostino, 2005). Physical assessment also should include an abdominal examination to assess for decreased bowel sounds and abdominal distension as a result of decreased bowel motility.

### TABLE 13-10 Diagnostic Tests and Indications for Hypokalemia

<table>
<thead>
<tr>
<th>Test</th>
<th>Rationale and Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum electrolytes (sodium [Na⁺], potassium [K⁺], chloride [Cl⁻], magnesium [Mg²⁺], and carbon dioxide [CO₂])</td>
<td>K⁺: Decreased Na⁺: Low level indicates thiazide diuretic use or gastrointestinal (GI) volume depletion. High level could indicate nephrogenic diabetes insipidus or primary hyperaldosteronism. Mg²⁺: If low, correct for magnesium first, then reassess K⁺. CO₂: Check for alkalosis versus acidosis.</td>
</tr>
<tr>
<td>Arterial blood gas</td>
<td>pH: Assesses acid-base balance Acidosis: Suggests renal tubular acidosis, found with use of drugs such as amphotericin or gentamicin Alkalosis: Suggests vomiting, diuretics, mineralocorticoid excesses, or congenital disorders</td>
</tr>
<tr>
<td>Urine K⁺</td>
<td>&lt; 20 mEq/L suggests poor intake of K⁺, intracellular shifts, or GI loss. &gt; 40 mEq/L suggests renal loss of K⁺.</td>
</tr>
<tr>
<td>Urine Na⁺ and osmolality (OsM)</td>
<td>OsM: Urine concentration affects the true value and presence of urine K⁺ wasting. Na⁺: Helps refine results of urine K⁺ (high K⁺ and low Na⁺ indicates hyperaldosteronism)</td>
</tr>
<tr>
<td>24-hour urine K⁺ and creatinine</td>
<td>Helps to determine precise amount of K⁺ excretion over time; the kidneys are able to conserve up to 10–15 mEq/day of K⁺.</td>
</tr>
<tr>
<td>Blood urea nitrogen/creatinine</td>
<td>To assess kidney function: High with dehydration (GI and non-GI fluid and K⁺ losses), renal tubular damage</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>To identify any dysrhythmias: Flat T wave, ST depression, or U wave elevation may be seen with hypokalemia.</td>
</tr>
<tr>
<td>Glucose</td>
<td>Glucose tolerance can be impaired by long-term or severe K⁺ loss; insulin production causes K⁺ to shift intracellularly.</td>
</tr>
<tr>
<td>Digoxin levels (if applicable)</td>
<td>Decreased K⁺ increases risk of digitalis toxicity.</td>
</tr>
</tbody>
</table>

Note. Based on information from Berendt & D’Agostino, 2005; Kurtin, 2014b; Lederer et al., 2014b.
Evidence-Based Interventions

The goals of treatment are to determine the underlying cause of hypokalemia and restore the potassium balance to alleviate symptoms and prevent future toxicities. Treatment must be patient specific, accounting for rapidity of onset and severity of the potassium imbalance, with identification of risks through a history and physical assessment and management of conditions predisposing patients to potassium imbalance to prevent further episodes.

The initial step in treatment should be to identify and interrupt ongoing losses of potassium. This may be accomplished by (a) controlling diarrhea or vomiting, (b) discontinuing potassium-wasting medications if possible (e.g., diuretics) or transitioning to potassium-sparing medications (e.g., spironolactone, amiloride), (c) discontinuing laxatives, (d) restoring magnesium balance (if applicable), and (e) controlling hyperglycemia if present (Lederer et al., 2014b).

The second step of treatment should focus on repletion of potassium stores by rapidly raising the serum potassium to a safe range and then slowly replacing losses at a slower rate (Kurtin, 2014b). This may be accomplished with simple dietary replacement, although oral potassium supplements often are required in cases of mild to moderate (3–3.5 mEq/L) potassium losses. Potassium chloride is the supplement of choice, especially for those with preexisting alkalosis (Lederer et al., 2014b).

Oral potassium supplement doses are 20–40 mEq two to four times a day (Lederer et al., 2014b). An oral dose of 75 mEq potassium generally raises serum potassium by 1–1.4 mEq/L within 90 minutes (Kurtin, 2014b). Slow-release potassium chloride also may be given; these tablets should not be crushed or chewed. Potassium bicarbonate or potassium citrate tablets can be used in patients with metabolic acidosis or urinary stones, as they act as alkalinizing agents (Lederer et al., 2014b).

Oral potassium supplements are readily absorbed via the GI tract. The main side effects are related to GI irritation such as a bitter aftertaste, indigestion, or nausea and vomiting. The supplements should be given with a full glass of water with or just after meals to help prevent GI symptoms (Lederer et al., 2014b). Oral supplements can be given safely with concurrent IV replacement.

For patients with symptomatic or severe hypokalemia (potassium less than 2.5 mEq/L), those who cannot tolerate oral supplements, or those with coexisting cardiac arrhythmias, IV replacement is indicated. Oncology nurses should be aware of maximum infusion rates of IV potassium, which differ depending on whether patients have peripheral or central IV access. IV potassium is a vascular irritant; therefore, it should be diluted in normal saline and administered slowly (typically 10–20 mEq/hr). All IV potassium should be administered via a controlled infusion pump, and concentrations greater than 40 mEq/L must be administered through a central line to prevent phlebitis (Kurtin, 2014b); concurrent cardiac monitoring may be indicated. Potassium must never be given as an IV push, as overly rapid administration can be fatal (Kurtin, 2014b).

While correcting severe potassium imbalances, cardiac and renal function monitoring is crucial, most often in a critical care setting. Adequate renal function must be present to prevent overcorrection and to ensure that any excess potassium is excreted during supplementation. Serum and urine potassium should be monitored frequently during replacement until the patient is stabilized.

ACE inhibitors, angiotensin II receptor blockers, and selective aldosterone blockers may be useful in some patients, particularly those with congestive heart failure. These drugs decrease aldosterone secretion, thereby reducing renal potassium losses. They are often given concurrently with a low-sodium diet and potassium-sparing diuretics (Kurtin, 2014b; Lederer et al., 2014b). Concurrent potassium replacement with the use of ACE inhibitors and po-
Potassium-sparing diuretics can cause severe hyperkalemia; therefore, monitoring potassium levels is particularly important in that situation.

**Expected Patient Outcomes**

Quick identification and correction of potassium imbalances will minimize symptoms and reduce the risk of significant sequelae, most importantly the critical cardiac effects it can cause. Patients with hypokalemia may need only a simple correction of potassium related to poor intake, dehydration, or medication side effects. However, many potassium imbalances are related to complex medical conditions such as leukemia, acid-base imbalances, unstable diabetes, renal function abnormalities, adrenal carcinomas or metastasis, or congenital disorders. These complex conditions require close attention by nurses, effective patient education, and a collaborative approach by the multidisciplinary medical team.

Figure 13-10 describes important patient education points related to hypokalemia.

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**Hyperkalemia**

**Overview**

Hyperkalemia is an increase in serum potassium level and occurs in up to 8% of hospitalized patients (Garth, 2014). Mild hyperkalemia is a serum potassium level of 5.5–6 mEq/L; moderate hyperkalemia is 6.1–7 mEq/L; and severe hyperkalemia is defined as any serum level greater than 7 mEq/L (Garth, 2014). Mild hyperkalemia is generally asymptomatic and often well tolerated, but it must be managed to prevent continued increases to critical levels. If not recognized promptly and treated appropriately, severe hyperkalemia can result in cardiac arrest with a mortality rate up to 67% (Garth, 2014).

Hyperkalemia can occur as a result of increased potassium intake, decreased potassium excretion, cellular shifts of potassium into the extracellular spaces, or false indications of increased serum potassium, termed *pseudohyperkalemia* (Garth, 2014). Increased potassium intake may be in the form of (a) increased intake of potassium-rich foods such as bananas, oranges, tomatoes, and high-protein diets, (b) salt substitutes, which often contain high levels of potassium, and (c) use of potassium supplements, either oral or IV (for the treatment of hypokalemia), and total parenteral nutrition fluids (Lederer, Alsauksas, Mackelaite, & Nayak, 2014a).

The most common reason for hyperkalemia is decreased renal potassium excretion, which is most often secondary to acute or chronic renal failure. Decreased potassium excretion can result from acute or chronic renal insufficiency, glomerulonephritis or any other disease that affects the kidneys such as lupus, or medications that may decrease potassium excretion (e.g., ACE inhibitors, beta-blockers, potassium-sparing diuretics, NSAIDs, digoxin, cyclosporine, succinylcholine, digitalis glycoside, pentamidine) (Garth, 2014; Kurtin, 2014b). Older adults are at increased risk for hyperkalemia because of physiologic chang-
es of aging, comorbidities, and polypharmacy (McIntyre, Femenía, Arce, Pérez-Riera, & Baranchuk, 2011).

Additional causes of hyperkalemia include conditions that move potassium into extracellular spaces (e.g., trauma, burns, rhabdomyolysis, tumor lysis), extracellular shifts of potassium such as in acidosis or because of medication effects (e.g., digitalis toxicity), or pseudohyperkalemia resulting from incorrect collection or handling of blood specimens (e.g., poor venipuncture technique, errors in laboratory processing), leukocytosis, or thrombocytosis (Garth, 2014; Handy & Shen, 2005; Kurtin, 2014b).

Even small changes in extracellular potassium levels can have profound effects on the cardiac and neuromuscular systems. Patients with hyperkalemia may initially be asymptomatic or report vague symptoms of nausea, fatigue, muscle weakness, palpitations, or tingling (Garth, 2014). However, if hyperkalemia progresses, electrical conduction is affected, which can result in clinically significant ECG changes and can lead to cardiac arrest (Kee et al., 2010; Kurtin, 2014b). In rare cases, muscular paralysis also can occur as a result of suppressed electrical activity in the muscles.

**Clinical Assessment**

Identifying and monitoring patients who are at risk for hyperkalemia is important because hyperkalemia often can be asymptomatic or have vague clinical symptoms until it becomes severe; it is frequently identified as an incidental laboratory finding (Garth, 2014). Obtaining a thorough history that includes all current medications, supplements, any cancer diagnoses or cancer treatments, changes in activities of daily living, and past medical history is important in directing workup and management. Vital signs and complete physical examination should be completed, noting any signs or symptoms of hyperkalemia (see Clinical Manifestations). Neuromuscular and cardiorespiratory assessments are critical to identify potentially serious symptoms of a severe potassium elevation. Nurses should note any signs of recent trauma, which may provide information regarding the etiology of the imbalance.

Diagnostic tests for identifying the presence and cause of hyperkalemia are listed in Table 13-11. If hyperkalemia is suspected, an ECG should be performed to quickly identify any cardiac rhythm disturbances requiring intervention (Garth, 2014; McIntyre et al., 2011). Additional diagnostic tests may be needed if an underlying medical condition such as diabetes (i.e., glucose level), renal failure (i.e., BUN and creatinine), or mineralocorticoid deficiencies (i.e., cortisol and aldosterone levels) is suspected, or if medication toxicity from drugs such as digitalis (i.e., digoxin level) is suspected (Garth, 2014).

Determining whether an elevated potassium level reflects pseudohyperkalemia is essential to prevent unnecessary treatment and any potentially harmful consequences. If pseudohyperkalemia is suspected, plasma potassium levels should be drawn and serum potassium levels redrawn. Excessive trauma or probing, fist-clenching, or prolonged tourniquet application during venipuncture all may contribute to elevation of the potassium level in the blood sample and subsequent false diagnosis of hyperkalemia (Asirvatham, Moses, & Bjornson, 2013). The specimen must be collected in the correct tube and processed within 30 minutes of the blood draw, and the venipuncture site should not be near an infusion line. If pseudohyperkalemia is present, plasma potassium levels will be normal while serum potassium levels are elevated, and the patient will not exhibit clinical symptoms or ECG changes (Handy & Shen, 2005).

**Clinical Manifestations**

Physical symptoms of hyperkalemia often are vague until moderate or severe levels are reached. The most common symptoms, if present, are muscle weakness; tingling or twitching, paresthesias involving the face, tongue, feet, or hands; decreased deep tendon reflex-
es, generalized fatigue, palpitations, and increased bowel sounds with diarrhea, nausea, or vomiting. As hyperkalemia progresses, edema, oliguria, syncope, arrhythmias, bradycardia, weakening pulse, and ECG changes will develop (Berendt & D’Agostino, 2005; Garth, 2014; Kurtin, 2014b). In rare cases, ascending flaccid paralysis can occur, leading to cardiorespiratory collapse (Berendt & D’Agostino, 2005). A slow-rising potassium level may be tolerated more easily without presenting symptoms, whereas an abrupt rise is more likely to cause symptoms. Information obtained in the history and presenting clinical symptoms may help to identify the underlying medical condition contributing to the potassium imbalance (e.g., a patient with congestive heart failure who is on potassium-sparing diuretics; a patient who has had recent chemotherapy for leukemia).

### Evidence-Based Interventions

The initial goal of treatment is to protect the body from the effects of hyperkalemia, correct the potassium imbalance, and treat the underlying cause. If mild, asymptomatic hyperkalemia is present, patients may only require measures that lower the total body potassium, such as oral sodium polystyrene sulfonate (SPS) or a low-potassium diet. However, patients with symptomatic or moderate to severe hyperkalemia may require hospitalization for monitoring and management. Moderate to severe hyperkalemia can be identified by a rapid rise in serum potassium and/or potassium levels greater than 6 mEq/L, decreased renal function, the presence of significant acidosis, or ECG changes, which is a medical emergency (Hollander-Rodriguez & Calvert, 2006; Kurtin, 2014b). Urine and serum potassium, creatinine, and osmolality should be assessed prior to initiation of treatment that will significantly alter serum potassium levels (Hollander-Rodriguez & Calvert, 2006).

When moderate to severe or symptomatic hyperkalemia exists, the primary goals of treatment include the following.

- **Stabilize the myocardium:** Limit or antagonize cardiac effects. IV calcium gluconate (10 ml of 10% infused over two to three minutes) or calcium chloride (500–1,000 mg over 5–10 minutes) may be given as first-line treatment to those with ECG changes (e.g., widen-
ing of QRS interval, loss of P wave, cardiac arrhythmias) in the context of severe electrolyte imbalance (Garth, 2014; Kurtin, 2014b). Calcium gluconate is generally the preferred formulation; however, calcium chloride delivers three times the amount of calcium and may be used in cases of severe hyperkalemia with hemodynamic changes (Lederer et al., 2014a). IV calcium acts quickly to reduce the risk of ventricular fibrillation and can be life-saving. Serious drug interactions can occur with certain antibiotics, and IV calcium should be avoided in patients who may be experiencing digoxin toxicity (Garth, 2014).

• **Shift potassium intracellularly:** This can be accomplished using a few strategies. However, these only temporarily redistribute potassium into cells and do not clear excess potassium from the body.
  – Administer regular insulin (10 units IV) followed immediately by glucose (50 ml of 50% dextrose). Effects on serum potassium may occur as quickly as 20–30 minutes after infusion and can cause a reduction of 0.5–1.2 mEq/L. Nurses should monitor for hypoglycemia (Kurtin, 2014b).
  – A beta-2 antagonist such as nebulized albuterol, 10–20 mg in 4 ml normal saline, inhaled over 10 minutes, can reduce serum potassium by up to 0.5–1 mEq/L within 30 minutes. IV sodium bicarbonate may be used for hyperkalemic patients with severe acidosis; however, its use is controversial and its effects are variable, so it is no longer generally recommended (Kurtin, 2014b; Parham, Mehdirad, Biermann, & Fredman, 2006).

• **Increase potassium excretion.**
  – Increase renal excretion using potassium-wasting diuretics (i.e., loop and thiazide diuretics).
  – Stimulate GI excretion: SPS drives the exchange of sodium for potassium in the gut, resulting in fecal elimination of potassium. However, the use of SPS has been associated with the development of colonic necrosis, especially in patients with acute kidney injury, chronic kidney disease, or end-stage renal disease or those who are in the postoperative or post-transplant period (Harel et al., 2013). Colonic necrosis has been associated with the use of SPS in sorbitol (Harel et al., 2013). Nevertheless, SPS remains a mainstay in the management of hyperkalemia.
  – Hemodialysis may be required to rapidly correct life-threatening hyperkalemia or for patients in renal failure (Garth, 2014; Kurtin, 2014b).

**Expected Patient Outcomes**

If not treated promptly, hyperkalemia can result in cardiac arrest or death. Even small changes in potassium levels can cause severe effects on the cardiac and neuromuscular systems. The most important elements in achieving optimal patient outcomes are the performance of thorough patient assessment, identification of patients who are at risk for hyperkalemia, and prevention of potassium imbalance. Long-term treatments should be directed to the cause of the imbalance such as treatment of renal failure, dietary changes, or medication management.

Patient teaching points relevant to hyperkalemia are presented in Figure 13-11.

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**FIGURE 13-11 Teaching Points for Hyperkalemia**

- Encourage a low-potassium diet, and review potassium-rich foods to minimize.
- Educate patients with a history of hyperkalemia or chronic renal failure to avoid salt substitutes as part of a low-salt diet.
- Instruct patients that follow-up may be required to monitor potassium levels, as well as calcium and magnesium if they are taking sodium polystyrene sulfonate, as it decreases these levels.
- Educate patients on the side effects of diuretic use.

*Note. Based on information from Kurtin, 2014b; Lederer et al., 2014a.*
Magnesium Imbalances

Pathophysiology

Magnesium is the second most abundant intracellular cation, with 99% of the body’s magnesium being intracellular: approximately 50%–60% is stored in the bone, 20% in muscle, and 20% in the liver and soft tissues (Fulop & Agarwal, 2013; Kurtin, 2014c). This leaves approximately 1% in the extracellular fluid. Of this extracellular magnesium, 30% is bound to protein, while 60% is ionized, or “free,” in the serum (Kurtin, 2014c). Normal serum levels should be 1.8–3 mg/dl (Kee et al., 2010; Kurtin, 2014c).

Magnesium is important in a large number of cellular and enzyme reactions, including DNA and protein synthesis, ATP activation and production, nerve impulse transmission, and hormone modulation (Fulop & Agarwal, 2013; Kurtin, 2014c). Magnesium helps to regulate calcium absorption and contributes to the structural integrity of bones and teeth. It is necessary for proper heart cell function, playing an important role in the polarization function of the sodium-potassium ATPase pump, regulating intracellular potassium, and ultimately regulating heart muscle contraction. Neuromuscular effects of magnesium include neural transmission in the CNS, a smooth muscle relaxation effect in the periphery, and impact on myocardial contractility (Kee et al., 2010; Kurtin, 2014c).

The daily dietary requirement of magnesium is approximately 300 mg (Kurtin, 2014c; Novello & Blumstein, 2012). Magnesium can be found naturally in green leafy vegetables (i.e., chlorophyll-containing foods), various fruits, cocoa derivatives, legumes, nuts, seeds, whole wheat, and certain seafood (Fulop & Agarwal, 2013). Thirty percent to 40% of dietary magnesium is absorbed, primarily by the ileum of the small intestine. The remaining unabsorbed magnesium is excreted through the feces (60%) and kidneys (40%) (Kurtin, 2014c). However, the regulation of serum magnesium, via excretion or absorption, is controlled mainly by the renal system, with 60%–70% of exchange occurring at the thick ascending limb of the loop of Henle (Fulop & Agarwal, 2013; Kurtin, 2014c; Novello & Blumstein, 2012). Overall magnesium balance is maintained by renal excretion, intestinal uptake, and exchange in the bone (Kurtin, 2014c).

Hypomagnesemia

Overview

Magnesium deficiencies are generally caused by GI malabsorption, increased renal excretion, insufficient dietary intake, shifts in skeletal magnesium, or other electrolyte imbalances (Kurtin, 2014c). Magnesium imbalances rarely occur alone and usually are accompanied by imbalances in calcium, potassium, and phosphorus. For example, reductions in serum potassium (40%–60%), phosphorus, or sodium often coexist with hypomagnesemia (Fulop & Agarwal, 2013). Low serum magnesium levels impair the release of or sensitivity to PTH in the bones and kidneys and can cause hypocalcemia; this is a classic finding with severe hypomagnesemia (Suneja & Muster, 2014).

Hypomagnesemia is common, found in 10%–20% of hospitalized patients and up to 60% of intensive care unit patients (Fulop & Agarwal, 2013). It is common among alcoholics (20%–30%) and diabetics (13%–47%) (Fulop & Agarwal, 2013; Kurtin, 2014c). Hypomagnesemia is defined as a serum magnesium level less than 1.5 mEq/L (approximately 1.8 mg/dl). It is generally related to inadequate intake, impaired GI absorption (e.g., celiac disease, inflammatory bowel disease, surgical resection of distal small intestine, diabetes), GI losses (e.g., diarrhea), or renal losses (e.g., impaired absorption, renal magnesium wasting) (Kurtin, 2014c).
In patients with cancer, hypomagnesemia is most often related to renal losses induced by administration of various chemotherapy drugs, most commonly cisplatin. 5-Fluorouracil/leucovorin combinations, cetuximab, panitumumab, and decitabine (approved for myelodysplastic syndrome) also can cause a decrease in magnesium levels. Other drug-related causes include diuretics (especially loop diuretics because of their action in the loop of Henle), antibiotics (e.g., aminoglycosides, amphotericin B, pentamidine), cyclosporine, digitalis, or fluoride poisoning (Kee et al., 2010; Kurtin, 2014c). More recently, proton pump inhibitors have been associated with low serum magnesium (Fulop & Agarwal, 2013; Kurtin, 2014c).

**Clinical Assessment**

Nurses should obtain a thorough history that includes nutritional assessment, history of alcohol intake, and past medical and surgical history including diabetes, cardiac conditions, endocrine disorders, and GI or kidney disorders. A current list of all medications should be obtained, paying special attention to antibiotics, chemotherapy drugs (especially cisplatin), heart medications such as digitalis, and use of diuretics, especially loop or thiazide diuretics, as well as any exposure to or ingestion of fluoride. Diagnostic laboratory values for hypomagnesemia are described in Table 13-12.

The physical examination for hypomagnesemia should include neurologic and neuromuscular evaluation, noting mental status and looking for confusion, mood changes, vertigo, nystagmus, tetany-like symptoms, or hyperreflexia, and assessment for positive Chvostek or Trousseau signs (Kee et al., 2010; Kurtin, 2014c). Vital signs and a cardiac examination should be performed, looking for dysrhythmias and hypertension.

**Clinical Manifestations**

Signs and symptoms of hypomagnesemia may take several weeks to develop and often are similar to those of other electrolyte abnormalities, including hypocalcemia (Fulop & Agarwal, 2013). Clinical effects are exhibited primarily as signs and symptoms of CNS hypersensi-

<table>
<thead>
<tr>
<th>TABLE 13-12</th>
<th>Diagnostic Tests for Hypomagnesemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnostic Test</strong></td>
<td><strong>Findings/Indicators</strong></td>
</tr>
<tr>
<td>Serum magnesium (Mg(^{2+})), calcium (Ca(^{2+})), potassium (K(^{+})), and phosphorus</td>
<td>A total body Mg(^{2+}) deficit can be present with a normal serum Mg(^{2+}). An ionized serum Mg(^{2+}) level is recommended. Any low serum Mg(^{2+}) level indicates a clear Mg(^{2+}) deficiency. K(^{+}), Na(^{+}), and phosphorus may be decreased. Ca(^{2+}) may be increased or decreased.</td>
</tr>
<tr>
<td>Blood urea nitrogen and creatinine</td>
<td>To assess kidney function</td>
</tr>
<tr>
<td>Urine Mg(^{2+})</td>
<td>May indicate deficiencies from renal losses</td>
</tr>
<tr>
<td>Protein levels</td>
<td>To aid in interpreting “true” Mg(^{2+}) level, because some extracellular Mg(^{2+}) is bound to protein</td>
</tr>
<tr>
<td>Glucose, parathyroid hormone, and aldosterone levels</td>
<td>To determine link to diabetes or endocrine disorders Increases in aldosterone cause renal loss of Mg(^{2+})</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>To assess for cardiac arrhythmias and ventricular tachycardia; may be nonspecific to include ST segment depression, altered T waves, or loss of voltage</td>
</tr>
</tbody>
</table>

tivity, neuromuscular irritability, and cardiac arrhythmias. Early symptoms may include painful muscle cramps, nausea, vomiting, lethargy, and mental confusion and can develop into more significant neuromuscular abnormalities, decreased respiratory effort, and seizures when magnesium levels are less than 1 mEq/L (Fulop & Agarwal, 2013; Kurtin, 2014c).

Evidence-Based Interventions

Treatment should be directed toward identifying and treating or removing any underlying cause of hypomagnesemia (e.g., chronic diarrhea, recent chemotherapy treatments with cisplatin or cetuximab) and correcting the resultant magnesium levels, as well as any other electrolyte abnormalities. As with most other electrolyte abnormalities, the appropriate intervention depends not only on the severity of the imbalance but also the rapidity of onset.

Mild hypomagnesemia (i.e., serum magnesium levels between 1.2 mg/dl and the lower limit of institutional normal) can be treated with increased dietary magnesium and oral magnesium replacement (i.e., magnesium oxide, magnesium gluconate) as long as the patient is asymptomatic. Prescribed doses vary depending on the formulation and patient needs. Absorption of oral preparations is variable, generally around 30% (Fulop & Agarwal, 2013). Patients with normal renal function generally will excrete any excess magnesium without any problems; therefore, renal function should be assessed prior to replacement therapy to ensure safety of renal clearance. In cases of renal impairment, doses should be decreased and patients should be monitored closely. The main side effect of oral replacement therapy is diarrhea. Divided doses may decrease the incidence of diarrhea, and adequate hydration should be maintained.

Moderate to severe hypomagnesemia (serum magnesium levels less than 1.2 mEq/L or symptomatic) should be treated with IV magnesium replacement such as magnesium sulfate. IV replacement is the most common modality in oncology (Kurtin, 2014c). For asymptomatic hypomagnesemia, 4 g of magnesium sulfate in 250–500 ml of diluent can be infused over four to six hours. Stable but symptomatic hypomagnesemia should be corrected with an initial infusion of 2 g magnesium sulfate in 100 ml of diluent over 20 minutes, followed by 4 g in 250 ml over two to four hours. For unstable, symptomatic hypomagnesemia, 2 g of magnesium sulfate in 20 ml normal saline should be infused over two minutes, followed by the treatment detailed for stable but symptomatic imbalance (Kurtin, 2014c). The IV infusion rate should never exceed 1.2 mEq/min, as rapid IV administration can be life threatening, causing sudden hypotension, hypermagnesemia, and hypocalcemia. Other common issues with IV magnesium infusion include facial flushing and decreased deep tendon reflexes (Kurtin, 2014c). It is important to continue monitoring serum magnesium and renal function during repletion.

It may take several days to correct intracellular magnesium imbalances. Continuous IV magnesium infusions may be recommended until symptoms resolve. IV maintenance doses typically are 30–60 mg/kg/day (Fulop & Agarwal, 2013). Slow-release magnesium also may be helpful in elevating intracellular magnesium levels.

Magnesium sulfate infusions may be given to replace magnesium from renal wasting associated with chemotherapy regimens. It often is standard procedure to administer magnesium-containing prehydration and posthydration infusions for patients receiving platinum agents. Oncology nurses should be aware of this treatment indication.

Expected Patient Outcomes

Once the cause of hypomagnesemia has been identified, symptoms generally are reversible and patients have a very good prognosis. Symptoms of hypomagnesemia often are non-
specific and rarely occur in isolation of other electrolyte disturbances. Primary nutritional
deficiencies, alcoholism, malnutrition or malabsorption, renal deficiencies, drug interac-
tions, and endocrine disorders should all be considered as risk factors for electrolyte imbal-
ances, including hypomagnesemia.

Figure 13-12 lists important patient teaching points for hypomagnesemia.

<table>
<thead>
<tr>
<th>FIGURE 13-12</th>
<th>Teaching Points for Hypomagnesemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High intakes of calcium, vitamin D, and protein may increase the requirement for magnesium.</td>
<td></td>
</tr>
</tbody>
</table>
| • Several chemotherapy regimens may predispose patients to magnesium losses (e.g., cisplatin, cetux-
imab). Patients should be educated about the early signs and symptoms of hypomagnesemia to report to |
| the healthcare team. |
| • Proper nutrition, including consuming foods high in magnesium, decreasing or ceasing alcohol consump-
tion, and controlling diabetic conditions, are all important in the control of magnesium levels. |
| • Diarrhea is the primary side effect of oral magnesium supplementation and should be reported to the |
| healthcare team if it develops. |

Note. Based on information from Chen et al., 2013.

**Hypermagnesemia**

**Overview**

Hypermagnesemia occurs with serum magnesium levels greater than 2.5 mEq/L (ap-
proximately 3.0 mg/dl) (Kee et al., 2010). Hypermagnesemia is an uncommon electrolyte
imbalance because the kidneys are generally very effective at eliminating excess magne-
sium by regulating renal tubular reabsorption (Fulop, Agraharkar, Workeneh, & Fahlen,
2014). Magnesium is absorbed via the GI tract and excreted primarily in the urine and
stool. Elevated magnesium levels are found most often in patients with acute or chronic
renal disease (most commonly, end-stage renal disease), especially in the absence of di-
alysis (Fulop et al., 2014; Novello & Blumstein, 2012). Hypermagnesemia may also result
from the following.

• Increased intake or absorption: Dietary magnesium, antacids, laxatives (milk of magne-
sia), enemas, excessive amount or rate of IV magnesium repletion, increased GI absorp-
tion due to slowed GI motility (e.g., narcotics, anticholinergics, bowel obstruction, chronic
constipation)

• Drug effects (e.g., lithium, which decreases renal magnesium excretion)

• Medical conditions (e.g., GI disorders, hypothyroidism, adrenal insufficiency, diabetic ke-
toacidosis, tissue breakdown or rapid cell destruction) (Fulop et al., 2014; Kee et al., 2010;
Kurtin, 2014c)

**Clinical Assessment**

The patient history and assessment should focus on identifying the reason for the in-
creased magnesium levels. It should include a history of any cancer and chemotherapy
treatments; a list of current medications, especially narcotics, anticholinergics, or mag-
nesium supplements; changes in bowel habits or chronic bowel disease, including any
use of antacids or laxatives; and evaluation of kidney function and current hydration sta-
tus. Any recent hospitalizations should be identified, especially those that involved treat-
ment for hypomagnesemia or other electrolyte imbalances, intensive care unit stays,
or prescription of magnesium supplementation at discharge. The diagnostic tests de-
scribed in Table 13-13 will aid in the diagnosis and determination of the cause for hypermagnesemia.

The physical examination should include neurologic assessment to evaluate mental status, alertness, reflexes, and pupillary responses. Cardiac examination should include vital signs to identify hypotension or bradycardia, with consideration of ECG to identify clinically significant ECG changes or arrhythmias.

**Clinical Manifestations**

Laboratory assessments may demonstrate elevated serum magnesium, as well as myriad other electrolyte abnormalities. Renal function laboratory values may be abnormal. Delays in clotting time through interference with thrombin formation and clumping of platelets also may be observed (Fulop et al., 2014; Novello & Blumstein, 2012).

Physical manifestations of hypermagnesemia generally result from the effects of excess magnesium on neuromuscular, cardiac, and central nervous systems. Although symptomatic hypermagnesemia is rare, presenting early symptoms (with magnesium levels of 2–4 mEq/L) are nausea, vomiting, sweating, confusion, muscle weakness, and a reduction in deep tendon reflexes. As magnesium levels increase, progressive muscle weakness may develop, and vasodilation and hypotension may occur. At higher magnesium levels (greater than 8 mEq/L), flaccid paralysis can develop, proceeding to respiratory paralysis, arrhythmias, heart block, and eventually asystole, coma, or death (Novello & Blumstein, 2012).

**Evidence-Based Interventions**

Identification of risk factors and preventive strategies should be the initial intervention for patients prone to hypermagnesemia, such as those receiving magnesium repletion, patients with cancer, and those who have impaired renal function. Discontinuing magnesium supplements, reducing intake of magnesium-rich foods, and avoiding magnesium-containing laxatives or antacids can often correct mild hypermagnesemia. Further treatment for hypermagnesemia depends on the presence of symptoms, renal impairment, and the serum magnesium level.

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Findings/Indicators</th>
</tr>
</thead>
</table>
| Serum electrolyte panel to include magnesium (Mg$^{2+}$), potassium (K$^+$), calcium (Ca$^{2+}$), and phosphate (PO$_4^-$) | Will often find hyperkalemia and hypercalcemia with elevated Mg$^{2+}$.
If associated with tumor lysis syndrome, will find hyperkalemia, hyperuricemia, hyperphosphatemia, and resultant hypocalcemia |
| Platelet count and thrombin time | Increased Mg$^{2+}$ levels can be associated with delayed thrombin formation and platelet clumping. |
| Blood urea nitrogen and creatinine, creatinine clearance | To assess kidney function.
Serum Mg$^{2+}$ rises when creatinine clearance levels are less than 30 ml/min. |
| Arterial blood gas | May reveal respiratory acidosis with hypermagnesemia |
| Thyroid function tests | Hypothyroidism can be rare cause of hypermagnesemia. |
| Electrocardiogram | To assess for cardiac arrhythmias and bradycardia; generally nonspecific but may show prolongation of PR intervals |

*Note. Based on information from Fulop et al., 2014; Novello & Blumstein, 2012.*
The use of IV hydration for volume expansion with diuresis is the recommended treatment for moderate hypermagnesemia; however, this strategy should only be employed in patients with normal renal function (Chang, Radin, & McCurdy, 2014). Isotonic IV fluids (normal saline or lactated Ringer’s solution) work by diluting the extracellular magnesium, and diuretics (e.g., furosemide) act to promote the renal excretion of magnesium at the loop of Henle. IV fluid rates will vary depending on the patient’s fluid status and comorbidities (e.g., congestive heart failure). Diuretics (e.g., furosemide 20–80 mg PO or IV daily) should be given in divided doses (Kurtin, 2014c). Close monitoring of cardiovascular, pulmonary, and renal function is necessary. IV fluids and diuretics should be stopped when the desired response is obtained or if pulmonary edema develops.

For patients with severe or life-threatening symptomatic hypermagnesemia, calcium gluconate may be administered. It acts as a direct antagonist for the neuromuscular and cardiovascular effects of magnesium and should be reserved for patients with cardiac effects or respiratory distress from hypermagnesemia (Novello & Blumstein, 2012). The recommended dose is 1 g of 10% calcium infused over two to five minutes, repeating if needed after five minutes has elapsed (Kurtin, 2014c). Calcium gluconate is contraindicated in patients on digitalis and those with respiratory failure, acidosis, or severe hyperphosphatemia (Novello & Blumstein, 2012).

A renal consult is necessary for patients with renal impairment. Dialysis may be indicated if the patient is in renal failure (Kurtin, 2014c).

**Expected Patient Outcomes**

Sudden elevations of magnesium are more likely to produce symptoms of hypermagnesemia than slow rises. The degree and severity of symptoms will have a direct effect on the outcome of treatment. However, prompt treatment of the underlying cause, appropriate supportive care, and correction of serum magnesium levels can produce a positive outcome in most patients. Patients with end-stage renal disease may continue to need dialysis and require close monitoring and management.

Figure 13-13 describes teaching points that may be helpful for patients with hypermagnesemia.

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**FIGURE 13-13 Teaching Points for Hypermagnesemia**

- Identify foods high in magnesium, which may need to be avoided, such as green leafy vegetables, chlorophyll-containing foods, various fruits, cocoa derivatives, nuts, wheat, seafood, and meat.
- Instruct patients to notify the healthcare team of severe constipation, nausea, vomiting, poor appetite, and any progressing muscle weakness.
- Follow-up electrolyte laboratory values will be necessary, with frequency based on patients’ overall status and other contributing medical problems.

*Note. Based on information from Fulop & Agarwal, 2013; Kurtin, 2014c; Novello & Blumstein, 2012.*

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**Syndrome of Inappropriate Antidiuretic Hormone**

**Overview**

SIADH can present as a life-threatening oncologic emergency. It is rare in patients with cancer, developing in 1%–2% of all people with neoplasms (Pelosof & Gerber, 2010). How-
ever, approximately two-thirds of all patients diagnosed with SIADH will have a neoplasm (Myers, 2007). The most common malignancy associated with SIADH is lung cancer, specifically, small cell lung cancer. As many as 15%–50% of patients with small cell lung cancer will develop SIADH (Keenan, 2011). Other cancers associated with SIADH include cancers of the head and neck, esophagus, prostate, pancreas, bladder, breast, ovaries, genitourinary tract, skin, CNS, or duodenum, as well as lymphoma, thymoma, acute myeloid leukemia, and sarcomas (Keenan, 2011; Shelton, 2014).

SIADH is an endocrine-related syndrome causing an abnormal production or secretion of AVP, or ADH. Normally, the posterior pituitary gland releases ADH in response to increased plasma osmolality or decreased plasma volume and sends signals to the collecting ducts of the kidneys to reabsorb water, concentrating the urine and normalizing serum osmolality (Shelton, 2014). SIADH is characterized by the production or secretion of ADH despite normal or low osmolality, resulting in an inappropriate reabsorption of free water by the kidneys (Keenan, 2011). The result is a hallmark syndrome of euvolemic hyponatremia, increased urine osmolality, decreased plasma osmolality, and urine sodium elevation (Keenan, 2011; Pelosof & Gerber, 2010; Thomas & Fraer, 2014). In SIADH, hyponatremia is a direct result of excess water, not a deficiency in sodium. The presence of a euvolemic state, consistent with SIADH, is supported by the absence of edema or alterations in hemodynamic status and renal, thyroid, adrenal, and hepatic function (Pelosof & Gerber, 2010; Thomas & Fraer, 2014). The mechanisms and systemic effects of SIADH are described in Table 13-14.

**Pathophysiology**

Three pathophysiologic mechanisms generally are responsible for the inappropriate secretion of ADH. The first is primary inappropriate secretion of ADH from the hypophyseal system within the hypothalamus, such as with CNS disorders, head trauma, brain tumor, CNS hemorrhage, shock, stroke, or any other condition causing an increase in intrathoracic pressure or a decrease in venous return. The second mechanism is ADH or ADH-like substances being secreted by cells outside of the hypophyseal system, referred to as ectopic secretion. This is the primary reason for cancer-related SIADH. The third pathophysiologic mechanism is enhanced release or activity of ADH on the renal tubules caused by various drugs such as narcotics, nicotine, diuretics, tricyclic antidepressants, antipsychotics, barbiturates, chlorpropamide, selective serotonin reuptake inhibitors, NSAIDs, ACE inhibitors,

| TABLE 13-14 Systemic Effects of Syndrome of Inappropriate Antidiuretic Hormone |
|-----------------------------|-----------------------------|
| **Mechanism of Action**     | **Resulting Effect**        |
| Increased water reabsorption by renal tubules | Decreased serum osmolality; hyponatremia |
| Decreased excretion of water by renal tubules | Increased urine osmolality |
| Increased total water in intra- and extracellular fluids | Decreased serum osmolality |
| Decreased sodium plasma concentration secondary to excess water | Hyponatremia |
| Increased urine concentration | Increased urine osmolality |
| Increased sodium secretion by kidneys | Increased urine sodium |

*Note. Based on information from Keenan, 2011; Shelton, 2014.*
and carbamazepine (Keenan, 2011; Thomas & Fraer, 2014). Various anticancer agents can produce the same effect, including cisplatin, alkylating agents (e.g., cyclophosphamide, ifosfamide, melphalan), vinca alkaloids, and interferons (Keenan, 2011; Myers, 2007; Shelton, 2014). Cancer- and cancer therapy–related symptoms including pain, stress, and pulmonary disease (e.g., pneumonia) have been associated with the development of SIADH (Keenan, 2011).

**Clinical Assessment**

A thorough clinical history and physical examination should be performed to determine whether patients are experiencing true SIADH versus another form of hyponatremia or electrolyte imbalance. Obtaining a history related to the diagnosis and type of cancer or recent cancer treatments is important. Any ongoing side effects, current medications, presenting symptoms, and changes in activities or mental status should be noted, as well as a history of fluid I&O within the past 24 hours. A pulmonary assessment is important to identify any infection or pulmonary disease processes, as is a neurologic examination to identify any changes in level of consciousness or loss of deep tendon reflexes (Gobel, 2005; Shelton, 2014). SIADH is diagnosed based on the combination of the following: (a) hyponatremia (less than 135 mEq/L) with normal or increased intravascular volume, (b) decreased plasma osmolality (less than 275 mOsm/kg), (c) increased urine osmolality (greater than 100 mOsm/kg), and (d) increased urine sodium (Keenan, 2011). The tests described in Table 13-15 should be obtained to determine the diagnosis of SIADH.

**Clinical Manifestations**

Clinical signs and symptoms of SIADH are similar to those for general hyponatremia (see Figure 13-7) and are directly related to the rate of onset and the severity of hyponatremia, as well as the degree of water intoxication. In mild or chronic cases, patients may be asymptomatic. With an acute onset (typically defined as within 48 hours) or with a severe drop in

### TABLE 13-15 Diagnostic Tests for Syndrome of Inappropriate Antidiuretic Hormone

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Findings/Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum electrolytes and osmolality</td>
<td>Serum sodium (Na⁺) and OsM (&lt; 275 mOsm/kg): Decreased</td>
</tr>
<tr>
<td>(OsM)</td>
<td>Serum potassium (K⁺) and bicarbonate levels: Normal</td>
</tr>
<tr>
<td></td>
<td>Serum phosphorus: May be decreased</td>
</tr>
<tr>
<td>Urine Na⁺, OsM, and specific gravity</td>
<td>Urine Na⁺ &gt; 30 mEq/L</td>
</tr>
<tr>
<td></td>
<td>Urine OsM &gt; 100 mOsm/kg</td>
</tr>
<tr>
<td></td>
<td>Urine specific gravity: Increased &gt; 1.015</td>
</tr>
<tr>
<td>Blood urea nitrogen (BUN), creatinine,</td>
<td>All may be decreased</td>
</tr>
<tr>
<td>and uric acid</td>
<td></td>
</tr>
<tr>
<td>Renal, thyroid, and adrenal function</td>
<td>Will be normal with syndrome of inappropriate antidiuretic hormone</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>To identify any tumors or pulmonary disease</td>
</tr>
<tr>
<td>Computed tomography scan of head</td>
<td>To evaluate for anatomic lesions or evidence of cerebral edema</td>
</tr>
</tbody>
</table>

*Note.* Based on information from Gobel, 2005; Gross, 2012; Keenan, 2011; Myers, 2007; Shelton, 2014.
serum sodium level (less than 110–125 mEq/L), SIADH symptoms will be related to neurologic effects and will present as an acute emergency.

SIADH usually presents with a normal blood pressure and pulse, normal skin turgor with moist mucous membranes, and little to no peripheral edema. Patients with SIADH may present with vague symptoms including thirst, anorexia, nausea, vomiting, fatigue, oliguria (less than 400 ml/24 hours of urine), incontinence, and weight gain. They may have hypoactive reflexes, muscle weakness, myoclonus, tremors, and an unsteady gait. Left untreated, these symptoms could lead to seizures, coma, and eventually death (Myers, 2007; Shelton, 2014).

Evidence-Based Interventions

Treatment for SIADH differs slightly from that for other types of hyponatremia because it occurs in a euvolemic state; therefore, volume expansion should be avoided. The only curative intervention is to determine and treat or remove the underlying cause (e.g., tumor) (Keenan, 2011; Myers, 2007). Some chemotherapy agents (e.g., cyclophosphamide, cisplatin) may cause or exacerbate SIADH, especially when aggressive hydration is required. Hydration with normal saline may need to be given sparingly, with the additional use of furosemide and electrolyte replacement. If the SIADH is severe, the sodium level and neurologic complications will need to be stabilized before initiation of any chemotherapy treatments (Gobel, 2005).

The treatment approach for SIADH should be based on correcting the hyponatremia as defined previously in Table 13-9. It is recommended that serum sodium correction not exceed a rate of 0.5 mmol/L/hr, or 8–10 mmol/L in 24 hours, to prevent serious clinical sequelae of rapid correction such as osmotic demyelination syndrome (Gross, 2012; Keenan, 2011).

Patients with mild to moderate hyponatremia (131–134 mEq/L) generally are asymptomatic. Fluid restrictions of 500–1,000 ml/day will promote a negative water balance, and nurses should monitor for correction of plasma sodium levels within three to five days (Keenan, 2011; Myers, 2007). It is imperative to identify and discontinue (if possible) any offending medications while prioritizing initiation or continuation of treatment for the underlying cause (e.g., chemotherapy).

Mild to moderate hyponatremia may be chronic in nature. Nurses should anticipate possible use of demeclocycline (a tetracycline antibiotic) at doses of 600–1,200 mg/day in divided doses if fluid restriction is intolerable or ineffective (Gross, 2012; Keenan, 2011). Demeclocycline acts by inhibiting the action of ADH on the renal tubules, causing a nephrogenic form of diabetes insipidus to increase free-water excretion. Time to effect can be as long as two to four days (Gross, 2012). Fluid restriction is not required in patients receiving demeclocycline. This medication should not be taken with food. Side effects generally are mild but may include nausea, photosensitivity, nephrotoxicity, and reversible azotemia (Ghali, Farah, Daifallah, Zabalawi, & Zmily, 2009).

Severe hyponatremia (less than 120 mEq/L) usually develops rapidly. Severe, symptomatic, acute hyponatremia requires initiation of seizure precautions with intensive inpatient monitoring and management. Treatment includes fluid restriction or, in some emergent cases, the administration of IV hypertonic (3%) saline. This strategy may require concurrent administration of loop diuretics and poses the risk for excessively rapid correction of hyponatremia (Gross, 2012); therefore, laboratory and neurologic assessment should be conducted very frequently. The same precautions for the treatment of severe hyponatremia should be followed (see Table 13-9). In cases of symptomatic or severe hyponatremia, an initial correction rate of 1–2 mmol/L/hr is acceptable, not to exceed 8–10 mmol/L in 24 hours.
Two AVP-receptor antagonists, termed *vaptans*, have been developed and FDA-approved for the treatment of euvoletic and hypervolemic hyponatremia. Naturally, AVP-mediated stimulation of V1 (vascular) and V2 (renal) G protein–coupled receptors causes a cascade of physiologic responses, which ultimately function to modulate water reabsorption (Ghali et al., 2009). Vaptans, including V2 (tolvaptan, oral) and combination V1-V2 (conivaptan, IV) vasopressin receptor antagonists, provide a targeted approach to inhibiting ADH-mediated free-water reabsorption without associated sodium wasting (Aditya & Rattan, 2012; Gross, 2012). Fluid restriction is not required with these agents. Noted adverse events or side effects for tolvaptan include thirst, dry mouth, and urinary frequency; for conivaptan, they include infusion-site reaction, postural hypotension, elevations in BUN or creatinine, and increased thirst (Aditya & Rattan, 2012; Gross, 2012). Limited postmarketing research and investigation in the oncology population exists for these novel agents at this time, but they provide a potential therapeutic option for severe hyponatremia.

**Expected Patient Outcomes**

SIADH, although not necessarily preventable, can be successfully treated. In cases associated with CNS and spine disorders, it was reported to be self-limiting and remit spontaneously within two to three weeks (Amini & Schmidt, 2004). The goal of treatment is for patients to be asymptomatic with a return to normal levels of urine and serum osmolality and sodium, and normal urine specific gravity. Neurologic impairment is usually reversible with appropriate treatment. SIADH often resolves with treatment of the underlying disease (e.g., tumor regression). However, it may recur while disease burden remains stable and patients are undergoing chemotherapy or with tumor progression. Recurrent SIADH may require ongoing intermittent management (Myers, 2007).

Patient teaching points should include those points already discussed in the management of hyponatremia (see Figure 13-8). Nursing implications include the points presented in Figure 13-14.

**FIGURE 13-14** Nursing Implications for Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

- Be aware of any medications, chemotherapy agents, or treatments that may predispose patient to SIADH.
- Conduct a thorough pain assessment because SIADH may be precipitated or worsened by pain and stress.
- Ensure that appropriate pain medications are used, or that substitutions are used for pain medications that may precipitate the release of antidiuretic hormone.
- When assessing the volume status of patients, be aware that signs and symptoms of hypervolemia or hypovolemia exclude the diagnosis of SIADH.
- Continued assessment of physical symptoms and diagnostic findings is necessary to detect early signs of recurrent hyponatremia to prevent neurologic complications.

*Note.* Based on information from Gross, 2012; Keenan, 2011; Shelton, 2014.

**Tumor Lysis Syndrome**

**Overview**

TLS is a potentially life-threatening electrolyte and metabolic complication and is considered an oncologic emergency. It occurs as a result of rapid tumor cell destruction, or *tumor lysis*. As tumor cells die, they *lyse*, or burst open, and release their intracellular contents into
the bloodstream at a rate that overwhelms the body’s ability to clear the excess serum electrolytes. This accumulation of intracellular contents produces the hallmark electrolyte and metabolic disturbances of TLS: hyperkalemia, hyperuricemia, hyperphosphatemia, and resultant hypocalcemia. If not prevented, detected, or treated early, TLS can lead to neurologic and GI complications, cardiac arrhythmias, acute renal failure, acute respiratory distress syndrome, and eventual death (Gobel, 2005; Lydon, 2011).

TLS is most commonly found in patients with bulky, rapidly growing tumors with high growth fractions or those with highly sensitive responses to cancer treatment (Fojo, 2011). TLS occurs most frequently in patients with high-grade lymphomas, such as Burkitt and diffuse large B-cell lymphomas, and those with high white blood cell counts, as in acute lymphoblastic leukemia. TLS can occur in acute myeloid leukemia, chronic myeloid leukemia in blast crisis, other myeloproliferative disorders, and some solid tumors including but not limited to small cell and non-small cell lung cancer, breast cancer, medulloblastoma, and testicular cancer (Lydon, 2011). Factors that place patients at increased risk for TLS include elevated LDH level associated with high tumor volume, preexisting renal dysfunction, baseline hyperuricemia or uremia, dehydration, splenomegaly, bulky lymphadenopathy, and the administration of potentially nephrotoxic drugs (Fojo, 2011; Lydon, 2011).

Although most commonly associated with chemotherapy, TLS can occur with any form of treatment that causes rapid cell death and necrosis of tumor mass such as radiation, immunotherapy or hormonal therapy, surgery, chemoembolization, and hyperthermia (Fojo, 2011; Lydon, 2011). Chemotherapy agents commonly associated with TLS incidence include cisplatin, etoposide, cytosine arabinoside, paclitaxel, fludarabine, intrathecal methotrexate, and hydroxyurea (Lydon, 2011).

Although rare, TLS can occur spontaneously prior to the initiation of cancer treatment, especially in patients with leukemia and lymphoma because of the high proliferative tumor rate or the large, bulky tumors associated with these cancers (Fojo, 2011; Ikeda, Jaishankar, & Krishnan, 2012). In previous studies of incidence, TLS occurred in 42% of adults with high-grade lymphomas and 70% of children with acute lymphoblastic leukemia; clinically significant TLS occurred in only 6% of adults and 3% of children (Fojo, 2011; Ikeda et al., 2012; Pession et al., 2011).

TLS can occur within 24 hours to seven days after chemotherapy is initiated but most often presents 48–72 hours after initiation and usually resolves within seven days if treated. In the early stages, TLS is a preventable and treatable condition. Therefore, the primary clinical approach to TLS is early identification of at-risk patients and institution of preventive measures, followed by early identification of any metabolic or renal consequences with rapid treatment (Lydon, 2011). By analyzing the three categories of risk factors associated with TLS (see Figure 13-15), oncology nurses can identify patients who are at increased risk.

Mato et al. (2006) and Montesinos et al. (2008) developed predictive scoring and classification mechanisms to assist in the identification of patients who are at highest risk for TLS. The risk factors these investigators identified included higher prechemotherapy levels of LDH, uric acid, creatinine, and white blood cells; male gender; and history of chronic myelomonocytic leukemia (Lydon, 2011; Mato et al., 2006; Montesinos et al., 2008). Nurses and other healthcare providers can use such tools to successfully identify patients who are at increased risk for TLS.

Pathophysiology

When tumor cells are killed, potassium, phosphorus, and nucleic acids are released into the bloodstream. The liver then converts the nucleic acids to uric acid, and the kidneys ex-
crete the resulting uric acid. The kidneys also act as filters for necessary electrolytes, reabsorbing the amount needed and excreting the excess into the urine.

During rapid cell turnover (e.g., acute leukemias) or large-volume cell destruction (e.g., chemotherapy treating a large disease burden), the high rate of tumor lysis and release of intracellular contents into the bloodstream results in sudden elevations of serum potassium, phosphorus, and uric acid. The kidneys become overwhelmed and are unable to sufficiently excrete these byproducts of cell death, resulting in hyperkalemia, hyperphosphatemia, and hyperuricemia. Because of the inverse relationship between calcium and phosphorus, as phosphorus levels increase, calcium levels decrease, thereby resulting in hypocalcemia (Lydon, 2011).

Some tumor cells, such as in lymphoblastic leukemia, may have more than four times the amount of phosphorus found in normal cells and may be richer in purine nucleic acids, which convert to uric acid when released. These additional tumor characteristics may exacerbate the elevations of phosphorus and uric acid with rapid tumor lysis (Lydon, 2011).

Hyperuricemia, the most common complication of TLS, can result in the formation and deposition of uric acid crystals in the collecting ducts of the kidneys and ureters, thereby causing obstruction, increased pressure, and decreased glomerular filtration, all of which lead to renal failure (Fojo, 2011; Lydon, 2011). Hyperphosphatemia results in the binding of phosphorus and calcium to create calcium phosphate salts, the precipitation of which contributes to the blockage of the kidneys and resultant kidney failure. This can be exacerbated by alkalinization of the urine, a previous TLS management strategy, which is now controversial and not often recommended (Pession et al., 2011).

Hyperkalemia, often the first life-threatening sign of electrolyte imbalance in TLS, can lead to cardiac arrhythmias, respiratory failure, and neuromuscular dysfunction if not detected and treated (Ikeda et al., 2012; Lydon, 2011). Hypocalcemia, a consequence of acute hyperphosphatemia, can cause cardiac arrhythmias and heart dysfunctions and can contribute to the neuromuscular and renal toxicity of TLS (Fojo, 2011; Ikeda et al., 2012).

**Clinical Assessment**

Prevention and early detection of risks and symptoms are key factors in preventing the life-threatening consequences of TLS. Oncology nurses play a critical role in baseline and

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**FIGURE 13-15** Associated Risks for Tumor Lysis Syndrome

<table>
<thead>
<tr>
<th>Tumor Risks</th>
<th>Treatment Risks</th>
<th>Patient Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma</td>
<td>Chemotherapy (e.g., cisplatin, etoposide, cytarabine, paclitaxel, fludarabine, hydroxurea, intrathecal methotrexate)</td>
<td>Increased uric acid, phosphate, potassium, or lactate dehydrogenase prior to and/or after initiation of treatment</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Immunotherapy (e.g., interferons, interleukins, tumor necrosis factors, monoclonal antibodies [rituximab])</td>
<td>Elevated white blood cell count</td>
</tr>
<tr>
<td>High growth fraction</td>
<td>Hormonal therapy (tamoxifen)</td>
<td>Preexisting renal impairment</td>
</tr>
<tr>
<td>Large and/or bulky mass</td>
<td>Corticosteroids</td>
<td>Splenomegaly</td>
</tr>
<tr>
<td>B-cell/activated T-cell phenotypes</td>
<td>Radiation</td>
<td>Extensive lymphadenopathy</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>Surgery</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Tumor sensitivity to chemotherapy</td>
<td></td>
<td>Ascites</td>
</tr>
</tbody>
</table>

**Note.** Based on information from Lydon, 2011; Montesinos et al., 2008.
ongoing clinical and laboratory assessment to monitor for the development and progress of metabolic abnormalities. Prior to initiating treatment for cancer, nurses should obtain baseline serum electrolytes, especially potassium, phosphorus, calcium, uric acid, and sodium levels. Renal function studies (BUN, creatinine, urine pH) and liver function tests (LDH, aspartate aminotransferase, alanine aminotransferase) should be obtained at baseline as well, to identify any preexisting abnormalities. Monitoring of laboratory values may be necessary before treatment and several times a day for the first 48–72 hours after initiation of treatment in patients who are at high risk for TLS (Lydon, 2011). Baseline and daily weights, vital signs, and I&O measurements should be obtained during the initial treatment phase to aid in monitoring renal and cardiac function.

The history should include nutrition and hydration assessments, past and current medications, a history of any chronic health problems or past organ dysfunctions, such as kidney or liver problems, and any recent cancer diagnosis or treatments. A baseline ECG or echocardiogram may be recommended before initiation of cancer treatment and in those with preexisting or at high risk for hyperkalemia (Gobel, 2005; Ikeda et al., 2012).

**Clinical Manifestations**

Early symptoms of TLS may be vague, including nausea, vomiting, anorexia, diarrhea, cloudy urine, lethargy, and joint discomfort or muscle aches. Continued progression of TLS leads to the development of more critical symptoms. GI symptoms may become increasingly severe, including cramping and pain. Neurologic impairments can occur, which may lead to memory loss, hallucinations, and delirium. Neuromuscular manifestations include paresthesias, muscular irritability, tetany, and seizures. Blood pressure and heart rate will initially be elevated, followed by hypotension, bradycardia, and possible ventricular arrhythmias. Progressive renal impairments, including azotemia and anuria, may develop (Gobel, 2005; Lydon, 2011). If TLS is not recognized and treated promptly, progression may lead to acute kidney failure, stimulation of disseminated intravascular coagulation, cardiac arrest, and death (Gobel, 2005). Early and late symptom presentations are described in Table 13-16 for each imbalance present with TLS.

**Evidence-Based Interventions**

The most important key to managing TLS is to identify patients who are at highest risk and initiate preventive or prophylactic measures prior to any treatments for cancer. Close monitoring of laboratory values and associated symptoms of imbalances is crucial to identify abnormalities before they become life threatening (Ikeda et al., 2012). Patients considered to be at high risk for TLS should be placed in a specialized oncology or intensive care setting and may benefit from establishing central venous access before initiation of cancer treatment (Ikeda et al., 2012; Lydon, 2011).

The preventive interventions for TLS are multifaceted and include frequent laboratory monitoring, aggressive hydration, control of hyperuricemia, and treatment of electrolyte alterations.

Laboratory monitoring should include obtaining potassium, phosphorus, calcium, uric acid, BUN, creatinine, and LDH levels at baseline, with reassessment taking place up to every 4–6 hours daily during the first 48–72 hours after initiation of treatment in high-risk patients. If TLS develops, laboratory values should continue to be checked at least twice daily and then less frequently according to risk and response to treatment. Frequent cardiac assessment including ECG may be indicated to monitor for rhythm changes that may be caused by hyperkalemia and hypocalcemia (Ikeda et al., 2012).
Hydration should be aggressive and begin 24–48 hours prior to chemotherapy and continue for at least 72 hours after treatment. Continuous infusion of approximately 2–3 L/m²/day of normal saline or 5% dextrose solution should be administered to maintain urine output of at least 100 ml/m²/day (Lydon, 2011; Pession et al., 2011). Aggressive hydration will expand intravascular fluid volume, enhance renal blood flow and glomerular filtration, drive diuresis, and promote elimination of soluble acids and electrolytes in the urine. Nurses should monitor patients for symptoms of fluid overload by (a) assessing vital signs frequently to look for changes in blood pressure and heart rate, (b) identifying any signs of edema, (c) maintaining strict I&O, (d) monitoring for respiratory or cardiac changes (including auscultation of the lungs and heart), and (e) weighing patients daily.

Forced diuresis with loop diuretics, such as furosemide, may be helpful to prevent fluid overload, maintain urinary output, and promote the excretion of potassium, phosphate, and uric acid in the urine. However, diuretics should be used only with patients who are well hydrated and should be used with caution or avoided in those with acute kidney injury (Pession et al., 2011).

Urinary alkalinization is a controversial intervention that historically was one of the primary focuses of TLS prevention. This strategy had been used in the past to increase the solubility of uric acid, promote its excretion, and prevent it from forming into insoluble crystals in the tubules of the kidney. However, urinary alkalinization can lead to the precipitation of calcium phosphate and xanthine crystals in the renal tubules, causing increased

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**TABLE 13-16 Symptom Presentation of Tumor Lysis Syndrome**

<table>
<thead>
<tr>
<th>Imbalance Presentation</th>
<th>Symptoms</th>
</tr>
</thead>
</table>
| Hyperkalemia | Gastrointestinal: Nausea, diarrhea, vomiting  
Neuromuscular:  
• Early: Twitching, cramping, muscle weakness, paresthesias  
• Late: Ascending flaccid paralysis, positive Chvostek sign, positive Trousseau sign  
Cardiac:  
• Early: Hypertension, tachycardia, electrocardiogram changes  
• Late: Electrocardiogram changes, bradycardia, heart block, asystole |
| Hyperphosphatemia | Cardiac: Hypertension  
Renal: Azotemia, oliguria, anuria, renal failure |
| Hyperuricemia | Gastrointestinal: Nausea, vomiting, diarrhea, anorexia  
Neuromuscular:  
• Early: Fatigue, lethargy, pruritus  
• Late: Acute articular distress (similar to gout)  
Renal:  
• Early: Mild azotemia, flank pain, oliguria, increased urine osmolarity  
• Late: Edema, crystalluria, hematuria, profound azotemia, anuria, renal failure |
| Hypocalcemia | Neuromuscular:  
• Early: Restlessness, irritability, impaired memory, muscle cramps, twitching, muscle weakness, paresthesias  
• Late: Positive Chvostek sign, positive Trousseau sign, seizures, tetany  
• Cardiac: Hypotension, heart block, cardiac arrest |

**Note.** Based on information from Lydon, 2011; Myers, 2007.
risk of renal failure without clearly demonstrated benefit in correcting the metabolic abnormalities of TLS (Lydon, 2011; Pession et al., 2011). Therefore, urinary alkalinization is no longer recommended unless a patient has metabolic acidosis, and it may be unnecessary in the context of other pharmacologic management strategies (Lydon, 2011; Pession et al., 2011).

Pharmacologic control of hyperuricemia is used in the prevention and treatment of TLS. Hyperuricemia and resultant crystal deposition can block the tubules throughout the kidney, preventing proper filtration and causing acute kidney damage, ultimately leading to kidney failure. Drugs such as allopurinol and rasburicase often are used in the prevention and treatment of TLS. Allopurinol blocks the formation of uric acid, whereas rasburicase promotes the breakdown of uric acid to the more soluble allantoin (Lydon, 2011).

Allopurinol is a xanthine oxidase inhibitor and works by interfering with purine metabolism and inhibiting xanthine oxidase enzyme, which is essential for converting nucleic acid into uric acid (Lydon, 2011). This decreases the deposits of uric acid in the kidneys, but allopurinol cannot decrease uric acid that has already formed prior to its initiation. As a result, its effect on serum uric acid levels is typically not observed until one to three days after initiation, and the drug becomes maximally effective approximately one week into treatment (Lydon, 2011). Allopurinol can be given orally in adults at 600–800 mg/day (up to a maximum of 600 mg/m$^2$/day) for prophylaxis and treatment of TLS (Ikeda et al., 2012; Physicians’ Desk Reference, 2014b). It should be initiated one to two days before treatment for cancer and should continue for two to three days following treatment (Lydon, 2011; Pession et al., 2011). For patients unable to tolerate oral dosages, allopurinol may be given IV as a single dose or in equally divided doses at 6-, 8-, or 12-hour intervals at total dosages of 200–400 mg/m$^2$/day (up to maximum of 600 mg/day) with the same initiation times as oral allopurinol (Physicians’ Desk Reference, 2014a). Allopurinol is renally eliminated and can decrease the metabolism or clearance of some chemotherapeutic drugs (e.g., 6-mercaptopurine, azathioprine, cyclophosphamide); therefore, doses may need to be reduced in patients with impaired renal function or in the case of drug-drug interactions (Lydon, 2011).

Oncology nurses should educate patients and family members about precautions associated with taking allopurinol, such as dietary restrictions of foods high in purine, the potential risk of allergic reactions, including Stevens-Johnson syndrome, and drug incompatibilities. Possible side effects include nausea and vomiting, rash, fever, and renal failure and insufficiency. If a rash develops, the drug should be stopped (Gobel, 2005; Physicians’ Desk Reference, 2014a, 2014b).

Rasburicase was FDA-approved in 2009 for the treatment or prevention of hyperuricemia in high-risk adult patients initiating antineoplastic therapy expected to result in TLS (Sanofi-Aventis, 2011). It is a recombinant urate oxidase enzyme that converts circulating uric acid into a highly water-soluble metabolite (allantoin), therefore quickly decreasing both plasma and urinary uric acid levels (Pession et al., 2011). Rasburicase is given at a dose of 0.2 mg/kg IV as a single daily dose for up to five days starting 4–24 hours prior to chemotherapy. It should be given as an infusion over 30 minutes and should not be administered as a bolus (Sanofi-Aventis, 2011).

When patients are receiving rasburicase, nurses should be aware that alternative dosing schedules may be used because of costs, and results often are seen in decreasing uric acid levels as soon as four hours after administration (Cortes et al., 2010). Patients receiving rasburicase do not need urinary alkalinization. A risk of an anaphylactic reaction is present with each dose, so appropriate emergency medications should be at the bedside and the patient
monitored closely. Although generally well tolerated, side effects may include headache, nausea and vomiting, fever, abdominal pain, diarrhea, and rash (Cortes et al., 2010; Lydon, 2011). The use of rasburicase in patients with a glucose-6-phosphate dehydrogenase (G6PD) deficiency is contraindicated because of the risk of severe hemolysis. Patients should be assessed for risk of G6PD deficiency (i.e., patients of African or Mediterranean ancestry), and high-risk individuals should be screened for this deficiency prior to the use of rasburicase (Fojo, 2011; Sanofi-Aventis, 2011). Measures should be taken to immediately place blood specimens for testing of uric acid levels on ice after the initiation of rasburicase in order to prevent continued drug activity and breakdown of uric acid in the specimen tube, which results in inaccurate laboratory results (Fojo, 2011; Sanofi-Aventis, 2011). Given the cost of this medication, some recommend its use only in patients with persistent or progressive hyperuricemia (Pession et al., 2011).

Hyperkalemia can be a very serious electrolyte disturbance causing irregular cardiac rhythms and neuromuscular dysfunctions, especially when it develops in conjunction with oliguria or anuria. Therefore, careful monitoring and prompt treatment of elevated potassium levels should be initiated as soon as possible. Refer to the section on the treatment of hyperkalemia for management recommendations.

Hyperphosphatemia can be managed with oral phosphate binders, such as phosphate-binding antacids, or aluminum antacid gels, such as aluminum hydroxide, which form an insoluble complex that is excreted by the bowel. Hypertonic infusions of glucose and insulin, as used in the treatment of hyperkalemia, may help to lower severely elevated phosphate levels (Ikeda et al., 2012; Lydon, 2011). Medications containing phosphate should be discontinued, and phosphate-rich foods should be restricted. Close monitoring of electrolytes, especially calcium levels with hyperphosphatemia, is critical because of the reciprocal relationship of calcium and phosphorus.

Hypocalcemia often will resolve itself as hyperphosphatemia is corrected. Concurrent diuretic therapy for TLS in normovolemic patients helps to promote the excretion of phosphorus, thereby aiding in the normalization of calcium levels. Pession et al. (2011) recommended that hypocalcemia not be corrected except to correct arrhythmias secondary to potassium imbalance. If it is necessary to specifically treat hypocalcemia, refer to the section on hypocalcemia for treatment recommendations.

In cases of acute renal failure or severe or persistent electrolyte abnormalities, hemodialysis should be initiated promptly. Dialysis most often is temporary and will help to avoid irreversible renal failure. Critical parameters that may indicate the need for dialysis include levels of potassium greater than 6 mEq/L, phosphate greater than 10 mg/dl, or uric acid greater than 10 mg/dl (Myers, 2007). Persistent hyperkalemia and hyperphosphatemia, fluid overload, uremia, and symptomatic hypocalcemia also can be critical indicators for dialysis (Ikeda et al., 2012).

**Expected Patient Outcomes**

TLS, if treated promptly, can be managed and the sequelae reversed. However, prevention of TLS is the main goal, and oncology nurses play a critical role in the detection and prevention of TLS. Thorough assessment, close laboratory monitoring, expert knowledge of signs and symptoms related to the hallmark electrolyte disturbances of TLS, and identification of high-risk patients are all essential in preventing TLS. Collaborating with other members of the healthcare team to screen patients and initiate prophylactic treatments can aid in the prevention of this oncologic emergency. Refer to Figure 13-16 for nursing implications related to TLS.
**FIGURE 13-16 Nursing Implications for Tumor Lysis Syndrome**

- **Diet history:** Patients may need to be on a renal diet low in potassium and phosphorus. Potassium-rich foods include oranges, bananas, orange juice, tomatoes, and chocolate; foods with phosphorus include milk, meat, cheese, eggs, bread, fish, nuts, poultry, legumes, cereal, chocolate, and carbonated drinks (Kurtin, 2014b; Lederer et al., 2012).
- **Medication history:** Avoid medications that contain or preserve potassium (e.g., potassium-sparing diuretics) or phosphate (e.g., clindamycin) or those that have a propensity to increase uric acid levels (e.g., thiazide diuretics, aspirin).
- **Be aware of nephrotoxic agents,** such as amphotericin B, aminoglycoside antibiotics, or nonsteroidal anti-inflammatory drugs, which may need to be avoided in high-risk patients.
- **Explain to patients the need for aggressive hydration before and after chemotherapy treatments.**
- **Closely monitor intake and output; teach patients the symptoms of fluid overload such as shortness of breath, peripheral edema, distended neck veins, and “rattling” in lungs.**
- **Use allopurinol as directed:** Instruct patients about the importance of following the medication regimen. Foods high in purine, such as organ meats, sardines in oil, salmon, scallops, anchovies, fish roes, mince-meat, and meat extracts, may need to be avoided while taking allopurinol.

*Note.* Based on information from Kurtin, 2014b; Lydon, 2011; Qazi & Lohr, 2012.

**Conclusion of Case Study**

T.C. is most at risk for TLS. He is about to receive chemotherapy for a highly proliferative malignancy, acute myeloid leukemia. He is already dehydrated and has poor urine output; laboratory values reveal an elevated BUN and creatinine, potentially indicating poor renal function, as well as elevated LDH and uric acid levels. The nurse should immediately anticipate giving T.C. aggressive IV hydration with isotonic or hypotonic IV fluids to restore fluid balance, promote renal blood flow, and decrease acidic concentration of the urine. Strict I&O should be monitored along with frequent vital sign monitoring to detect any early hemodynamic signs of TLS. Oral or IV allopurinol should be initiated one to two days prior to chemotherapy administration and continued for up to two to three days following chemotherapy. Electrolytes should be checked frequently along with BUN, creatinine, LDH, and uric acid levels. Nurses should vigilantly watch for any signs or symptoms of developing hyperkalemia, hypophosphatemia, hyperuricemia, and hypocalcemia, which are the hallmark abnormalities of TLS. Initiation of preventive measures, thorough patient assessment, and application of knowledge related to the risks and symptoms of TLS are all critical in providing high-quality patient care and promoting optimal outcomes for T.C.

**Conclusion**

Oncology nurses need to understand the dynamic balance of electrolytes in the body, their importance in cellular function, and the metabolic implications of their function throughout the entire body. Patients with cancer commonly experience side effects of the disease and the treatment modalities employed. Oncology nurses must be aware of preventive measures and high-risk situations that patients may encounter throughout the spectrum of their care that could put them at risk for electrolyte imbalances, SIADH, or TLS. It is critical for oncology nurses to understand the indicators, preventive measures, assessment tools, and treatment modalities discussed in this chapter. Patient education should be provided at the time of diagnosis and frequently reviewed and revised throughout treatment. Nurs-
es play a vital role in identifying the risks, signs, and symptoms that may indicate an electrolyte imbalance or clinical emergency and in providing treatment, supportive care, and education to patients and their families.

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References


CHAPTER 14

End of Life

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Case Study

K.N. is a 72-year-old man with stage IV adenocarcinoma of the lung diagnosed six months ago. At that time, he was healthy without other medical history and was started on chemotherapy. Initially, he tolerated chemotherapy very well and remained able to continue his usual activities without difficulty. Today he is following up in the oncology clinic and unfortunately over the past several weeks he has experienced increasing symptom burden and functional decline. He notes a new pain in his low back that started about one week ago that he describes as a severe ache, nonradiating, and fairly acute in onset. The patient has already tried multiple pain medications for this, including oxycodone, which caused nausea; morphine, which caused hives; and hydromorphone, which was tolerated but did not help with the pain. He notices increasing dyspnea with any exertion that improves with rest; to this point he has had no shortness of breath at rest. After starting the opioids, he has now noted constipation to be an issue as well. The patient wishes to address these issues so that he can “get back to his chemotherapy schedule.” His wife is present for the visit and relates additional concerns. She notes that over the past several weeks K.N. has had less energy during the day and has spent much of his time sitting in a chair or in bed. He has had a declining appetite and has lost 10 pounds in the past two weeks. Secondary to his functional decline, his wife has had to help more with his activities of daily living and is concerned about her ability to help him “if he declines further.” On examination, the nurse finds the patient to have normal vital signs except for a resting oxygen saturation of 88%. He appears fatigued and cachectic. He has tenderness to palpation over L1 but is without neurologic deficits. He is noted to have diminished breath sounds halfway up his left lung field. He becomes short of breath trying to walk down the hallway, and his oxygen saturation drops to 82%.

Overview

The provision of end-of-life care is essential in the care of patients with advanced cancer. For those with incurable disease, barring an acute event, the terminal stages of cancer are accompanied by a steady decline in functional status, as well as the potential for new or worsening symptoms. Management of these symptoms in accordance with the established goals for medical care for each individual patient is crucial in allowing for a dignified and peace-
ful death. A multitude of symptoms can occur at the end of life; most commonly, patients who have symptoms are afflicted with pain, dyspnea, agitation, or secretions. Other issues that may arise are bleeding, seizures, wounds, and anorexia. All of these symptoms may be managed anywhere from the home hospice setting to the inpatient setting, depending on the clinical situation. Although some research is available regarding terminal care, many of the recommendations are based largely on anecdotal data in this patient population. This chapter presents a review of the hallmarks of end-of-life symptoms, the expected course, and treatment that will aid in the provision of expert support and care of patients with cancer who are at the end of life.

**Pain**

Cancer pain management is covered in depth as a separate chapter in this textbook (see Chapter 20), but the final days and hours of patients’ lives can provide a unique set of challenges in pain management that oncology nurses should understand. It is worth noting that randomized studies about pain control and other symptom management topics, in general, are especially difficult to conduct at the end of life because of the vulnerable state of patients and the sensitive nature of the dying process. Therefore, evidence provided for interventions used during this time is often based on expert opinion or extrapolated from their efficacy during prior periods of life when patients were not actively dying.

First, patients’ pain can escalate significantly (e.g., as the cancer continues to spread) and may require rapid dose titration or other aggressive measures to provide adequate pain relief. The options that are considered, and how they are implemented, will vary depending on a variety of factors, such as the potential risk versus benefit to the patient in light of the current stage of the dying process, renal and liver function, ability to swallow, and patient and family preferences, among others (Dalal & Bruera, 2011). Therefore, options that are available one day may no longer be offered the next, and vice versa.

**Risk-Benefit Analysis**

Within the last week or so of life, some interventions are best avoided, even though they might have otherwise been beneficial for patients at an earlier stage of their disease process. For example, palliative chemotherapy and radiation therapy to help treat painful bone metastases are now usually best eschewed because the benefit would not be experienced soon enough and the monetary cost and taxation on the patient is likely too high compared to potential benefit (Swetz & Smith, 2008). Bisphosphonates may no longer be indicated to help treat bone metastasis–related pain. If a patient is bedbound, which is usually the case within the last week or so of life, these kinds of aggressive and expensive treatments, which have the potential for more significant harm, are no longer routinely offered. Conversely, other treatments that might have been avoided in earlier stages of disease because of higher risk compared to potential benefit (e.g., methadone with prolonged QTc interval, steroids/nonsteroidal anti-inflammatory drugs for patients with a history of gastrointestinal bleeding) are now potentially a good option to help with pain control or are no longer discontinued.

**Renal or Hepatic Failure**

With renal failure, certain frequently used opioids, especially morphine and hydromorphone, are best used cautiously to avoid accumulation of potentially harmful metabolites
and associated toxicity (e.g., myoclonus) (Nayak-Rao, 2011). Methadone and fentanyl, on
the other hand, have not been found to have harmful metabolites and are considered the
safest opioids to use in patients with renal failure (Nayak-Rao, 2011). In the setting of hepatic
failure, opioid metabolism is generally slower, and the opioids’ effect may last longer for
all opioids without a clear-cut best option to use in this situation.

**Inability to Swallow**

If or when patients are no longer able to swallow medications during the last week of life,
nurses must be prepared to find alternate routes of administering the necessary medications
to control their pain. Morphine, even in liquid form, does not appear to be absorbed when
administered sublingually, but instead it is absorbed gastrointestinal as it trickles into the
stomach (Gordon, 2006; Reisfield & Wilson, 2007). Administration of highly concentrated
liquid morphine on the back of the tongue should be a more effective method and is par-
ticularly useful in the home setting. As long-acting opioids, transdermal fentanyl patches or
liquid methadone can be good options. Uncontrolled pain requiring frequent opioid escala-
tion, large doses of opioids, or simply fast-acting pain relief can often be managed very well
with IV or subcutaneous (SC) patient-controlled analgesia (Weinstein, Arnold, & Weissman,
2006). For patients without IV access, especially in the home setting but also in the hospital
when peripheral IV insertion is being avoided, the SC route has been found to be a very effi-
cacious alternative (Radbruch, Trottenberg, Elsner, Kaasa, & Caraceni, 2011). A continuous
infusion as well as a patient/family-controlled analgesia option can be given and adjusted as
needed and tolerated. A 25- or 27-gauge butterfly needle, or a specifically designed round
SC needle “button,” may be used for SC infusion, with infusion rates not to exceed around 4
ml/hr to avoid pain at the site and erratic absorption (Dalal & Bruera, 2011).

For comatose and semicomatose patients who are actively dying, it is frequently appropri-
ate and necessary to be slightly more aggressive with opioid escalation to ensure their com-
fort, a medically and ethically appropriate practice as long as the goal is to achieve patients’
comfort and not hasten death. In rare instances, truly refractory pain can potentially be
treated with intraspinal analgesia via an epidural or intrathecal catheter infusion at the end
of life, possibly even at home (Thomas & von Gunten, 2003). Certain medications and lo-
cal anesthetics such as bupivacaine can only be given intraspinally for effective pain control.

**Patient and Family Preferences**

Patients themselves may have strong opinions about which medications should be used
or how aggressive they want their providers to be in controlling pain during or prior to
their final hours to days of life. Additionally, family members may have equally strong feel-
ings throughout the dying process, and negotiation or compromise is sometimes necessary
to achieve adequate pain control for patients. At times, nurses caring for dying patients may
need to advocate strongly for them, amid family objections, to ensure they receive the neces-
sary pain control, and confrontation with family members cannot always be avoided.

**Dyspnea**

Dyspnea can be a very distressing symptom anywhere along the trajectory of life-threat-
ening illness, but more acutely so at the end of life. Patients may be afflicted with dyspnea
either as a consequence of the primary diagnosis (e.g., end-stage chronic obstructive pul-
monary disease, lung cancer) or as a secondary event to the primary diagnosis (e.g., post-obstructive pneumonia related to lung cancer). Many of the differential diagnosis items, supportive care recommendations, and treatment guidelines for dyspnea are discussed in Chapter 12. All of the therapeutic suggestions contained in that chapter would also be reasonable considerations for dyspnea occurring at the end of life.

**Life-Supportive Therapies in Dyspnea**

One of the concerns regarding dyspnea in the context of terminal states is limitations of life-supportive therapies that are sometimes offered in respiratory failure. Mechanical ventilation is a very burdensome but potentially lifesaving technology depending on the etiology of the respiratory failure (Mendelsohn et al., 2002). It is sometimes very difficult for patients and their families to decide to forgo this intervention, considering subspecialists may not agree on what the likelihood of success for this therapy would be for any one patient. This may be particularly true for patients who have in the past successfully utilized and weaned from ventilator therapy. For patients who have determined they would not want to pursue mechanical ventilation via endotracheal intubation for respiratory failure, another gray area in therapeutics is the potential for use of bilevel positive airway pressure, continuous positive airway pressure, and noninvasive positive pressure ventilation (Marik, 2007). For patients whose main goal is to be at home with their families, it is sometimes easy to discount the use of these therapies, as they would clearly not be consistent with pursuing the goals of the patient. For hospitalized patients who suffer respiratory failure from a potentially reversible cause, however, recommendations on these bridge therapies are often more difficult (Marik, 2007). Certainly the administration of noninvasive ventilation therapies in patients with a terminal condition should be accompanied by a very detailed discussion on the goal of care with patients and their family members.

Detailed discussions should be had with patients and families regarding advanced supportive therapies for dyspnea and respiratory failure describing the benefits and burdens of the intervention, as well as those related to not pursuing treatment. For patients who wish to continue to accept therapy with mechanical ventilation when the available data predict a suboptimal outcome, discussion should be encouraged to elucidate the reasoning behind this decision. At times, patients who have suffered severe respiratory distress in the past may believe that mechanical ventilation is the only way to prevent a distressing death experience (Mahler et al., 2010). In these instances, a thorough explanation of the treatment options for terminal dyspnea should be undertaken, as this may give patients an opportunity to better align their medical decision making with their actual goals. If patients are still interested in pursuing life support for respiratory failure after a full supportive conversation, discussion should be held to consider a time-limited trial of therapy. This conversation may help alleviate the burden on family members who are left to provide medical decisions after the patient is started on mechanical ventilation and no longer has capacity to communicate his or her wishes.

**Home Care of Dyspnea at the End of Life**

For patients who have determined that use of advanced therapies for support in the event of respiratory failure is not in line with their goals, hospice and palliative sedation should be discussed. Hospice is a model of care designed to provide comfort care for patients with a terminal diagnosis who have an expected prognosis of six months or less (Centers for Medicare and Medicaid Services, 2013). Most patients who are enrolled in
hospice are receiving it in the home setting, although other levels of care (e.g., respite, inpatient hospice) do exist. Hospice care provides continued symptom management and family support to allow patients to maximize the quality of time lived near the end of life. At a time when symptom management can change on a daily or even hourly basis, hospice can play a pivotal role in helping patients and families achieve their goals for care in a comfortable manner. Hospice nurses visit the patients regularly at home to best determine supportive care needs, and a team of professionals, including social workers, chaplains, nutritionists, and physicians, are available if applicable concerns are identified. Medications are procured by the hospice nurses and are titrated to allow for comfort at home. In the rarer instances where this is not feasible because of the patient’s symptom pattern, the patient may be transferred to an inpatient setting for management (Negron & McKinnis, 2011). If dyspnea is difficult to manage, some patients and families opt for inpatient care for respiratory failure. Most hospice patients will have access to as-needed oral opioid medications at home for the occurrence of acute symptoms, but if these do not work quickly enough or cannot be titrated for symptom control, admission to a facility to stabilize symptoms with IV therapy may be pursued.

**Palliative Sedation for Intractable Dyspnea**

In the event of failure of traditional agents from symptom management guidelines (i.e., IV opioids, nebulized opioids, oxygen, agents aimed at treatment of the underlying disorder such as steroids, nebulized albuterol, and diuretics), benzodiazepines may provide benefit (Gomutbutra, O’Riordan, & Pantilat, 2013). If none of these measures produces acceptable symptom management, palliative sedation may be considered for end-of-life care. In this instance, proportional palliative sedation can be employed where the target of sedation is the relief of symptoms rather than achieving coma (Hasselaar, Verhagen, & Vissers, 2009). Patients may be somewhat responsive to their environment under this therapy, but family members should be aware that complete unresponsiveness to the environment may occur depending on symptom management needs (Mercadante et al., 2009). IV hydration and nutrition are often less of a consideration for patients who are candidates for palliative sedation and thought to have a prognosis of hours to days or less (Kirk & Mahon, 2010). Various agents are used for this practice; most commonly, IV benzodiazepines are employed, such as lorazepam, diazepam, or, in more advanced settings, midazolam because of its easy titration (Mercadante et al., 2011). Other agents that do not provide anxiolysis but are primarily sedating agents (e.g., chlorpromazine, which can be administered rectally) are at times used for palliative sedation if the primary goal is to return the patient home (Caraceni et al., 2012). Patients and families should be well counseled on the use of palliative sedation for intractable symptoms at the end of life. Some sources advocate for the use of informed consent to ensure understanding of the process (Mercadante et al., 2009).

**Discontinuation of Mechanical Ventilation**

Another situation where dyspnea may occur is during the process of weaning a terminal patient from mechanical ventilation. Once the family (or in rarer instances the patient) has determined that continued respiratory support is not in accordance with the goals of care, therapy should be discontinued with aggressive symptom management for the patient and support for the family. Pre-extubation discussion with family, as well as key staff such as nursing and respiratory therapy, is essential to success (Kompanje, van der Hoven, & Bakker, 2008). Family may or may not remain with the patient during weaning and extubation, but
if they are present, ideally a staff member (from nursing or chaplaincy) would be available for support. Medications should be readily available for possible symptoms that may develop during the process, and patients who are not on continuous opioid therapy should usually receive at least a low-dose IV opioid just prior to extubation. IV opioids and benzodiazepines may be used for the tachypnea or respiratory distress that occurs after extubation, and, depending on patient needs, starting a continuous infusion for symptom control may be considered. IV scopolamine is recommended for use prior to extubation to diminish the secretions that can occur (Kompanje et al., 2008). For the uncommon instance where a patient has been endotracheally intubated for a prolonged period of time, IV corticosteroids may be administered to help prevent stridor after the tube is removed (Cheng, Hou, Huang, Lin, & Zhang, 2006). Families should be counseled that following extubation, patients may survive for an unpredictable amount of time that may be measured in hours to days to even a week or two. They should be aware that comfort care measures will continue during this time and that transition to hospice in either the home or inpatient setting may be appropriate depending on symptom management needs (Kompanje et al., 2008).

Delirium

Overview and Associated Incidence

Delirium is a common complication associated with the dying process in the last hours to days of life; up to 80%–85% of all dying patients will experience some form of it (Breitbart & Alici, 2008). The two major subtypes of delirium are hyperactive and hypoactive delirium (Boettger & Breitbart, 2011b), and both will be described in more detail. Within the last week of life, delirium is usually irreversible and most commonly is hypoactive (Irwin, Pirrello, Hirst, Buckholz, & Ferris, 2013).

Pathophysiology

Both hyperactive and hypoactive delirium are generally further classified into reversible and irreversible. The irreversible form at the end of life, sometimes referred to as terminal delirium (Breitbart, 2008), is usually caused by some form of sepsis or major organ failure (Breitbart & Alici, 2008).

Assessment

The hallmark characteristic of delirium is “an abrupt onset of disturbances of consciousness (i.e., arousal), attention, cognition, and perception that fluctuate over the course of the day” (Breitbart & Alici, 2012, p. 1207). Some of the clinical symptoms nurses should carefully assess for include agitation, confusion, lack of inhibition, change in level of consciousness, inattentiveness, irritability, and disorganized thinking (Irwin et al., 2013). Patients may demonstrate these symptoms by becoming upset easily, demonstrating a labile affect, being frequently lethargic or drowsy and/or intermittently impulsive, being disoriented and unable to concentrate, or having hallucinations (Irwin et al., 2013). Formal assessment tools for delirium exist, including the Confusion Assessment Method, the Delirium Rating Scale–Revised-98, and the Memorial Delirium Assessment Scale (Breitbart & Alici, 2012). Hypoactive delirium, the most common form at the end of life, usually is “characterized by decreased or slow speech, reduced awareness of surroundings, and reduced activity,” whereas hyperactive...
delirium is typically “characterized by increased psychomotor activity such as loss of activity control, mood lability[,] restlessness, and wandering” (Kang, Shin, & Bruera, 2013, p. 107).

Interventions

Interventions to help treat irreversible delirium at the end of life can be separated into pharmacologic and nonpharmacologic options (see Figure 14-1). Worth noting is that signs and symptoms of uncontrolled pain should be assessed for and distinguished from delirium or agitation, as the treatment of delirium with opioids is ineffective (Irwin et al., 2013).

Pharmacologic Interventions

The first option for treating irreversible, hyperactive delirium is generally antipsychotic medications (haloperidol 1–2 mg, either PO, IV, SC, intramuscular [IM], or per rectum [PR], or chlorpromazine 25–50 mg via the same routes, as starting doses and titrated as needed) (Irwin et al., 2013). In the population of dying patients who have less than a week to live, however, it may be more helpful to use benzodiazepines as the first-line treatment (midazolam 0.1–0.2 mg/kg IV, SC, or IM initial bolus dose and every 30 minutes followed by continuous infusion if needed, or lorazepam 1–2 mg IV, PO, PR, SC, or IM) followed by phenobarbital or, if refractory, propofol (Irwin et al., 2013).

It may become necessary to treat refractory hyperactive delirium with continuous-infusion/scheduled administration of the aforementioned medications with the intent to achieve full palliative sedation (Irwin et al., 2013). A recent systematic review of palliative sedation found that delirium was the primary symptom being treated with palliative sedation (median 57.1%) and that palliative sedation was not associated with decreased survival (Maltoni et al., 2012).

Irreversible, hypoactive delirium may not warrant treatment with medications, depending on the goals of care and how bothersome it is, or a trial of antipsychotics at aforementioned doses for hyperactive delirium may be attempted (Irwin et al., 2013). However, a recent trial by Boettger and Breitbart (2011a) showed that aripiprazole could be particularly helpful, and safe, in treating hypoactive delirium in hospitalized patients with cancer.

Nonpharmacologic Interventions

A number of nonpharmacologic interventions can help minimize delirium, but some of these interventions may be less helpful in patients with hours to days left to live, depending on how severe the delirium is or how alert the patient remains at the time of initiation of the interventions. No research exists to support their use, but the interventions most likely to

<table>
<thead>
<tr>
<th>FIGURE 14-1</th>
<th>Summary of Treatment Options for Irreversible Delirium</th>
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<tbody>
<tr>
<td>Irreversible Hyperactive Delirium</td>
<td>Irreversible Hypoactive Delirium</td>
</tr>
<tr>
<td>• Antipsychotics (haloperidol, chlorpromazine)</td>
<td>• Trial of antipsychotics (haloperidol, chlorpromazine)</td>
</tr>
<tr>
<td>• Benzodiazepines (midazolam, lorazepam)</td>
<td>• Aripiprazole</td>
</tr>
<tr>
<td>• Propofol</td>
<td>• Nonpharmacologic interventions (same as for hyperactive delirium)</td>
</tr>
<tr>
<td>• Phenobarbital</td>
<td>• Nonpharmacologic interventions (e.g., reorienting patients regularly, avoiding restraints, monitoring bowel and bladder function carefully, and promoting good sleep)</td>
</tr>
</tbody>
</table>

Note. Based on information from Boettger & Breitbart, 2011a; Breitbart & Alici, 2012; Irwin et al., 2012.
be beneficial include controlling pain, including nonpharmacologic treatments such as repositioning every two hours, reorienting patients regularly, avoiding restraints, monitoring bowel and bladder function carefully, and promoting good sleep (Breitbart & Alici, 2012).

**Patient and Family Teaching Points**

Seeing a loved one in a delirious state at the end of life, particularly a hyperactive delirium, can be very frightening, sad, and frustrating. Oncology nurses can play a crucial role in helping to comfort and reassure patients and families while providing care for them. They can explain what interventions are being performed or medications are being given and what to expect from treatment if it is effective, or even ineffective, and how family can best help take care of and interact with their loved one. Obtaining support from ancillary services, such as a chaplain, in response to assessment of their needs can be instrumental in helping family, in particular, to better cope with this difficult situation. If palliative sedation is implemented, oncology nurses can continue to reassure and educate the family about the process while frequently monitoring patients and families.

**Expected Outcomes**

A study by Leonard et al. (2008) found that shorter survival in terminal delirium was related to increased patient age, presence of organ failure, and increased cognitive impairment. The goal of treatment is to ensure the patients’ delirium, whether hypoactive or hyperactive, is controlled adequately and to ultimately allow patients to die comfortably with their friends and family at peace about the outcome as much as possible.

**Secretions at the End of Life**

A significant number of patients at the end of life are noted to have noisy respiration that is referred to as secretions at the end of life or death rattle. Patients who develop this symptom are generally very near the end of life; the majority will die within 16–60 hours of noting the symptom (Clark & Butler, 2009). Many of these patients are thought to be unaware of the environment and are without any other signs of respiratory distress, and it is therefore generally assumed that the sign is not bothersome to them (Protus, Grauer, & Kimbrel, 2013). However, it can be very troubling to families who are concerned that the respiratory noise is causing distress to their dying loved one. Because of this, the most important feature of therapy is frequent reassurance to families that the presence of the death rattle is not causing suffering to their loved one. Although this is the appropriate place to start and may be the only intervention that is needed for some families, many family members will not be able to comfortably sit with their loved one unless further treatment is undertaken (Clark & Butler, 2009). Pharmacologic therapy in the form of various anticholinergic medications is usually effective in reducing or ameliorating the finding.

Several agents are available for use in treating the death rattle. Scopolamine is one of the more frequently used medications and is available in a patch that is usually placed near the ear. Each patch is effective for 72 hours, and depending on response, some resources recommend placement of additional patches. In the inpatient setting, scopolamine is available in an IV form that can be given every four to six hours for recurrent symptoms (Müller-Busch & Jehser, 2009). Glycopyrrolate is also available in an IV form that is given every six hours as needed (Back, Jenkins, Blower, & Beckhelling, 2001).
For home hospice patients who do not have a complete response to scopolamine patches, atropine drops may be employed to diminish symptoms of death rattle. The ophthalmic solution of atropine is often employed for this use, and one to two drops can be given sublingually as needed every two to four hours (Protus et al., 2012). Hyoscymamine may be available in a sublingual form if other agents have not been effective (Negron & McKinnis, 2011).

**Hemorrhage**

Bleeding can be a significant source of distress at the end of life. Although the occurrence itself may not be associated with a symptom, it can certainly be alarming to patients and their families. Bleeding may occur at the end of life either as the primary cause of a terminal event (e.g., inoperable gastrointestinal bleeding) or as a complication of the life-limiting illness (e.g., in association with malignancy, hepatic failure) (Pereira & Phan, 2004).

For bleeding that is not life threatening, attempts at achieving hemostasis are of first priority. Wounds that are a source of bleeding may be amenable to packing or a pressure dressing. Other topical lesions of the skin and oral cavity may be managed with topical cocaine as needed (Pereira & Phan, 2004). Clearly, reversal of an underlying coagulopathy (when able) will provide benefit to bleeding; consider the provision of vitamin K in instances of hepatic insufficiency or therapeutic/supratherapeutic anticoagulation on warfarin (Pereira & Phan, 2004). Newer agents that are direct thrombin inhibitors do not at this time have any universally accepted forms of reversal of bleeding.

Bleeding as a terminal event is seen less often in end-of-life care but can be very traumatic for patients and even more so for families. This may be seen in the setting of significant inoperable gastrointestinal bleeding or perhaps visible hemorrhage related to malignant erosion of major blood vessels. The threat of impending life-threatening bleeding is so distressing to many patients and families that they opt for inpatient hospice care so as to have trained staff present when it may occur. In the home setting, options are limited and include support of patients and families and palliative sedation for patients depending on the event. In the inpatient setting, depending on the overall patient course and goals, tranexamic acid and aminocaproic acid may be given to encourage coagulation and temporarily stop the bleeding (Pereira & Phan, 2004).

Decisions regarding continued blood product transfusion often arise in the setting of life-threatening bleeding and may be difficult for patients and families. Certainly transfusion of blood products at times can be a palliative measure and lead to improvement in symptoms of fatigue and dyspnea on exertion for the patient, but this must be counterbalanced against the goals of the patient to leave the inpatient setting, the risk of prolonging of the dying process, and the potential for volume overload related to repeated transfusions (Pereira & Phan, 2004).

**Wounds**

Wounds can be a common symptom at the end of life, especially in the later stages of chronic illnesses during which patients may have suffered a long period of significant decline. Pressure ulcers may be seen in increasing frequency in patients who have functional decline related to underlying diseases and become bedbound, requiring frequent turning that family members may not be able to be provide (Coleman et al., 2013). In an inpatient
setting, ideally all of these wounds would be prevented by frequent turning, specialty mattresses, and support from a specialized wound care team (Graves & Sun, 2013). There is, however, a wound that occurs at the end of life that is referred to as *Kennedy terminal ulcer* and is not thought to be preventable by these methods. It occurs in the sacrococcygeal area, is often of sudden onset and in the shape of a butterfly or pear, and is thought to be related to failure of the skin as an organ during the dying process (Yastrub, 2010). The area usually expands rapidly, regardless of intervention, and often death occurs from the underlying terminal disease within hours to days of its appearance. It is important to distinguish the Kennedy terminal ulcer from a pressure ulcer so as not to attempt to establish unrealistic treatments and expectations for wound healing (Yastrub, 2010).

When wounds develop at the end of life, the goal shifts from healing the wound to instead palliating the related symptoms. Wound dressing changes are recommended far less often, perhaps two to three times per week, to prevent discomfort related to the procedure (Graves & Sun, 2013). For wounds with associated perceived discomfort, pain medications should be given 15–30 minutes before planned dressing changes, depending on the route administered. If the area surrounding the wound is painful or sensitive, use of topical lidocaine or lidocaine patches may be considered, noting that the manufacturer does not recommend placement on broken skin (Endo Pharmaceuticals, 2013; Graves & Sun, 2013).

At times, drains placed at a prior time may become dislodged, or fistulas may occur in the course of a terminal disease. A fistula is a passage between two hollow organs or a hollow organ and the body surface. Fistulas from the bowel may drain enteric contents over the skin (Vasilevsky, 2014). Ostomy bags may be a helpful way to keep these areas clean and allow them to drain without having patients return to the hospital or endure repeat procedures.

Wound odor can become a distressing issue for patients and families at the end of life. It is theorized to result from the metabolic byproducts of anaerobic bacteria that are sometimes found in conjunction with devitalized tissue (Patel & Cox-Hayley, 2009). For milder symptoms, room deodorizers or odor-absorbing dressings (e.g., silver dressings, activated charcoal) can be helpful. For continued odor despite these measures, topical metronidazole gel may be applied as needed to the wound. If the odor is severe, metronidazole can be given systemically to reduce the symptom (Graves & Sun, 2013).

**Seizures**

Seizures at the end of life can have multiple etiologies. At times they result from structural effects on the brain from a terminal disease (e.g., brain metastasis), and at other times they may result from toxic or metabolic complications related to medications or electrolyte disturbances (Kinzbrunner, Maluso-Bolton, & Schlecter, 2011). They also may be a consequence of the patient’s inability to continue taking oral medications to control an underlying epileptic disorder (Pace et al., 2013). Although in general seizures are responsive to medications, they can, especially if repeated or protracted, be a very distressing symptom and one that may require transition to an inpatient level of care, either to gain control and establish an at-home medication regimen or, more rarely, to provide treatment for seizures that continue persistently without remitting (Kinzbrunner et al., 2011).

For those receiving home hospice care, treatment options may be more limited, especially on an acute basis. Many hospices provide liquid benzodiazepines that can be given in repeated doses in the event of a seizure or on a scheduled basis for prevention of seizures (Sizoo, Grisold, & Taphoorn, 2014). For patients still able to take oral medications, preven-
tion of seizures can be addressed in a similar manner to outpatients without terminal diseases. For patients who are unable to take oral medications for seizure prophylaxis at home, it may become more challenging, and generally medications are administered rectally, which is possible with phenobarbital, diazepam, carbamazepine, and valproic acid (Sizoo et al., 2014). Depending on local pharmacy resources, phenobarbital and diazepam can be made into rectal suppositories and given every 6–12 hours to prevent seizures. In patients with a history of epilepsy, every effort should be made to transition to another route of medication administration to continue treatment when the patient can no longer take oral medications (Pace et al., 2013).

More rarely, patients may develop intractable seizures not responsive to these treatment methods. In such instances, transfer of the patient to an inpatient level of care (whether inpatient medicine or inpatient hospice level of care) to control symptoms is appropriate. Phenytoin, levetiracetam, fosphenytoin, phenobarbital, and valproic acid are antiepileptic drugs that are available intravenously for seizure control (Pace et al., 2013). In the case of failure of scheduled doses of multiple IV antiepileptic therapies, pharmacologic coma with continuous IV infusions of benzodiazepines, propofol, and pentobarbital may be initiated (Brophy et al., 2012).

Anorexia

One of the more difficult issues in end-of-life care is the question of artificial nutrition and hydration (Dev, Dalal, & Bruera, 2012). Families can become very concerned regarding their loved ones’ lack of oral intake in the terminal stages of many diseases, and these conversations may be difficult for healthcare providers to have. A multitude of factors may contribute to anorexia. In cancer cachexia in particular, multiple mechanisms are responsible, and in relation to the terminal stages, patients almost universally have anorexia, as well as inconsistent liquid intake (Gillespie & Raftery, 2014). Usually a significant degree of weight loss precedes this stage, causing well-meaning family members to more vehemently try to persuade patients and their providers to somehow improve nutritional status. Many families will ask about the potential for artificial nutrition in these situations, and supportive but clear guidance from healthcare providers is of the utmost importance. Families should be assured that their loved ones, especially if they cannot communicate, are not suffering related to the lack of oral intake (Prevost & Grach, 2012). They should be encouraged to provide whatever food or fluids the patient wishes in order to promote comfort. Families should be aware that the provision of artificial nutrition in most patients with end-stage cancer potentially increases the risk of infection and agitation (related to IV or SC access), as well as volume overload, without necessarily improving patients’ outcomes or comfort (Dev et al., 2012). Given the balance of benefit and burden in relation to nutrition, detailed education of family members in conjunction with supportive decision making is vital.

Some exceptions may arise where the provision of artificial nutrition may actually contribute to patients’ comfort or perhaps add time to their expected prognosis. Select patients who develop complete bowel obstruction but otherwise retain good functional status may be candidates for total parenteral nutrition to promote resolution of hunger and potentially prolong life (Soriano & Davis, 2011). If pursuing this option, a thorough discussion of the goals of care for patients should be undertaken to discuss expectations regarding when to stop nutrition and patients’ wishes for aggressive treatment if serious complications of therapy occur (including bacteremia or fungemia) (Soriano & Davis, 2011).
Conclusion of Case Study

K.N. and his wife had a long discussion with his oncologist regarding his current symptom burden and care. Unfortunately, his decline in functional status in the setting of metastatic cancer predicts a poorer prognosis, usually measured in weeks to months. Given his decline in functional status, his oncologist opted to not suggest further chemotherapy and talked with K.N. about hospice. Goals of care were discussed at length, including the low likelihood of successful resuscitation attempts and mechanical ventilation in his situation, as well as the limitations of artificial nutrition and hydration. On evaluation, he was found to have evidence of metastatic disease at L1 that was treated with a short course of radiation that markedly decreased his pain. He was noted on chest x-ray to have a pleural effusion, for which thoracentesis improved his dyspnea. After discussion with his family, K.N. realized that hospice would meet his goals of care now that he and his wife were more understanding of the expected course for his cancer. Their children planned prolonged visits to spend time with their father and also to help their mother with his care. A hospice agency was arranged to care for the patient at home, with his oncologist overseeing the plan of care. He was started on an escalated dose of hydromorphone with an effective dose of 8 mg every two to three hours for both his residual back pain and his dyspnea. His dyspnea worsened over time, and repeat evaluation was consistent with recurrence of his pleural effusion. A PleurX® catheter was placed to allow for repeated drainage of his effusion at home, and this continued to improve his symptoms. Oxygen was started by hospice and titrated as needed for desaturations associated with dyspnea. During the month after his office visit, his functional status continued to decline with good symptom control until he was bedbound and sleeping much of the day. Several days before his death, he became largely unresponsive and was not able to take oral medications, and his hydromorphone was transitioned to a SC infusion with boluses available if needed for episodes of respiratory distress. He remained comfortable with few medication boluses necessary and died peacefully with his family at his bedside. His family expressed gratitude for the honest discussions held by his healthcare team and for the support of hospice in allowing the patient to die comfortably at home.

Conclusion

A multitude of symptoms can occur at the end of life. Pain is a common problem throughout the trajectory of cancer; special considerations in the terminal phase include dosing in the setting of renal or hepatic failure and continued treatment in patients who can no longer take oral medications. Dyspnea can be a very distressing symptom and must be carefully addressed if it is an intractable symptom at the end of life, especially because palliative sedation may be a viable option based on patient and family goals. For those patients who are placed on mechanical ventilation, it can be discontinued, with pre-extubation measures, at any time the family believes that the intervention no longer matches the goals of the patient. Delirium is a common and very distressing symptom for which multiple treatment options are available, depending on whether the patient is in the home or inpatient setting. Death rattle can be improved with nonpharmacologic (such as discontinuing artificial nutrition and hydration) and pharmacologic (anticholinergic agents including scopolamine and glycopyrrolate) treatments. Seizures and hemorrhage are less common presentations at the end of life, and patients experiencing these conditions may be considered for treatment in an inpatient rather than home hospice setting. Anorexia commonly occurs during the
later stages of cancer and can be difficult for families to accept. Therefore, addressing anorexia often requires thoughtful communication and support from the team caring for the patient. Successful end-of-life care requires careful consideration of numerous factors in relation to the underlying cancer, symptoms, psychosocial support, and goals for medical care. Although at times emotionally and intellectually challenging, the provision of good supportive care for patients in the terminal stages of cancer can allow for peaceful last memories for surviving family members, as well as a rewarding experience for involved team members.

References


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Case Study

J.B. is a single 46-year-old African American woman admitted for vertebroplasty and to receive her first cycle of chemotherapy (bortezomib, cyclophosphamide, and dexamethasone) for newly diagnosed stage IIIA immunoglobulin G kappa multiple myeloma complicated by compression fractures of thoracic vertebrae T4–T8. She has severe bone pain, which is currently well managed with a controlled-release narcotic agent. After two cycles of therapy, if her disease response has been satisfactory, the plan is for her to receive high-dose melphalan chemotherapy followed by autologous peripheral blood stem cell transplant.

With the new diagnosis of multiple myeloma, J.B. admits to feeling anxious, fearful, and somewhat discouraged, and she is tearful as she discusses her concerns. She is worried about how she will maintain her job and health insurance given the anticipated need for intensive treatment over several months. She is sleeping poorly, due to both the stress of the diagnosis and hospitalization as well as to bone pain and the insomnia that has resulted from treatment with dexamethasone. She tells the nurse that her most bothersome issues are the difficulty sleeping and the severe fatigue. In gathering a history, the nurse learns that the fatigue had predated her diagnosis for approximately three to four months, and excessive fatigue was one of the reasons she had originally presented to her primary care provider for evaluation. On examination she is mildly cachectic, with point tenderness of the spine in the thoracic region. Laboratory data reveal a hemoglobin level of 9.4 g/dl and a serum creatinine level of 1.7 g/dl.

Overview

Cancer-related fatigue (CRF) is recognized as one of the most common symptoms in patients receiving treatment for cancer, often persisting beyond the conclusion of active treatment and even at the end of life (Mystakidou, Parpa, Katsouda, Galanos, & Vlahos, 2006; Prue, Rankin, Allen, Gracey, & Cramp, 2006). Longitudinal and comparative studies indicate that fatigue may also be a significant problem for cancer survivors, with many survivors reporting fatigue scores higher than that of an age-matched general population (Braun, Greenberg, & Pirl, 2008; Goedendorp, Gielissen, Verhagen, & Bleijenberg, 2013; Ness et al.,
Across the cancer care continuum, depending on how fatigue is defined and measured, prevalence estimates of fatigue vary from 25% to 99% (Campos, Hassan, Riechelmann, & Del Giglio, 2011; Dhruva et al., 2013; Humpel & Iverson, 2010; Langston, Armes, Levy, Tidey, & Ream, 2013; Neefjes, van der Vorst, Blauwhoff-Buskermolen, & Verheul, 2013; Peters, Goedendorp, Verhagen, van der Graaf, & Bleijenberg, 2014; Weis, 2011). A recent survey of more than 500 patients and nearly 100 clinicians found that across all cancer types, fatigue was ranked as the most important symptom or concern (Butt, Rosenbloom, et al., 2008). Fatigue may occur both as an isolated symptom and as one element in a cluster of symptoms, which also may include depression, pain, sleep disturbance, and menopausal symptoms (Chen et al., 2012; Kirkova, Aktas, Walsh, & Davis, 2011; Kirkova, Aktas, Walsh, Rybicki, & Davis, 2010; Thavarajah et al., 2012; Thomas et al., 2014).

Fatigue is distressing to patients and has adverse effects on functional status, mood, and well-being. Studies suggest that CRF is a multifaceted condition characterized by diminished energy and an increased need to rest, disproportionate to any recent change in activity level and accompanied by a range of other characteristics, including generalized weakness, diminished mental concentration, insomnia or hypersomnia, and emotional reactivity (Barsevick et al., 2013; Cella, Peterman, Passik, Jacobsen, & Breitbart, 1998; Piper & Cella, 2010). Consequences of CRF include decrements in physical, social, and vocational functioning (Curt & Johnston, 2003; de Jong, Candel, Schouten, Abu-Saad, & Courtens, 2006; Escalante & Manzullo, 2009; Mallinson, Cella, Cashy, & Holzner, 2006; Minton & Stone, 2012), and mood (Dimeo et al., 2004) and sleep disturbances (Andrykowski, Curran, & Lightner, 1998; Lindqvist, Widmark, & Rasmussen, 2004; Magnusson, Möller, Ekman, & Wallgren, 1999), as well as emotional and spiritual distress for both patients and their family members (Borneman et al., 2012; Magnusson et al., 1999; Mystakidou et al., 2006; Servaes, Verhagen, & Bleijenberg, 2002; Wang et al., 2002).

Despite its prevalence, consequences, and importance to patients and those who care for them, published reports suggest that fatigue is underrecognized and undertreated, perhaps in part because patients may hesitate to discuss fatigue treatment options with their healthcare team (Vogelzang et al., 1997) or may be unaware of interventions that have shown to be effective in the management of fatigue (Passik et al., 2002). Improved communication between patients and the healthcare team about CRF and efforts to reduce the barriers clinicians encounter in translating evidence-based fatigue interventions into clinical practice are critical to improving clinical outcomes (Borneman et al., 2007; Butt, Wagner, Beaumont, Paice, Straus, et al., 2008).

This chapter reviews the state of the science concerning CRF and offers guidance for practice and continued research. Five major content areas relative to CRF are addressed: (a) definition, incidence, pathophysiology, and risk factors, (b) measurement instruments, (c) clinical evaluation, (d) evidence-based pharmacologic and nonpharmacologic management to prevent and manage fatigue during and following cancer and its treatment, and (e) principles of patient and family education. The application of these concepts in the care of patients with CRF across the illness trajectory is illustrated.

Definition

Although no universally accepted definition of CRF has been established, the National Comprehensive Cancer Network® (NCCN®) defines it as an unusual, persistent, and subjective sense of tiredness that interferes with usual functioning (NCCN, 2014b). Based on the diagnostic criteria (see Figure 15-1), CRF is of a markedly different quality and severity from
ordinary fatigue, adversely affects function, and is unrelieved by rest or sleep (Cella, Lai, Chang, Peterman, & Slavin, 2002; Donovan, McGinty, & Jacobsen, 2013; Yeh et al., 2011). For the clinician to make the diagnosis of CRF, fatigue must be persistent and accompanied by associated symptoms such as increasing need for rest, limb heaviness, diminished concentration, inertia, emotional lability, and postexertional malaise. The clinician must also be fairly certain that the underlying cause is cancer or its treatment.

Etiology

The etiology and clinical expression of CRF is multidimensional. An inherently subjective condition, fatigue may be experienced and reported differently by each individual. Qualitative studies of fatigue underscore the fact that the cancer fatigue experience is unlike any other fatigue the patients have previously experienced, and patients emphasize that its unpredictability and refractoriness to self-management strategies that were previously effective make it a particularly distressing symptom (Glaus, Crow, & Hammond, 1996; Wu & McSweeney, 2007). Personality and coping style also may influence the experience of CRF (Andrykowski, Schmidt, Salsman, Beacham, & Jacobsen, 2005; Lukkahatai & Saligan, 2013; Menshadi, Bar-Tal, & Barnoy, 2013; Modlińska, Kowalik, Buss, Janiszewska, & Lichodziejewska-Niemierko, 2013). Some patients complain of a loss of efficiency, mental fogginess, inertia, and nonrestorative sleep, whereas others describe an excessive need to rest, the inability to recover promptly from exertion, or muscle heaviness and weakness (Scott, Lasch, Barsevick, & Paualt-Louis, 2011). Further research is needed to determine whether these represent variable features of fatigue, suggest the presence of fatigue subtypes, or are the cause or sequelae of fatigue (de Raaf, de Klerk, Timman, Hinz, & van der Rijt, 2012; Piper & Cella,
A Guide to Oncology Symptom Management (Second Edition)

2010; Sadler et al., 2002; Tchekmedyan, Kallich, McDermott, Fayers, & Erder, 2003). Efforts continue to be directed toward clarifying the defining features of fatigue (Jacobsen, Donovan, & Weitzen, 2003) and determining how CRF may be distinguished from syndromes such as depression, cognitive dysfunction, or asthenia that have overlapping symptoms or may share neurophysiologic mechanisms (Bower, 2012; Bower & Lamkin, 2013; Hinshaw, Carnahan, & Johnson, 2002; Minton, Alexander, & Stone, 2012; Minton & Stone, 2012; Reuter & Härter, 2004; Valentine & Meyers, 2001; Van Belle et al., 2005).

A large body of research exists describing the relationships between the occurrence and severity of CRF and treatment type, stage of tumor, time since treatment completion, and clinical and demographic factors. However, because of the variability in the association between CRF and disease- and treatment-related variables, few conclusions can be drawn (Prue et al., 2006). Understanding is further limited by the use of cross-sectional study designs, although fatigue symptoms are known to fluctuate across the course of cancer treatment. Despite these limitations, fatigue has been reported by 40%–90% of patients undergoing chemotherapy and radiation therapy (Campos, Hassan, et al., 2011; Donovan et al., 2013; Giacalone et al., 2013; Langston et al., 2013; Peters et al., 2014; Weis, 2011). Longitudinal studies suggest that in patients receiving cyclic chemotherapy, fatigue is most severe during the first three days after chemotherapy is administered and gradually improves until approximately the next treatment cycle (Hartvig, Aulin, Wallenberg, & Wagenius, 2006; Trudel-Fitzgerald, Savard, & Ivers, 2013a). During a course of fractionated radiation therapy, fatigue is often cumulative, and its peak of severity may occur after radiation is concluded (Karthikeyan, Jumnani, Prabhu, Manoor, & Supe, 2012). Severe fatigue is almost universal with the use of biologic response modifiers, including interferon alpha and the interleukins and following autologous or allogeneic hematopoietic stem cell transplantation. Little is known, however, concerning the prevalence of fatigue in patients receiving molecularly targeted agents such as tyrosine kinase inhibitors and agents that promote apoptosis. Moreover, the trajectory of fatigue experienced by individuals undergoing surgery for cancer has not been well characterized. Few consistent associations between treatment-related variables such as dose intensity, radiation fractionation schedule, and time since treatment completion have been observed (Prue et al., 2006).

The correlates of fatigue also appear to vary across the disease trajectory. For example, during active cancer treatment, fatigue has been shown to correlate with the presence of other distressing symptoms such as pain, sleep disturbances, dyspnea, and anorexia (Davis, Khoshknabi, & Yue, 2006; Kim, Barsevick, Beck, & Dudley, 2012; Trudel-Fitzgerald, Savard, & Ivers, 2013b; Yennurajalingam, Palmer, Zhang, Poulter, & Bruera, 2008). Across the cancer continuum, a systematic review has documented consistent associations between fatigue and both depression and anxiety (Brown & Kroenke, 2009). Associations between the occurrence and severity of CRF and demographic variables such as gender, age, marital status, and employment status have not been consistently identified. Studies suggest that fatigue may be related to anemia; mood disorder; concurrent symptoms such as pain, depression, or sleep disturbances; electrolyte imbalances; cardiopulmonary, hepatic, or renal dysfunction; hypothyroidism; hypogonadism; adrenal insufficiency; infection; malnutrition; deconditioning; and the sedative side effects of drugs that act on the central nervous system such as opioid analgesics, benzodiazepines, or anticonvulsants (Bruera, 2010; Horneber, Fischer, Dimeo, Rüffer, & Weis, 2012; Minton et al., 2012; Morrow, Shelke, Roscoe, Hickok, & Mustian, 2005; Mortimer et al., 2010; Nail, 2004; Neefjes et al., 2013; Oh & Seo, 2011; Purcell et al., 2010; Seo, Oh, & Seo, 2010; Strasser et al., 2006; Zick, Sen, Han-Markey, & Harris, 2013). A number of metabolic and endocrine disorders can exacerbate CRF, including hypothyroidism, hypogonadism, adrenal insufficiency, hypercalcemia, hypomagnesemia, and dehydration.
Cancer anorexia-cachexia syndrome and resultant protein-calorie malnutrition leads to increased proteolysis in skeletal muscles, producing muscle wasting, weakness/asthenia, and reduced endurance (Gould, Lahart, Carmichael, Koutedakis, & Metsios, 2013).

Accumulating evidence also suggests that gene polymorphisms, altered circadian rhythmicity, immune dysregulation, and proinflammatory cytokine activity may directly or indirectly contribute to CRF (Ancoli-Israel et al., 2006; Bower & Lamkin, 2013; Massacesi et al., 2006; Reyes-Gibby et al., 2013; Schubert, Hong, Natarajan, Mills, & Dimsdale, 2007). Etiologic factors associated with CRF are listed in Figure 15-2.

Pathophysiology

The precise pathophysiology of CRF is poorly understood. In some instances, fatigue is temporally related to treatment and resolves after its completion. However, fatigue also may persist for months or even years after treatment concludes. In any one individual, the etiology of CRF is likely to be multifactorial, and across the disease trajectory the relative contribution of each etiology can fluctuate.

Although study findings are not consistent, perhaps in part because of the challenges in studying the mechanisms of fatigue in humans, evidence suggests that a proinflammatory immune response and elevated circulating levels of inflammatory cytokines are one of the major contributing factors to fatigue (Bower & Lamkin, 2013; Minton & Stone, 2013). Elevated concentrations of inflammatory cytokines such as interleukin (IL)-1 receptor antagonist, IL-6, and neopterin in association with fatigue have been described in patients receiving chemotherapy or radiation therapy and in long-term survivors (Saligan & Kim, 2012; Schubert et al., 2007). The precise mechanisms by which proinflammatory cytokines initiate or promote CRF are a topic of continued study, but evidence suggests that a proinflammatory state may lead to fatigue by alteration of muscle metabolism, through dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, and via direct effects on the mechanisms of arous-

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**FIGURE 15-2  Etiologic Factors for Cancer-Related Fatigue**

- Adrenal insufficiency
- Anemia
- Cancer treatment
- Cardiopulmonary, hepatic, or renal dysfunction
- Concurrent symptoms (e.g., pain, dyspnea)
- Deconditioning
- Depletion of vitamins B₁, B₆, and B₁₂
- Electrolyte disturbances (calcium, magnesium, phosphorus)
- Generalized inflammation
- Hypogonadism
- Hypothyroidism
- Impaired sleep quality
- Infection
- Malnutrition
- Psychological distress (depression, anxiety)
- Side effects of medications that act on central nervous system (e.g., narcotics, anxiolytic antiemetics)
- Underlying disease

*Note. Based on information from Horneber et al., 2012; Mortimer et al., 2010; Radbruch et al., 2008; Weis, 2011.*
al within the central nervous system (Barsevick, Frost, Zwinderman, Hall, & Halyard, 2010; Bower & Lamkin, 2013; Miller, Ancoli-Israel, Bower, Capuron, & Irwin, 2008). The concept of “sickness behavior” may be particularly relevant to understanding the link between pro-inflammatory cytokine elevations, arousal and affect, and CRF (Dantzer, O’Connor, Freund, Johnson, & Kelley, 2008; Johnson, 2002; Miller, 2003). The indicators of sickness behavior include a loss of energy and motivation, changes in sleep and appetite, and a decrease in exploratory and mating behaviors. During recovery from acute inflammation, such as occurs with infection, sickness behavior is part of an adaptive motivational state that focuses the organism’s priorities on recovery. However, in patients whose immune system is chronically activated, sickness behavior may be among the pathophysiologic mechanisms for CRF. In support of the importance of sickness behavior in CRF is the fact that proinflammatory cytokines also play a role in cachexia, anemia, sleep disturbances, depression, fever, and infection, all of which can worsen fatigue (Kamath, 2012; Wood & Weymann, 2013).

Proinflammatory cytokines also result in altered serotonin metabolism within the brain, and serotonin is involved in many biological processes, including muscle contraction. Alterations in synaptic levels of serotonin or in serotonin receptor function within the brain have been associated with reduced capacity for voluntary activation of muscle and the sensation of a reduced ability to perform physical work (Jager, Sleijfer, & van der Rijt, 2008). Thus, serotonin dysregulation may be a contributing factor to CRF and is perhaps responsible for the sensation of muscular weakness and/or the sense of greater effort required to accomplish a task that many patients with CRF describe (Kisiel-Sajewicz et al., 2012; Ryan et al., 2007).

Disturbed sleep also may be an intermediary factor that explains the relationship between CRF and one or more of the mechanisms discussed previously, including disruptions in the HPA axis and circadian rhythms, serotonin metabolism, and proinflammatory cytokine expression (Berger & Mitchell, 2008; Liu et al., 2012; Payne, 2011). Studies suggest that cancer and its therapy dysregulate the HPA axis and adversely affect the secretion of corticotropin-releasing hormone (Ryan et al., 2007). Changes in this essential neuroendocrine hormonal milieu can impair several aspects of sleep, including depth of sleep, slow-wave sleep, rapid eye movement sleep, and waking (Parker et al., 2008). These adverse changes in sleep architecture act together with psychological stressors to produce significant sleep disturbances in patients with cancer (Akechi et al., 2007).

Another postulated cause of CRF is altered energy metabolism within skeletal muscle. Substances in the muscle, including calcium, potassium, hydrogen peroxide–induced adenosine diphosphate, and adenosine triphosphate (ATP), all affect skeletal muscle energy metabolism, thereby influencing the muscle’s ability to perform mechanical work (Kilgour et al., 2010). Cancer, its treatment with chemotherapy and radiation therapy, and any resulting anemia or cachexia may contribute directly or indirectly to altered skeletal muscle energy metabolism and to reductions in the capacity for muscle contraction via the accumulation of metabolites, deprivation of nutrients, disruption of mitochondrial synthesis of ATP, or diminished oxygen delivery to muscle cells (Neil, Klika, Garland, McKenzie, & Campbell, 2013).

Several different conceptual models of CRF pathophysiology have been proposed. Although many of these models use similar constructs, they can be differentiated based on the extent to which they emphasize fatigue as caused by disturbances in energy balance, stress responses, or neuroendocrine regulation. Energy balance/energy analysis models depict energy as the major variable in fatigue and posit that alterations in the balance among intake, metabolism, and expenditure of energy as factors in producing fatigue. Examples of this thematic group of models include Piper’s Integrated Fatigue Model (Piper, Lindsey, &
Dodd, 1987), Irvine’s Energy Analysis Model (Irvine, Vincent, Graydon, Bubela, & Thompson, 1994), and Winningham’s Psychobiologic-Entropy Model (Winningham, 2001). Models that postulate fatigue as a response to stress posit that tiredness, fatigue, and exhaustion form an adaptational continuum of response to stress. Each state along this continuum from tiredness to exhaustion may be distinguished by different behavioral and symptom patterns. Examples of models included in this thematic class are those proposed by Aistars (1987), Rhoten (1982), Glaus (1998), and Olson (2007). Lastly, neuroendocrine regulatory fatigue models hypothesize that the multiple dimensions of fatigue are explained by dysregulation in the functioning of the regulatory systems controlling the neurologic, endocrine, and immune systems, including the HPA axis, circadian rhythms, and neuroimmune system transmitter secretion and function (Miller et al., 2008). Examples of fatigue models based on neuroendocrine dysregulation include those that have been proposed by Lee (Lee et al., 2004), Payne (2004), Morrow (Morrow, Andrews, Hickok, Roscoe, & Matteson, 2002), and Schubert (Schubert et al., 2007). These conceptual models may be helpful in generating testable hypotheses for continued research into CRF and in guiding the development and evaluation of interventions to limit and manage fatigue and to reduce its deleterious impact on health-related quality of life.

Assessment

Identifying patients with CRF is the first step in improving fatigue evaluation and management. Studies suggest that CRF is underdiagnosed, that the assessment of fatigue in patients with cancer is suboptimal, and that healthcare professionals may not fully appreciate the degree of distress and functional loss that fatigue produces (Hockenberry-Eaton & Hinds, 2000; Knowles, Borthwick, McNamara, Miller, & Leggot, 2000; Vogelzang et al., 1997). Identified barriers to communication between patients and their clinicians about fatigue include the clinician’s failure to offer interventions (47%), the patient’s lack of awareness of effective treatments for fatigue (43%), a desire on the patient’s part to treat fatigue without medications (40%), and the patient’s tendency to be stoic about fatigue to avoid being labeled as a “complainer” (28%) (Passik et al., 2002; Perl, Quigley, & Hevey, 2014; Shun, Lai, & Hsiao, 2009; Siegel, Lekas, & Maheshwari, 2012).

CRF assessment includes two aspects: (a) routine, periodic screening of all patients to identify the presence of CRF and gauge its severity and (b) detailed evaluation in patients with moderate or severe CRF, of the characteristics, consequences, and potential contributing factors. A wide range of approaches to the assessment of CRF exist in the literature, including single items that gauge fatigue severity, single items or subscales relevant to fatigue and drawn from measures of quality of life, psychosocial adjustment, mood or self-reported health status, and instruments that were designed specifically to evaluate CRF from a multidimensional perspective.

Although no consensus currently exists concerning the optimal method or frequency for CRF screening in the clinical or research setting (Alexander, Minton, & Stone, 2009; Davis, Lai, Hahn, & Cella, 2008; Strasser, Müller-Käser, & Dietrich, 2009), evidence of the widespread occurrence of CRF supports a conclusion that screening should occur at regular intervals throughout treatment, follow-up, and long-term follow-up. Evidence is accumulating that single-item measures to screen for fatigue are rapid and sensitive and can be applied efficiently in the clinic to identify patients who would benefit from more systematic evaluation (Danjoux, Gardner, & Fitch, 2007; Hwang, Chang, & Kasimis, 2003; Kirsh, Passik, Holtsclaw, Donaghy, & Theobald, 2001; Temel, Pirl, Recklitis, Cashavelly, & Lynch, 2006). In screening
for fatigue in the clinic, nurses must also consider the recall period (e.g., past 24 hours, past seven days, past month) that has the most clinical relevance for a specific patient population and that would be least affected by biases of recall or by transient changes in CRF severity. Streamlined approaches to screening may be offered by technologies that use electronic or web-based applications and emphasize real-time assessments of fatigue (Hacker & Ferrans, 2007) or computer-adapted testing (Lai et al., 2011). Figure 15-3 offers a screening measure for CRF that nurses can apply in their clinical setting to identify patients who warrant further evaluation and clinical intervention.

Although a single-item measure may provide rapid assessment of general fatigue or serve as a clinical screening tool (Butt, Wagner, Beaumont, Paice, Peterman, et al., 2008), evidence suggests that single-item measures do not fully capture all the dimensions of fatigue (Banthia et al., 2006; Sobel-Fox et al., 2013). More than 20 self-report measures (including single-item measures, multi-item unidimensional scales, and multidimensional inventories) have been developed to measure fatigue in patients with cancer (Agasi-Idenburg, Velthuis, & Wittink, 2010; Kirkova et al., 2011; Minton & Stone, 2009; Mota & Pimenta, 2006; Seyidova-Khoshknabi, Davis, & Walsh, 2011; Whitehead, 2009). These measures are summarized in Table 15-1.

Unidimensional fatigue measures typically focus on the severity of the fatigue, although multi-item unidimensional scales also may ask about the severity of other symptoms such as

<table>
<thead>
<tr>
<th>FIGURE 15-3</th>
<th>Screening Questions for Cancer-Related Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>On how many days in the past week have you felt somewhat to quite fatigued?</td>
<td></td>
</tr>
<tr>
<td>□ None □ 1–2 days □ 3–5 days □ More than 5 days</td>
<td></td>
</tr>
<tr>
<td>In the past week, on a scale of 0 to 10, what is the “worst” fatigue you have experienced?</td>
<td></td>
</tr>
<tr>
<td>None 0 1 2 3 4 5 6 7 8 9 10 Worst</td>
<td></td>
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<tr>
<td>Within the past week, to what extent has fatigued interfered with:</td>
<td></td>
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<tr>
<td>Performing the activities you need or want to do</td>
<td></td>
</tr>
<tr>
<td>Relationships with other people</td>
<td></td>
</tr>
<tr>
<td>Mood</td>
<td></td>
</tr>
<tr>
<td>Have you been experiencing any of the following symptoms during the past 7 days? Select all that apply:</td>
<td></td>
</tr>
<tr>
<td>□ I have no symptoms</td>
<td></td>
</tr>
<tr>
<td>□ Pain □ Nausea □ Poor appetite □ Difficulty sleeping</td>
<td></td>
</tr>
<tr>
<td>□ Shortness of breath □ Difficulty moving around</td>
<td></td>
</tr>
<tr>
<td>□ Problem with bowels □ Other</td>
<td></td>
</tr>
<tr>
<td>Would you like to discuss your fatigue with a member of your healthcare team?</td>
<td></td>
</tr>
<tr>
<td>□ No □ Yes</td>
<td></td>
</tr>
<tr>
<td>Measure</td>
<td>Dimensions of Fatigue Evaluated</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Brief Fatigue Inventory&lt;sup&gt;a&lt;/sup&gt; (Mendoza et al., 1999)</td>
<td>Severity and impact of fatigue</td>
</tr>
<tr>
<td>Cancer-Related Fatigue Distress Scale (Holley, 2000)</td>
<td>Consequences of fatigue relative to physical, social, or psychospiritual distress</td>
</tr>
<tr>
<td>Cancer Fatigue Scale&lt;sup&gt;a&lt;/sup&gt; (Okuyama et al., 2000)</td>
<td>Physical, affective, and cognitive dimensions of fatigue</td>
</tr>
<tr>
<td>Chalder Fatigue Scale (Armes et al., 2007)</td>
<td>Fatigue severity, associated distress, self-efficacy for coping, and the extent to which fatigue was overwhelming, uncontrollable, unpredictable, and abnormal</td>
</tr>
<tr>
<td>Fatigue Numerical Scale (Okuyama et al., 2000)</td>
<td>Severity of fatigue</td>
</tr>
<tr>
<td>Fatigue Scale–Adolescent (Hinds et al., 2007)</td>
<td>Multiple dimensions of fatigue including affective, behavioral, somatic, and cognitive aspects of fatigue and consequences for daily functioning</td>
</tr>
<tr>
<td>Fatigue Severity Scale (Krupp et al., 1989)</td>
<td>Single-item fatigue severity score and impact of fatigue on daily functioning</td>
</tr>
<tr>
<td>Fatigue Symptom Inventory (Hann et al., 1998)</td>
<td>Severity, frequency, and daily pattern of fatigue and its interference with quality of life</td>
</tr>
<tr>
<td>Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F)&lt;sup&gt;a,b&lt;/sup&gt; (Yelen et al., 1997)</td>
<td>Physical, affective, and cognitive dimensions of fatigue and consequences for daily functioning</td>
</tr>
<tr>
<td>Lee Fatigue Scale (Lee et al., 1991)</td>
<td>Fatigue, energy</td>
</tr>
<tr>
<td>Multidimensional Assessment of Fatigue (Belza, 1995)</td>
<td>Fatigue severity, timing, distress, and interference</td>
</tr>
</tbody>
</table>

(Continued on next page)
<table>
<thead>
<tr>
<th>Measure</th>
<th>Dimensions of Fatigue Evaluated</th>
<th>Number of Items</th>
<th>Scaling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multidimensional Fatigue Inventory(^{a}) (Smets et al., 1995)</td>
<td>Multiple dimensions of fatigue: global experience, somatic symptoms, cognitive symptoms, affective symptoms, and behavioral symptoms</td>
<td>20</td>
<td>5-point Likert scale</td>
</tr>
<tr>
<td>Multidimensional Fatigue Symptom Inventory (Stein et al., 1998)</td>
<td>Multiple dimensions of fatigue: global experience, somatic symptoms, cognitive symptoms, affective symptoms, and behavioral symptoms</td>
<td>83</td>
<td>5-point Likert scale</td>
</tr>
<tr>
<td>Patient-Reported Outcomes Measurement Information System (PRO-MIS) Fatigue(^{a,b,c}) (Christodoulou et al., 2008; Jung-Haenel et al., 2011; Lai et al., 2011, 2013)</td>
<td>The fatigue item bank evaluates a range of self-reported symptoms, from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one’s ability to execute daily activities and function normally in family or social roles. Fatigue is divided into the experience of the symptom (frequency, duration, and intensity) and its impact on physical, mental, and social activities. The fatigue short forms are generic rather than disease-specific. Each assesses fatigue over the past 7 days.</td>
<td>Item bank comprising 95 fatigue items</td>
<td>Each question has five response options ranging in value from 1 to 5. Higher scores represent greater fatigue.</td>
</tr>
<tr>
<td>Piper Fatigue Scale–Revised (Piper et al., 1998)</td>
<td>Fatigue severity and aspects of the fatigue experience including sensory, behavioral, affective/meaning, and cognitive/mood</td>
<td>22</td>
<td>11-point Likert scale</td>
</tr>
<tr>
<td>Rhoten Fatigue Scale (Schneider, 1998)</td>
<td>Fatigue severity</td>
<td>1</td>
<td>11-point linear analog scale</td>
</tr>
<tr>
<td>Schwartz Cancer Fatigue Scale (Schwartz, 1998)</td>
<td>Physical and perceptual fatigue</td>
<td>6</td>
<td>5-point Likert scale</td>
</tr>
</tbody>
</table>

\(^{a}\) Available in multiple languages  
\(^{b}\) Norms for comparison with health and cancer samples available  
\(^{c}\) Available in a pediatric version

Note. Based on information from Agasi-Idenburg et al., 2010; Kirkova et al., 2006; Minton & Stone, 2009; Mota & Pimenta, 2006; Seyidova-Khoshknabi et al., 2011; Shahid et al., 2010; Whitehead, 2009.
exhaustion, tiredness, or weakness. Examples of unidimensional fatigue measures include quality-of-life measures such as the Functional Assessment of Chronic Illness Therapy–Fatigue (FACT-F), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Fatigue Subscale, and the Patient-Reported Outcomes Measurement Information System (PROMIS) fatigue item banks for children and adults (Lai et al., 2011, 2013). Measures of symptoms, health, mood state, or psychosocial adjustment, such as the SF-36®, Profile of Mood States, Rotterdam Symptom Checklist, Brief Symptom Inventory, and Symptom Distress Scale, include single items that address fatigue or subscales that reflect fatigue, vigor, or vitality. In evaluating a potential measurement approach to fatigue assessment, muses must keep in mind that other subjective descriptors, such as “weakness” and “tiredness” or “absence of vigor,” are not necessarily equated with the measurement of fatigue.

According to the general consensus in the literature, fatigue generally consists of a sensory dimension (fatigue severity, persistence), a physiologic dimension (e.g., leg weakness, diminished mental concentration), and a performance dimension (reduction in performance of needed or valued activities). Multidimensional fatigue measures provide information about this full range of characteristics rather than simply intensity. The Fatigue and Contributing Factors Inventory is a self-report questionnaire designed to characterize factors that may contribute to CRF, including sleep disturbance, distress, inactivity, and concurrent medications (Mortimer et al., 2010). A new outcome measure to evaluate the construct of self-efficacy for fatigue management has also been recently tested (Hoffman et al., 2011), and may be useful in fatigue research that targets self-efficacy as an intermediate or distal clinical outcome. Ecological momentary assessment of fatigue (a technique that offers real-time measurement of a phenomenon as it occurs in a naturalistic setting) may overcome some of the methodologic limitations of fatigue assessment, including recall bias and the influence of current context on self-report of fatigue (Hacker & Ferrans, 2007).

Nurses should consider the measurement properties and strengths and limitations of these instruments, including reliability, validity, specificity, sensitivity to change, recall period, respondent burden, translation in multiple languages and the availability of normed values to aid interpretation, in determining the utility of a measure for specific clinical or research purposes (Barsevick, Beck, et al., 2010).

The NCCN (2014b) guidelines recommend that CRF be assessed using a two-tiered approach. First, every patient should be screened for the presence or absence of fatigue, and if present, fatigue should be assessed quantitatively on a 0–10 scale (0 = no fatigue and 10 = worst fatigue imaginable). Patients with a severity of more than 4 should be further evaluated by a history and physical examination, including an evaluation of whether disease progression or recurrence could be among the causes of fatigue. Components of fatigue assessment include its presence, intensity, persistence or pervasiveness, course over time, exacerbating and relieving factors, and impact on functioning and level of distress. Clinicians can obtain valuable information about the consequences of CRF by exploring its effects on patients’ self-esteem, mood, and ability to perform activities of daily living, fulfill important roles (e.g., parent, spouse, employee), and relate to family and friends. It is also important to evaluate what interventions patients are using to manage fatigue and the degree to which those interventions are effective in relieving fatigue. The presence of any treatable etiologic or contributing factors, such as hypothyroidism, hypogonadism, adrenal insufficiency, cardiomyopathy, pulmonary dysfunction, concurrent distressing symptoms, emotional distress, sleep disturbances, anemia, nutritional compromise, fluid and electrolyte imbalances, and inactivity/physical deconditioning, should be identified (Berger, Yennu, & Million, 2013; Horneber et al., 2012; Weis, 2011). Current medications (including over-the-counter medi-
cations and herbal supplements) should be reviewed to identify any agents or medication interactions that may contribute to worsening fatigue. The medication profile should also be reviewed to identify specific classes of medications with a sedative side effect profile. These may include opioid analgesics, sedative-hypnotic agents such as secobarbital, benzodiazepines such as lorazepam, and anxiolytics such as buspirone. A number of antidepressant agents, antiemetics, antihistamines, and anticonvulsant agents such as gabapentin, phenobarbital, and carbamazepine also have the potential to produce sedation and daytime sleepiness and fatigue. Certain cardiac medications (e.g., beta-blockers) may contribute to fatigue by causing bradycardia. Medications such as corticosteroids may cause fatigue by disrupting sleep. The coadministration of multiple agents with sedative, cardiac, or sleep-disrupting side effects may significantly compound fatigue symptoms. Figure 15-4 lists the dimensions of the fatigue experience that should be explored when evaluating patients with CRF.

Evidence-Based Interventions

Because fatigue typically has several different causes in any one patient, the treatment plan needs to be individualized. It is helpful to work with the patient and family caregivers to improve assessment of fatigue and identify management strategies. Open communication between the patient and family and the caregiving team will facilitate discussion about the experience of fatigue and its effects on daily life. General supportive care recommendations for patients with fatigue include encouraging a balanced diet with adequate intake of fluid, calories, protein, carbohydrates, fat, vitamins, and minerals, and balancing rest with physical activity and attention-restoring activities such as exposure to natural environments and pleasant distractions such as music (Horneber et al., 2012; NCCN, 2014b; Weis, 2011). The results of trials of interventions to reduce or manage fatigue are summarized in Figure 15-5, and selected findings are discussed in the following sections.

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**FIGURE 15-4** Dimensions to Include in a Fatigue Assessment

Fatigue is a common problem for patients with cancer. It is a feeling of weariness, tiredness, or exhaustion that can include a loss of physical and/or emotional energy. Many factors can contribute to the fatigue that a person with cancer experiences.

- On a scale of 0–10 where 0 is no fatigue and 10 is the worst fatigue imaginable, how severe has your fatigue been in the past 7 days?
- Would you say that your fatigue is mild, moderate, or severe?
- When did the fatigue start?
- Duration of fatigue: ____ days per week or ____ hours per day
- To what extent have you, because of fatigue, had to limit social activity, had difficulty getting things done, or felt like fatigue was making it difficult to maintain a positive outlook?
- To what extent does fatigue interfere with relationships or fulfilling responsibilities at work or in the home?
- What makes your fatigue better?
- What makes your fatigue worse?
- What do you do to help with fatigue or manage fatigue?
- Does rest relieve your fatigue?
- Do you have any trouble sleeping?
- Do you have other symptoms such as pain, difficulty breathing, or nausea and vomiting?
- Do you experience anxiety? If yes, how often?
- Do you feel discouraged, blue, or sad? If yes, how often?
- Have you discussed your fatigue with anyone on your healthcare team?
- Have you ever been given any recommendations for managing your fatigue?
### Evidence-Based Interventions for Managing Cancer-Related Fatigue

#### Interventions With Strong and Consistent Evidence Supporting Effectiveness
- Education/information provision
- Energy conservation and activity management
- Exercise
- Measures to optimize sleep quality
- Screening for potential etiologic factors and managing them as appropriate
- Structured rehabilitation

#### Interventions With Preliminary Evidence to Support Effectiveness
- Acupuncture
- Adenosine 5′-triphosphate infusion
- Cognitive behavioral therapy (CBT) for fatigue, sleep, or symptom distress
- Corticosteroids
- Distraction—virtual reality immersion
- Fish oil supplementation
- Ginseng
- Levocarnitine supplementation
- Management of concurrent symptoms
- Massage and healing touch
- Mindfulness-based stress reduction
- Relaxation
- Thyrotropin-releasing hormone
- Yoga

#### Interventions With Evidence Supporting Effectiveness but With Risk for Harm
- Correction of anemia with hemoglobin less than 10 g/dl

#### Interventions for Which Effectiveness Has Not Been Established
- Bupropion sustained-release
- Combination therapy: Aromatherapy, foot soak, and reflexology
- Combination therapy: Medroxyprogesterone, celecoxib, and enteral food supplementation
- Combination therapy: Soy protein supplementation and nutrition counseling
- Donepezil
- Expressive writing
- Individual and group psychotherapy
- Methylphenidate
- Modafinil
- Paroxetine

#### Interventions Supported by Expert Opinion
- Consider attention-restoring activities such as exposure to natural environments and pleasant distractions such as music.
- Encourage a balanced diet with adequate intake of fluid, calories, protein, carbohydrates, fat, vitamins, and minerals.
- Promote open communication between the patient and family and the caregiving team to facilitate discussions about the experience of fatigue and its effects on daily life.
- Work with the patient and family caregivers to improve assessment of fatigue and identify management strategies.

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**Note.** Based on information from Mitchell, 2010.
Pharmacologic Measures

More than 15 pharmacologic agents or nutraceuticals, either alone or in combinations, have been evaluated for their effectiveness in reducing fatigue during and following cancer treatment, including paroxetine, bupropion, amisulpride, methylphenidate, sertraline, dexamethasone, testosterone replacement, corticosteroids, American ginseng, multivitamin formulas, high-dose vitamin C supplementation, levocarnitine, and omega-3 fatty acid supplementation. These agents have been studied in randomized controlled trials as well as single-arm, open-label studies with small samples. A recent systematic review has summarized the trial results for a number of pharmacologic agents for CRF management (Minton, Richardson, Sharpe, Hotopf, & Stone, 2010).

Four trials have examined the effectiveness of the antidepressant paroxetine in treating fatigue during and following cancer treatment, with mixed findings. In two large multicenter, randomized, double-blind, placebo-controlled trials, paroxetine 20 mg PO daily did not have an effect on fatigue, although it improved depression and overall mood (Morrow et al., 2003; Roscoe et al., 2005). However, two small trials showed a trend toward a possible benefit for paroxetine in treating fatigue in women with hot flashes (n = 13) (Weitzner, Montello, Jacobsen, & Minton, 2002) and in patients receiving interferon alpha (n = 18) (Capurron et al., 2002).

A recent meta-analysis and a systematic review concluded that preliminary evidence supports the use of methylphenidate to treat CRF (Breitbart & Alici, 2010; Minton, Richardson, Sharpe, Hotopf, & Stone, 2011). Although several of the analyzed trials failed to find any benefit over placebo, they also showed no difference in the frequency of adverse events between methylphenidate and placebo. Since publication of the Minton et al. (2011) review, three additional randomized, blinded, placebo-controlled trials have demonstrated favorable effects on CRF despite the occurrence of side effects such as dry mouth, hypertension, and nausea (Kerr et al., 2012; Lower et al., 2009; Roth et al., 2010), while two other randomized, placebo-controlled trials showed no effects of methylphenidate (Bruera et al., 2013; Moraska et al., 2010). Recent evidence from a retrospective analysis across trials suggests that the D-isomer form of methylphenidate may be more effective than other forms and that patients with more severe fatigue and those demonstrating an improvement in fatigue within the first few days of methylphenidate treatment are the most likely to derive benefit (Yennurajalingam, Palmer, Chacko, & Bruera, 2011).

Modafinil is a novel psychostimulant, a member of the class of drugs commonly referred to as wakefulness-promoting agents. Modafinil at a daily or divided dose of 100–400 mg seems to be well tolerated among patients with cancer (Cooper, Bird, & Steinberg, 2009) and has shown improved fatigue outcomes in two single-arm open-label trials (Blackhall, Petroni, Shu, Baum, & Farace, 2009; Spathis et al., 2009) and a large placebo-controlled, randomized trial (Jean-Pierre et al., 2010). However, in another randomized placebo-controlled trial in patients with lung cancer (Spathis et al., 2014) and in a placebo-controlled, randomized, crossover trial in patients with primary brain tumors (Boele et al., 2013), the effects of modafinil on fatigue endpoints did not surpass those of placebo.

The antidepressants bupropion, sertraline, and venlafaxine have also been studied with mixed results. Bupropion sustained-release at a dose of 100–150 mg/day was found to be efficacious in the management of fatigue in two uncontrolled trials in small samples of patients with mixed tumor types (N < 25 in each trial) (Cullum, Wojciechowski, Pelletier, & Simpson, 2004; Moss, Simpson, Pelletier, & Forsyth, 2006). In those patients who derived benefit, the improvement occurred within two to four weeks. Controlled studies are neces-
sary to establish the efficacy of this intervention in larger and more homogeneous samples of patients with cancer and to determine whether this effect of bupropion is separate from its action as an antidepressant. In a randomized controlled trial in nondepressed patients with cancer, sertraline did not result in improvement (Stockler et al., 2007). Antidepressant treatment with venlafaxine, however, did produce improvement in fatigue, but only in patients who experienced significant improvement in the severity and degree of interference from hot flashes (Carpenter et al., 2007).

Donepezil is a centrally acting, reversible acetylcholinesterase inhibitor currently used to treat Alzheimer disease. In two open-label trials in patients with cancer, donepezil 5–10 mg/day was found to be effective in limiting CRF (Bruera et al., 2003; Shaw et al., 2006). However, a randomized, double-blind, placebo-controlled trial did not show an improvement in fatigue outcomes compared with placebo (Bruera et al., 2007).

A recent randomized, double-blind, placebo-controlled trial in 84 patients with advanced cancers demonstrated an improvement in fatigue outcomes in patients who received dexamethasone 4 mg twice daily for two weeks (Yennurajalingam, Frisbee-Hume, et al., 2013). Although adverse events were comparable between the dexamethasone and placebo groups, systemic corticosteroids could be associated with a prominent adverse effect profile in particular subpopulations, such as those at the end of life (Matsuo & Yomiya, 2014). A pilot, randomized, placebo-controlled, crossover study has also shown evidence for the effectiveness and tolerability of thyrotropin-releasing hormone in improving fatigue outcomes in a small sample of patients with cancer with significant fatigue (Kamath, Feinn, & Winokur, 2012).

Despite the fact that male hypogonadism is hypothesized to be a contributor to impairments in mood and well-being (Vigano et al., 2010), a recent blinded, placebo-controlled trial of testosterone replacement therapy in a small sample of men with advanced cancer did not demonstrate positive effects on fatigue experiences (Del Fabbro et al., 2013).

Several nutritional supplements including coenzyme Q10, levocarnitine, lectin-standardized mistletoe, omega-3 fatty acid supplements, ginseng, guarana, and valerian have been explored, either as single agents or as part of a combination therapy, to improve fatigue outcomes (Finnegan-John, Molassiotis, Richardson, & Ream, 2013; Gupta et al., 2011; Lesser et al., 2013; Sood, Barton, Bauer, & Loprinzi, 2007). Across single studies, improvements in fatigue endpoints were mixed, and interpretation of some of the study results is complicated by design or sampling limitations. However, notably, a randomized, double-blind, placebo-controlled trial (n = 364) demonstrated the effectiveness and tolerability of an eight-week course of Wisconsin ginseng in improving fatigue outcomes (Barton et al., 2013). Another randomized, placebo-controlled, crossover study (n = 75) showed that guarana 50 mg twice daily may be a safe and effective way to treat CRF in women with breast cancer who are receiving chemotherapy (Campos, Riechelmann, et al., 2011). However, guarana 75 mg once daily was not found to be effective in treating fatigue in a double-blinded, placebo-controlled trial in women with breast cancer undergoing radiation therapy (da Costa Miranda et al., 2009).

Four small, open-label trials have suggested the safety and potential efficacy of levocarnitine supplementation in treating fatigue in patients with cancer who have low serum carnitine levels (Cruciani et al., 2004, 2006; Gramignano et al., 2006; Graziano et al., 2002), and exploratory endpoints in a two phase III trials have suggested that levocarnitine may be effective in treating CRF (Cruciani et al., 2009; Mantovani et al., 2008). However, a large, recently completed double-blind, placebo-controlled, randomized trial failed to demonstrate an improvement in fatigue outcomes in patients with invasive malignancies and good performance status, even in study participants who were deficient in levocarnitine (Cruciani et al., 2012).
Correction of Anemia

The use of erythropoiesis-stimulating agents (ESAs) to correct anemia with hemoglobin levels less than 10 g/dl may result in increased vigor and diminished fatigue (Bohlius et al., 2009; Bohlius, Tonia, & Schwarzer, 2011; Eton & Cella, 2011; Tonia & Bohlius, 2011). However, only limited evidence supports that erythropoietin improves fatigue outcomes when anemia is less severe. A target hemoglobin level of 11–12 g/dl is associated with the greatest gains in fatigue and other quality-of-life outcomes (Eton & Cella, 2011). A recent systematic review also concluded that in many of the trials, the improvement in fatigue outcomes did not exceed the minimal clinically important difference (Grant et al., 2013). While both epoetin and darbepoetin are generally well tolerated, the use of these agents specifically for the management of fatigue must be considered in light of their safety issues, including a small increased risk of thrombotic events, hypertension, pure red cell aplasia, and theoretical concerns that ESAs may support or extend tumor growth in certain disease types (Bohlius et al., 2011; Boulaamane et al., 2013; Tonia et al., 2012).

Overall, better quality evidence is needed to unequivocally support the use of ESAs solely to improve patient-reported outcomes such as fatigue. National clinical practice guidelines (Lichtin, 2011; NCCN, 2014a; Rizzo et al., 2010) and the recommendations of the U.S. Food and Drug Administration (2013) should guide decisions about patient monitoring, treatment thresholds, dose reductions, treatment initiation and discontinuation, and the use of supplemental iron in patients receiving ESAs. Although specific clinical circumstances may necessitate treatment at higher than recommended hemoglobin thresholds (e.g., patients with substantially reduced exercise capacity or ability to carry out activities of daily living), evidence is lacking to recommend initiating ESAs at hemoglobin levels greater than 10 g/dl. The guidelines from the American Society of Clinical Oncology (Rizzo et al., 2010) recommend that hemoglobin be raised to (or near) a concentration of 12 g/dl, at which time the dose should be titrated to maintain that level. Dose reductions also are recommended when the hemoglobin approaches 12 g/dl or when the hemoglobin increases more than 1 g/dl in a two-week period. Iron stores should also be monitored, and iron intake should be supplemented in patients receiving ESAs. The guidelines also urge prescribers to use these agents cautiously in patients with an elevated risk for thromboembolic complications and caution against the use of these agents in patients with cancer who are not receiving chemotherapy, as recent trials have reported increased thromboembolic risks and decreased survival under these circumstances (Bormanis et al., 2013; Gao, Ma, & Lu, 2013; Tonia, Schwarzer, & Bohlius, 2013; Wauters & Vansteenkiste, 2012).

Exercise

Meta-analyses of randomized trials support the benefits of exercise in the management of fatigue during and following cancer treatment in patients with breast cancer and other solid tumors or undergoing hematopoietic stem cell transplantation, although effect sizes are generally small and positive results for the outcome of fatigue have not been observed consistently across studies (Cramp & Byron-Daniel, 2012; Eickmeyer, Gamble, Shahpar, & Do, 2012; Mustian, Sprod, Janelins, Peppone, & Mohile, 2012). The exercise modalities that have been applied differ in content (walking, cycling, swimming, resistive exercise, or combined exercise), frequency (ranging from two times per week to two times daily), intensity (with most programs at 50%–90% of the estimated VO₂ maximum heart rate), degree of supervision (fully supervised group vs. self-directed exercise), and duration (from two weeks up to one year). Knowledge about the type, intensity, and duration of physical exercise most
beneficial in reducing fatigue at different stages of disease and treatment is still developing (Puetz & Herring, 2012), and more research is needed to systematically assess the safety of exercise (both aerobic exercise and strength training) in cancer subpopulations (Wolin, Schwartz, Matthews, Courneya, & Schmitz, 2012).

**Psychoeducational, Cognitive Behavioral, and Rehabilitative Interventions**

Several adequately powered randomized controlled trials and systematic and meta-analytic reviews (Goedendorp, Gielissen, Verhagen, & Bleijenberg, 2009; Jacobsen, Donovan, Vadaparampil, & Small, 2008; Kangas, Bovbjerg, & Montgomery, 2008; van Weert et al., 2008; Wanchai, Armer, & Stewart, 2011) support the important role of educational interventions, psychological support, cognitive behavioral interventions, symptom management, and rehabilitative interventions in supporting positive coping in patients with CRF during and following treatment and that such interventions decrease fatigue severity and its interference with daily functioning. Across studies, a number of common elements were incorporated into the psychoeducational interventions. These included anticipatory guidance about fatigue patterns, tailored recommendations for self-management, including increased activity/exercise and measures to address sleep dysregulation, coaching to enhance motivation, and empower self-care and active coping, and praise and encouragement to promote self-efficacy and augment feelings of control. Other elements of effective psychoeducational interventions for fatigue included supportive counseling (to support in coping with fear of disease recurrence and to augment social support in patients with low social support), the use of a fatigue diary to record the affective consequences of fatigue, and cognitive restructuring to help normalize CRF and identify and manage negative thought patterns (e.g., this fatigue is so terrible, I can’t cope, I am helpless, there is nothing I can do) that diminish mood and interfere with goal setting and incremental goal attainment. Programs that are lengthy or with frequent treatment sessions may exacerbate fatigue levels in some patient populations, for example, those receiving radiation therapy or those with advanced cancers (Brown et al., 2006).

Many of the effective psychoeducational interventions included components of energy conservation and activity management (ECAM). ECAM is a self-management intervention that teaches patients to apply the principles of energy conservation and activity management and provides coaching to integrate these activities into their daily lifestyle. Principles of ECAM are summarized in Figure 15-6 (Barsevick, Beck, et al., 2010; Barsevick et al., 2004; Barsevick, Whitemer, Sweeney, & Nail, 2002; Kirshbaum, 2010; Yuen, Mitcham, & Morgan, 2006).

Studies also indicate that cognitive behavioral therapy (CBT) interventions designed to improve sleep quality also have a beneficial effect on fatigue (Dirksen & Epstein, 2008; Espie et al., 2008; Prinsen et al., 2013; Ritterband et al., 2012). These interventions to improve sleep quality can be delivered individually or in a group setting. They include relaxation training along with sleep consolidation strategies (avoiding long or late-afternoon naps, limiting time in bed to actual sleep time), stimulus control therapy (going to bed only when sleepy, using the bed/bedroom for sleep and sexual activities only, setting a consistent time to lie down and get up, and avoiding caffeine and stimulating activity in the evening), and strategies to reduce cognitive-emotional arousal (spending at least an hour to relax before going to bed and establishing a pre-sleep routine to be used every night).

Evidence shows that interventions to more effectively manage concurrent symptoms such as pain, shortness of breath, insomnia, and depression may also improve CRF (Berger et al., 2013; de Raaf et al., 2013). Although a randomized controlled trial of CBT for cancer pain (n = 131) demonstrated improvement in the outcomes of pain, the differences in fatigue were
FIGURE 15-6 | Patient Teaching Points on Energy Conservation and Activity Management for Cancer-Related Fatigue

Energy conservation means looking at your daily routines to find ways to reduce the amount of effort needed to perform certain tasks, eliminating other tasks, and alternating rest periods with activities throughout the day to prevent bursts of activity and to discourage physical inactivity. Although not every technique will work for you, these are suggestions that you can consider.

Rearrange Your Environment
- Keep frequently used items in easily accessible places.
- Adjust work spaces, such as raising a tabletop, to eliminate awkward positions; bad posture drains energy.
- Sit rather than stand whenever possible: while preparing meals, washing dishes, ironing, etc.
- Use adaptive equipment to make tasks easier; try a jar opener, a reacher, a shower chair to allow you to sit while bathing, etc.
- Soak your dishes before washing, and let them air dry after washing, or use paper plates and flatware.
- Use prepared foods when possible.
- Get a rolling cart to transport things around the house, rather than carrying them.
- See if your grocery store will deliver your groceries.
- Use store-provided wheelchairs or scooters when you shop.

Plan Ahead
- Gather all the supplies you need for a task or project before starting so that everything is in one place.
- Call ahead to stores to make sure the items you need are available.
- Cook in larger quantities and refrigerate or freeze extra portions for later.
- Work rest breaks into activities as often as possible. Take a break before you get tired.
- Schedule enough time for activities—rushing takes more energy.
- Try keeping a daily activity journal for a few weeks to identify times of the day or certain tasks that result in more fatigue.

Prioritize
- Eliminate or reduce tasks that are not that important to you.
- Delegate tasks to friends or family members who offer help.
- Consider hiring professionals, such as a cleaning or lawn care service, to cut down your workload.

Alternate Activity With Rest
- Avoid bursts of activity or prolonged activity that induces severe fatigue.
- With permission your healthcare team, begin a program of physical activity such as walking or cycling. Begin with 5 or 10 minutes twice daily, and increase the time by 1 minute a day.
- Do not be tempted to overdo it in exercise, but rather strive for consistency.

Note. Based on information from Barsevick et al., 2002, 2004; Yuen et al., 2006.

not statistically significant (Dalton, Keefe, Carlson, & Youngblood, 2004). However, three other randomized controlled trials (RCTs) (n = 200 patients with cancer with major depressive disorder [Strong et al., 2008]; n = 83 cancer survivors with fatigue [Gielissen, Wiborg, Verhagen, Knoop, & Bleijenberg, 2012]; n = 45 women with metastatic breast cancer who were depressed [Savard et al., 2006]) and a small case series (n = 6 women with metastatic breast cancer [Lévesque, Savard, Simard, Gauthier, & Ivers, 2004]) demonstrated that CBT interventions for symptoms may also alleviate CRF.

Complementary Therapies

Preliminary evidence supports the efficacy of a wide array of complementary and alternative therapies for CRF including yoga, relaxation, mindfulness-based stress reduction strat-
egies, acupuncture, expressive writing, massage, reflexology, and music therapy (Kwekkeboom, Cherwin, Lee, & Wanta, 2010). Several combined-modality interventions have also shown promise, including aromatherapy, lavender foot soak and reflexology, and yoga or Tai Chi combined with walking, although disentangling the effects of the separate components involved in these combined-modality therapies is a limitation. Many of these techniques share an emphasis on progressive muscle relaxation, mindfulness, meditation, and controlled movement (Stan, Collins, Olsen, Croghan, & Pruthi, 2012). These interventions have also been delivered in groups, and thus shared group experience and mutual support may be an additional mechanism for the improvements noted in fatigue.

Mindfulness-based stress reduction typically includes gentle yoga (stretches, poses, breathing, and meditation) and mindfulness (the practice of becoming more aware of the present moment rather than dwelling in the past or projecting into the future; it generally involves a heightened awareness of one’s breathing and the sensations of one’s body), coupled with relaxation and meditation. Single-arm and randomized controlled trials have generally demonstrated the preliminary effectiveness of mindfulness-based stress reduction interventions in reducing fatigue in patients with mixed tumor types and undergoing active treatment (Cramer, Lauche, Paul, & Dobos, 2012; Lengacher et al., 2012). Follow-up studies also suggest that the clinical improvements achieved with this practice can be sustained (Carlson, Speca, Faris, & Patel, 2007).

Recent observations about the positive effects on fatigue obtained with mindfulness-based stress reduction, as well as yoga, relaxation, acupuncture, massage, and foot reflexology (Boehm, Ostermann, Milazzo, & Büsing, 2012; Buffart et al., 2012; Cramer, Lange, Klose, Paul, & Dobos, 2012; Ernst, 2009; Finnegan-John et al., 2013; He, Wang, & Li, 2013; Lee, Han, Chung, Kim, & Choi, 2011; Molassiotis, 2013; Molassiotis et al., 2012; Myers, Walton, Bratsman, Wilson, & Small, 2008; Posadzki et al., 2013; Sadja & Mills, 2013; Towler, Molassiotis, & Brearley, 2013; Zhang, Yang, Tian, & Wang, 2012), are particularly encouraging because these self-management techniques are relatively inexpensive to deliver. Also, once learned, they can continue to produce a benefit without side effects.

Most of these studies are limited by their open-label, uncontrolled design and small sample, making it difficult to draw firm conclusions about efficacy. Of note, the studies evaluating acupuncture, expressive writing, and the combined aromatherapy, foot soak, and reflexology intervention included patients with advanced cancer and at the end of life. If found to be effective in larger randomized controlled trials, these approaches may offer treatment options for patients with advanced cancer and those at the end of life for whom other fatigue interventions, such as exercise, may not be feasible. Despite these limitations and with acknowledgment that inclusion of controls such as double-blinding and sham interventions presents methodologic challenges (Azad & John, 2013; Elam, Carpenter, Shu, Boyapati, & Friedmann-Gilchrist, 2006), results suggest that these complementary therapies should be considered for fatigue management in patients with cancer, particularly in situations with limited fatigue treatment options.

**Expected Patient Outcomes**

Expected outcomes of effective fatigue management include a reduction in severity and corollary improvements in the associated psychological distress and functional interference. In some clinical situations (e.g., patients undergoing hematopoietic stem cell transplant or beginning a course of radiation therapy), the achievable clinical goal is to attenuate the worsening of fatigue severity, distress, and interference across the course of treatment. Pro-
grammatic outcomes of an effective fatigue management program include that all patients with cancer are screened for fatigue during each encounter with the healthcare team while on active treatment and during long-term follow-up, and that in patients with moderate to severe fatigue, the presence of contributing factors (concurrent symptoms, emotional distress, sleep disturbances, anemia, nutritional alterations, inactivity/deconditioning, and comorbidities such as hypothyroidism and cardiomyopathy) and the management plan to address these issues are documented at regular intervals.

Evidence-based guidelines to support the achievement of these expected outcomes have been published by NCCN (2014b) and by the Oncology Nursing Society (Mitchell, Beck, Hood, Moore, & Tanner, 2009) and have been endorsed by other international groups (Howell et al., 2013).

**Patient and Family Teaching Points**

Education concerning fatigue and its anticipated characteristics, pattern of onset, duration, and consequences for mood and role function should be provided to all patients as they begin any fatigue-inducing treatment and reinforced at regular intervals across the treatment course. Patients receiving biotherapy, intensive chemotherapy and/or radiation therapy, or undergoing hematopoietic stem cell transplantation should be aware that they may develop moderate to severe fatigue. All patients and their families should be educated that supportive care interventions such as energy conservation, exercise, relaxation and stress management, psychosocial support, and measures to optimize sleep quality and reduce concurrent symptoms have been shown to be effective in limiting the severity of fatigue during treatment. Incorporating knowledge of the effectiveness of these interventions, patients should be encouraged to develop their own individualized plan for fatigue self-management. The importance of remaining active and participating in a consistent program of gentle exercise, individualized to the patient’s age, condition, and physical fitness level, should be communicated. Referral to physical therapy or physical medicine and rehabilitation should be considered, especially for those patients with significant comorbidities and deconditioning. It is important to offer anticipatory guidance that fatigue develops or worsens as a direct result of treatment and that this does not necessarily indicate that a treatment is ineffective or that the disease is progressing. Daily monitoring of fatigue levels and recording these in a log or diary can be helpful not only in identifying times of peak energy, but also in exploring the factors that may contribute to intensified fatigue, such as sleep disturbance, concurrent symptoms, or boredom.

The transition to long-term follow-up is another important point at which to provide anticipatory guidance concerning the pace at which fatigue symptoms may be expected to improve and energy levels normalize. Survivors and their families should be informed that the resolution of moderate to severe fatigue may require several months to even a year of recovery and that a subset of patients continue to experience levels of fatigue that interfere with function. The development of a survivorship care plan offers an opportunity to review strategies that may be effective for long-term fatigue management during survivorship (e.g., exercise, CBT and psychosocial support interventions, hypothyroidism screening, measures to improve sleep quality).

Individuals with fatigue who have advanced cancer or are at the end of life and those who care for them will benefit from education to understand the multiple causes and consequences of fatigue at this point in the disease trajectory. It may be helpful to normalize that fatigue may increase substantially or become more unpredictable as the disease progresses.
and that the effects of fatigue (e.g., sadness, isolation, fear) on well-being may become more prominent. Intervention strategies that may have worked in the past (e.g., distraction, exercise) may no longer be feasible, and patients and their families will benefit from guidance about options that may helpful in managing fatigue and alleviating suffering throughout the end of life, such as massage, yoga, aromatherapy, relaxation, acupuncture, counseling, and aggressive management of concurrent symptoms.

**Need for Future Research**

A wide range of pharmacologic and nonpharmacologic interventions for fatigue have been studied. However, many have only been tested in uncontrolled or pilot studies (Mitchell, 2010). Interventions for fatigue that are supported by one or more well-designed randomized trials include exercise, psychoeducational interventions, rehabilitation, ginseng, measures to optimize sleep quality, and correction of anemia with hemoglobin less than 10 g/dl, as well as yoga, acupuncture, relaxation, massage, and healing touch. Preliminary or inconclusive evidence exists to suggest that pharmacologic agents including paroxetine, methylphenidate, donepezil, bupropion sustained-release, modafinil, and levocarnitine have a role in the management of fatigue, although systematic drug development studies are needed to define the optimal dosing, gauge the toxicity profile, and determine the effectiveness of these agents in specific populations. Interventions for which preliminary evidence has shown effectiveness include individual and group psychotherapy and complementary therapies such as yoga and acupuncture. Rigorously designed and adequately powered randomized controlled trials of therapies for fatigue that have shown initial promise are urgently needed (Barsevick et al., 2013). Research focused on developing and testing interventions specifically for patients with fatigue in the setting of advanced cancer and at the end of life is an imperative (Yennurajalingam, Kang, et al., 2013).

With a substantial body of evidence now accumulating regarding exercise, rehabilitative, pharmacologic, psychoeducational, and supportive care interventions that are effective for CRF, questions remain concerning how best to deliver these programs on a widespread basis, to which patient populations, and at which phase in the illness trajectory. Strategies such as motivational interviewing and nurse coaching (Yun et al., 2012) in helping patients to make behavior and lifestyle changes also deserve further exploration.

**Conclusion of Case Study**

As an initial step in the management of CRF in J.B., who has moderate to severe fatigue (based on her severity rating of 8 out of 10), the nurse conducts a comprehensive assessment of J.B.’s fatigue. This assessment includes tracking the persistence of the fatigue across the course of the day and the week, noting any fluctuations and exacerbating or relieving factors and gauging the impact on functioning and level of distress. J.B. tearfully relates her fear that the continued persistent fatigue indicates that the chemotherapy will not be effective in treating her disease. She rates her pain as 2 out of 10 at most times but is most bothered by pain when she tries to go to sleep and admits she has slept for only a few hours in the past several nights, in part because of her treatment with dexamethasone. In addition to sleep disturbance and pain, J.B. admits to feeling profound sadness and discouragement and to feeling somewhat helpless to improve her cur-
rent situation. In screening her for contributing factors for CRF, the nurse notes that she has renal insufficiency and moderate anemia, as well as psychological distress, sleep disturbance, and suboptimally managed concurrent symptoms. The initial fatigue management for J.B. includes measures to improve pain management, particularly at night. To improve sleep quality, the nurse explores strategies with J.B., including progressive muscle relaxation with imagery and sleep hygiene measures, such as daytime sleep restriction and a warm shower and a quiet, restful routine prior to sleep. During these conversations, the nurse has an opportunity to provide guidance that fatigue is often a presenting symptom of multiple myeloma, and its continued presence arises from different causes (e.g., sleep problems, pain) than the original causative factors (often anemia). The nurse also provides coaching and encouragement for the positive steps (goal setting, self-management) the patient is taking to relieve her fatigue. At the weekly team conference, the oncology nurse can discuss the use of an ESA to improve anemia and sleep quality, along with the possibility of administering daily doses of dexamethasone in the morning to limit the effect on sleep.

As the patient prepares for discharge from the hospital, the nurse’s anticipatory guidance emphasizes the importance of hydration and improved nutrition. The patient is encouraged to keep a diary of her fatigue severity and its correlates to facilitate continued dialogue with the healthcare team regarding fatigue management interventions. As she returns to the home setting for continued chemotherapy treatments and to prepare for autologous transplantation, the healthcare team initiates referrals for physical therapy to design and supervise an exercise program. To enhance her limited social support in the community, the patient also can begin participating in a monthly myeloma support group. Her fatigue severity is monitored every two weeks at her clinic visits for blood counts and clinical evaluation. She notes some improvement in her level of fatigue (peak fatigue severity of 7 out of 10 in the past two weeks, despite onset of mild neutropenia), and she verbalizes greater self-efficacy in coping with fatigue and with her diagnosis. Sleep quality remains a problem, and she must continue to work on strategies of daytime sleep restriction, improved nighttime pain control, and stress management.

Conclusion

CRF is a prevalent, often persistent symptom during and following cancer treatment, producing marked effects on functional status, symptom burden, psychosocial adjustment, and well-being. Effective management of CRF requires that clinicians assess patients’ fatigue levels regularly, offer anticipatory guidance and ongoing education about fatigue and strategies for its management, and define a therapeutic plan with both pharmacologic and nonpharmacologic interventions. Based on the multiple etiologies and contributing factors, optimal CRF management must employ the skills of an interdisciplinary team. Research has identified a number of promising approaches for the treatment of CRF, although many of these require further evaluation in randomized controlled trials. As evidence-based treatment strategies for CRF continue to evolve, clinicians are challenged to synthesize this evidence base and to implement the interventions with the greatest likelihood of producing benefit. To achieve a rational approach to CRF management, continued research is needed to clarify the physiologic and psychological causes of CRF in specific disease- and treatment-related subpopulations and at each phase along the illness continuum and to develop and test mechanism-targeted interventions for CRF.
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CHAPTER 16

Hot Flashes

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Case Study

J.B. is a 58-year-old African American man with a history of advanced prostate cancer. Six months ago, at his annual checkup with his primary care nurse practitioner, J.B. complained of urinary hesitancy. The nurse practitioner drew blood for prostate-specific antigen (PSA) testing and palpated his prostate, which was found to be enlarged. A prostate biopsy confirmed the diagnosis of adenocarcinoma of the prostate, Gleason score of 4 + 4 = 8. His PSA level was 229 ng/ml at the time of diagnosis. J.B. was referred to medical oncology and urology for disease workup and treatment planning. A computed tomography scan of the chest, abdomen, and pelvis did not demonstrate evidence of metastatic disease; however, a bone scan revealed lesions in the right pelvis and at T11 and T12. Based on results of his disease workup, J.B.’s prostate cancer was staged T3 N0 M1. He was given the option of surgical castration via orchietomy or medical castration via drug therapy and opted for medical treatment with total androgen blockade. He received an intramuscular injection of leuprolide 22.5 mg to be repeated every three months and began taking daily oral bicalutamide 50 mg. J.B. is a financial adviser in a large banking firm meeting with clients daily and leading business meetings with his staff weekly. He is at the clinic today for his second injection of leuprolide and is complaining of profuse sweating during the day and at night that wakes him and is sometimes accompanied by palpitations and feelings of anxiety.

Overview

This chapter will discuss hot flashes in patients with cancer with a particular focus on women treated for breast cancer and men treated with androgen deprivation therapy (ADT) for prostate cancer. These two groups have a high incidence of hot flashes because they receive therapies that target hormone production (Dalal & Zhukovsky, 2006; Kaplan, Mahon, Cope, Keating, et al., 2011). The terms hot flashes, hot flushes, vasomotor symptoms, and night sweats are often used interchangeably in the literature. Hot flashes in both men and women have been defined as “a subjective sensation of heat that is associated with objective signs of cutaneous vasodilation and a subsequent drop in core temperature” (Boekhout, Beijnen, & Schellens, 2006, p. 642). In women, a hot flash is typically defined as a recurrent, transient
period of intense heat and profuse sweating and flushing that usually involves the face, neck, and chest, is often accompanied by palpitations and a feeling of anxiety or apprehension, and is sometimes followed by chills (Carpenter, Johnson, Wagner, & Andrykowski, 2002; Dalal & Zhukovsky, 2006; Finck, Barton, Loprinzi, Quella, & Sloan, 1998; Jones, Kohli, & Loprinzi, 2012; Morrow, Mattair, & Hortobagyi, 2011).

Hot flashes are characterized by their transient and unpredictable nature. Episodes may occur as frequently as every hour or as infrequently as several times a month and can last for seconds to minutes. Intensity can be described as mild, moderate, severe, or very severe (Jones et al., 2012). About 75% of postmenopausal women experience hot flashes, as do a similar percentage of men who receive ADT for prostate cancer (Shanafelt, Barton, Adjei, & Loprinzi, 2002). The vasomotor symptoms that characterize hot flashes have a negative effect on sleep, energy, sexuality, and overall quality of life (Kadakia, Loprinzi, & Barton, 2012).

Although much of the understanding of and investigation into hot flashes has focused on the female experience, it has been suggested that hot flashes are essentially gender neutral because both women and men share similar etiologies: the abrupt depletion of sex hormones. Evidence is accumulating that most treatment approaches for managing hot flashes are equally effective in men and women (Jones et al., 2012; Loprinzi & Wolf, 2010). Persistent hot flashes may cause both men and women to be nonadherent to hormone ablation therapies or to discontinue treatment prematurely (Boekhout et al., 2011; Engstrom, 2008; Kadakia et al., 2012). Tamoxifen has been shown to reduce breast cancer recurrence by 50% after five years of therapy (Batur, Blixen, Moore, Thacker, & Xu, 2006), but early discontinuation, especially in women experiencing side effects, is reported in 15%–35% of patients and may affect their potential survival benefit (Buijs et al., 2009). Strategies to mitigate hot flashes are important to increase compliance with hormonal therapies and improve quality of life in cancer survivors.

**Risk Factors and Incidence**

**Men**

Reports of hot flashes in men treated for prostate cancer with surgical castration go back to 1941 when hot flash symptoms were reported in almost half of the first 21 men to receive ADT for prostate cancer (Huggins & Hodges, 1941). Androgen ablation therapy in the form of surgical castration by bilateral orchietomy or medical castration by luteinizing hormone-releasing hormone (LHRH) agonists is commonly used to treat men with locally advanced or metastatic prostate cancer (Jones et al., 2012; Zaitzu et al., 2012). It is estimated that at least one-third of men with prostate cancer in the United States are treated with ADT during the course of their disease and that 80% of them will experience hot flashes (Jones et al., 2012). Currently, chemical castration with LHRH agonists has replaced surgical castration in most clinical settings (Alekshun & Patterson, 2006; Brawer, 2006).

ADT is associated with the occurrence of vasomotor symptoms, including skin reddening and profuse sweating (Baum & Torti, 2007; Brawer, 2006; Lee, Kim, Shin, Choi, & Ernst, 2009). Reports of hot flash incidence in these patients range between 35% and 80%, with most in the upper ranges (Alekshun & Patterson, 2006; Dalal & Zhukovsky, 2006; Frisk, 2010; Morrow et al., 2011). Hot flashes have been reported as the most distressing side effect of ADT (Alekshun & Patterson, 2006; Baum & Torti, 2007), although only about one-third of men seek help for them (Grunfeld, Halliday, Martin, & Drudge-Coates, 2012; Spetz, Zetterlund, Varenhorst, & Hammar, 2003). Episodes can occur infrequently or up to several times
a day and can last for five minutes or longer (Baum & Torti, 2007). Vasomotor symptoms persist for up to eight years in at least 40% of patients treated with ADT (Dalal & Zhukovsky, 2006; Frisk, 2010; Spetz et al., 2003). British researchers asked 129 men treated with ADT for locally advanced prostate cancer to evaluate their quality of life related to multiple symptoms and found that the men were willing to give up increased life expectancy (0.5 months) to avoid hot flashes (Sculpher et al., 2004). A small qualitative study of men receiving ADT for metastatic prostate cancer (N = 21) used semistructured interviews to explore the impact of therapy on andropause (male menopause) symptoms, with a focus on hot flashes. The majority of participants (n = 15) reported experiencing hot flashes that affected their daily functioning and usually were followed by a chilled sensation or night sweats that disrupted sleep. The men also reported distress caused by lack of control over their hot flashes and night sweats and a reluctance to inform others of their symptoms (Grunfeld et al., 2012).

Women

Hot flashes are reported to be significantly more frequent and severe in women diagnosed with breast cancer and breast cancer survivors than in healthy women of a similar age (Carpenter, 2005; Kadakia et al., 2012; Kaplan, Mahon, Cope, Keating, et al., 2011). Hot flashes are estimated to occur in two-thirds of women with a history of breast cancer and are categorized as moderate to severe and linked with decreased quality of life (Dalal & Zhukovsky, 2006; Savard, Savard, Quesnel, & Ivers, 2009). The findings of a large observational study conducted at the Menopause Symptoms After Cancer Clinic in Australia indicated that cancer survivors are twice as likely as other women to have severe menopausal symptoms (Marino et al., 2014). The symptom experience was compared in two groups: women with a cancer history (mostly breast cancer, n = 934) and women without a cancer history (n = 155). Participants were surveyed for vasomotor symptoms (hot flushes, night sweats, cold sweats, and sleep disruption) using a validated self-report questionnaire. Analysis of results indicated that by all measures, hot flushes and night sweats were significantly more frequent (6 events vs. 3 events in 24 hours, p < 0.001) and severe (p = 0.008) among the cancer survivors, even long past their cancer diagnosis, compared to participants without a cancer history. More than 200 cancer survivors reported experiencing more than 10 hot flashes a day (Marino et al., 2014).

Several breast cancer therapies are designed to induce estrogen withdrawal, including the antiestrogenic agents (e.g., tamoxifen, aromatase inhibitors) and chemical or surgical oophorectomy. Tamoxifen has been shown to produce more frequent and more severe hot flashes than the aromatase inhibitors based on analysis of the results of two large randomized clinical trials: the Breast International Group (BIG) 1-98 and the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trials. In the BIG 1-98 trial, hot flashes were more common among women randomized to a tamoxifen-containing regimen than among women who received letrozole (aromatase inhibitor) monotherapy (41.7%–44% vs. 37.7%, p = 0.003) (BIG 1-98 Collaborative Group, 2005; Morrow et al., 2011). Similarly, in the ATAC trial, hot flash incidence was greater in the tamoxifen-treated group (40.3%) than in the group treated with anastrozole alone (35%) (ATAC Trialists’ Group, 2005; Morrow et al., 2011).

An open-label phase III clinical trial that compared the steroidal aromatase inhibitor exemestane with tamoxifen as first-line therapy for postmenopausal women with metastatic breast cancer found that patients treated with exemestane had fewer complaints of grade 1–2 hot flashes (34.6 vs. 38.1) and fewer grade 2–3 hot flashes (6.5% vs. 12.2%) in comparison to the patients treated with tamoxifen, although both treatments were generally well tolerated (Paridaens et al., 2008). A small descriptive study of women older than 50 treat-
ed with tamoxifen (N = 50) used a questionnaire and hot flash diaries to assess the factors associated with hot flash frequency and intensity over a nine-month period (Loprinzi, Zakhasky, Sloan, Novotny, & Quella, 2000). Results revealed that a prior history of moderate to severe hot flashes with menopause and a history of prior estrogen therapy predicted an increased incidence of hot flashes. Hot flashes increased in severity over the initial two to three months and then appeared to plateau in severity or decrease in number (Loprinzi et al., 2000).

Chemotherapy can induce a premature menopause associated with increased incidence and severity of hot flashes due to the rapidity of estrogen withdrawal (Baber, Hickey, & Kwik, 2005; Dalal & Zhukovsky, 2006). Mar Fan et al. (2010) conducted a prospective controlled descriptive study using self-report Functional Assessment of Cancer Therapy subscales to assess for endocrine symptoms, quality of life, and fatigue in women with breast cancer who had undergone chemotherapy-induced menopause (n = 41) compared to women who had undergone natural menopause (n = 57). More women with chemotherapy-induced menopause reported moderate or severe hot flashes than controls undergoing natural menopause (51% vs. 19%, p = 0.003). Both groups reported fatigue due to menopausal symptoms. No difference in the quality-of-life scale was noted between the groups (Mar Fan et al., 2010).

Age and systemic chemotherapy (regardless of tamoxifen use) have been found to be important predictors of the onset of menopause in premenopausal women with newly diagnosed breast cancer. About 40% of 40-year-old patients experienced premature menopause, while almost 100% of 50-year-old patients had early menopause with chemotherapy (Goodwin, Ennis, Pritchard, Trudeau, & Hood, 1999). Higher cumulative doses and longer durations of cytotoxic therapies increase the risk of early menopause in younger patients and are associated with higher incidence of vasomotor symptoms (Morrow et al., 2011). It is estimated that about 80% of premenopausal women who receive both chemotherapy and endocrine therapy will experience premature menopause in the initial year following diagnosis (Baber et al., 2005). Certain chemotherapy agents used to treat breast cancer act on the ovaries to reduce the number and quality of oocytes, which leads to ovarian failure and amenorrhea (Partridge et al., 2007; Schover, 2008). Increasing doses of alkylating agents such as cyclophosphamide elevate the risk of premenopausal amenorrhea compared to therapy with anthracycline-based regimens such as doxorubicin and cyclophosphamide (AC). However, when taxanes are added to the AC regimen, the risk of amenorrhea increases slightly (Petrek et al., 2006). The regimen of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) and the regimen of cyclophosphamide, epirubicin, and 5-fluorouracil (CEF) confer a higher risk of ovarian failure and are associated with increased prevalence of hot flashes. Although data are limited, patients with cancers other than breast cancer who are receiving cytotoxic or hormonal therapies that lead to ovarian suppression and premature menopause can be expected to experience intense hot flashes (Dalal & Zhukovsky, 2006). Tumors that may be associated with hot flashes include medullary carcinoma of the thyroid, pancreatic islet-cell tumor, renal cell carcinoma, pheochromocytoma, and the carcinoid syndrome (Mohyi, Tabassi, & Simon, 1997).

A wide variety of potential triggers for hot flashes have been reported. Nonmodifiable risk factors include increasing age, gender, and race; lifestyle-associated risk factors that may influence hot flashes include smoking, increased body mass index (BMI), alcohol intake, emotional stress and excitement, minor changes in room temperature, use of tamoxifen or aromatase inhibitors, androgen ablation, and flushing associated with food additives, spicy foods, and hot beverages (Dalal & Zhukovsky, 2006; Glaus et al., 2006; Gold et al., 2006; Hardy, Kuh, & Wadsworth, 2000; Staropoli, Flaws, Bush, & Moulton, 1998; Whiteman, Staropoli, Benedict, Borgeest, & Flaws, 2003; Whiteman, Staropoli, Langenberg, et al., 2003). Gold et
al.’s (2006) longitudinal study reported that lower socioeconomic status and less than a high school education also were predictors of hot flashes. These hot flash risk factors were supported by another study of 468 perimenopausal women (Riley, Inui, Kleinman, & Connelly, 2004). Results of this study showed that after controlling for age, race, use of oral contraceptives and hormone replacement therapy, and depression, hot flashes in perimenopausal women were associated with BMI of 25 kg/m² or higher (adjusted overall risk [OR] = 1.03 per unit of increase, 95% confidence interval [CI] [1.01, 1.04]) and increasing age (adjusted OR = 1.17, 95% CI [1.13, 1.21]) (Riley et al., 2004).

Although hot flashes are associated with somatic, behavioral, and emotional manifestations in patients with cancer (Dalal & Zhukovsky, 2006), few qualitative studies have explained the experience of hot flashes in patients with cancer. Researchers conducting interviews with patients being treated for breast cancer and breast cancer survivors found similar themes of loss of control and vulnerability (Fenlon & Rogers, 2007), as well as behavioral responses such as changing clothing and bed linens (Finck et al., 1998). Carpenter, Wu, Burns, and Yu (2012) conducted a study to evaluate differences in perceived control over hot flashes between women who were breast cancer survivors (n = 99) and mid-life women without cancer (n = 138) who reported at least two hot flashes daily. Perceived control over hot flashes was considered to be the woman’s perception of her ability to manage or cope with her hot flashes by employing pharmacologic or nonpharmacologic methods. Several validated questionnaires and a prospective, electronic hot flash diary were used to assess the subjective hot flash experience (frequency, severity, bother, and interference in daily activities) and perceived control over hot flashes for both groups. Study findings revealed that hot flash severity, bother, and interference were more troublesome than hot flash frequency in both groups and that breast cancer survivors who used a hot flash treatment had poorer perceived control over their hot flashes than survivors not using a hot flash intervention. Midlife women reported opposite results (Carpenter et al., 2012). Further investigation is warranted with larger and more diverse populations.

Pathophysiology

The exact physiologic mechanisms of hot flashes are unknown. Much of what is known comes from studies of the physiology of hot flashes associated with menopause. The underlying hot flash mechanism is understood to originate in the hypothalamus, which acts to regulate core body temperature. In premenopausal women, negative feedback mechanisms involving circulating estrogen and its metabolites regulate the activity of neurotransmitters and receptors in the preoptic nucleus of the hypothalamus where central thermoregulation is controlled (see Figure 16-1). Core body temperature is maintained within a narrow physiologic range, termed the thermoneutral zone, by the effects of this feedback loop on the central hypothalamic thermoregulation center and the influence of the hypothalamus on peripheral vascular responses (Shanafelt et al., 2002). Estrogen withdrawal at the time of menopause leads to loss of the negative feedback mechanisms regulating core temperature and results in dysfunction of central thermoregulation in the hypothalamus (Boekhout et al., 2006; Shanafelt et al., 2002). As long as core body temperature remains within the narrow set points of the thermoneutral zone, no compensatory vascular responses leading to hot flashes are triggered (Sturdee, 2008). Elevation of core temperature above the upper threshold of the thermoneutral zone stimulates the hypothalamus to trigger the classic heat loss mechanisms of sweating and vasodilation. Characteristic hot flash symptoms, including sweating on the face, neck, and chest and cutaneous vasodilation, represent a heat dis-
sipation response. Core temperatures below the lower threshold of the thermoneutral zone lead to heat conservation measures, including vasoconstriction and shivering (Dalal & Zhu-kovsky, 2011; Huether, 2010; Morrow et al., 2011).

Results of a study measuring core temperatures in symptomatic postmenopausal women with hot flashes (n = 12) and asymptomatic postmenopausal women (n = 8) who ingested a sensitive telemetry pill revealed that the thermoneutral zone was essentially absent in symptomatic women (0°C) but was normal in asymptomatic women (0.4°C) (Freedman & Krell, 1999). These results suggest that the thermoregulatory zone is narrowed in symptomatic postmenopausal women, and thus, even small changes in core temperature can exceed the upper and lower thresholds and trigger the sweats and chills associated with hot flashes (Freedman, 2005; Freedman & Krell, 1999). In addition, analysis of estrogen levels in the two groups did not show a difference between the symptomatic and asymptomatic women, indicating that absolute lack of estrogen is not solely responsible for hot flashes (Freedman

![FIGURE 16-1 Pathways Involved in Hot Flashes](image)

* (+) = Stimulates downstream signal; (–) = inhibits downstream signal.
† Estrogen acts to down-regulate serotonin 2a receptor concentration.
‡ Catecholestrogen inhibits tyrosine hydroxylase metabolism of tyrosine to norepinephrine.
§ Luteinizing hormone (LH) release occurs in the pituitary gland.

GnRH—gonadotropin-releasing hormone

& Krell, 1999); rather, the rapidity of estrogen withdrawal triggered the hot flash mechanisms. For example, women with acute estrogen withdrawal due to bilateral oophorectomy experience more hot flashes than women who gradually lose ovarian function at menopause (Sturdee, 2008).

It has been postulated that estrogen depletion in women and withdrawal of gonadal hormones secondary to castration in men lead to an increase in hypothalamic receptors for noradrenaline and serotonin, two neurotransmitters that act to decrease the upper set point of the thermoregulatory zone. Thus, heat loss mechanisms associated with hot flashes are triggered by even normal, small, transient increases in the core temperature (Boekhout et al., 2006; Freedman, 2005; Morrow et al., 2011; Shanafelt et al., 2002).

In men, as in women, plasma sex hormones regulate the hypothalamic thermoregulatory center through negative feedback mechanisms. An abrupt decrease in sex hormones (due to castration) will result in loss of negative feedback and lead to a reset of the thermoregulatory center and activation of heat loss mechanisms that characterize hot flashes: cutaneous vasodilation and profuse sweating (Kourieff, Georgiou, & Ravi, 2002). In men, it is uncertain whether the development of hot flashes is due to low testosterone levels, a decline in estrogen levels, or a reduction of both hormones (Alekshun & Patterson, 2006; Baum & Torti, 2007).

Assessment

Hot flashes can be measured both subjectively and objectively. Subjective measures of hot flash frequency, severity or intensity, and distress can be collected using self-reported data from patients. Practitioners may simply ask patients if they do or do not have hot flashes or may ask patients to complete a hot flash diary. Research studies of hot flashes have used three different techniques for assessing the frequency of hot flashes. One is sternal skin conductance monitoring, an objective measure of increased electrical conductance on the skin caused primarily by sweating. Two are subjective methods: hot flash events recorded in real time by patients through use of electronic event markers, and retrospective daily self-report paper diaries, which is the most frequently used technique. Each method has drawbacks. Sternal skin conductance, although it does not rely on patient report, has been found to miss up to one-third of hot flashes in men and women in the laboratory setting and up to 43% of reported hot flashes in ambulatory women (Hanisch et al., 2009). Real-time reporting of hot flashes misses many episodes of hot flashes because of lack of adherence to reporting protocols, especially during sleep. Retrospective paper diaries are simple and easy to use but are subject to recall bias (Hanisch et al., 2009). Researchers conducted a study in men to determine how well the three assessment techniques measured hot flashes. Forty-seven patients with prostate cancer receiving ADT agreed to participate in all three data collection methods over two 24-hour periods. The highest number of hot flashes (478) was recorded by the electronic monitor the men wore to detect objective changes in sternal skin conductance levels. Real-time events were recorded on the same monitor when the men pressed a button each time they perceived a hot flash (410 events). Lastly, a paper diary was filled out by each patient every morning and evening, and 285 hot flashes were recalled. Analysis of data from all participants showed a significant difference in the detection of events by the three hot flash measures, with the self-reported diary being the least sensitive measure. However, the authors concluded that paper diaries may be sufficient for assessing hot flashes in clinical practice because they are inexpensive and easy to use. Sternal skin conductance monitoring and real-time event marking can be reserved for research and treatment stud-
A commentary on this study reiterated that “prospective hot flash diaries represent the gold standard measurement of hot flashes” (Loprinzi & Barton, 2009, p. 157) and observed that limitations are inherent in the other techniques, including activation of sweat glands by causes other than hot flashes (e.g., exertion or stress), lack of tolerance for wearing a monitor for extended periods, and potential technical problems with monitor software and hardware.

The Loprinzi and Sloan daily diary (see Figure 16-2) method has been validated in women with breast cancer and men with prostate cancer. Patients record a summary of events once a day, noting the number and severity of hot flashes. The daily hot flash score is computed by multiplying the frequency by the severity (Sloan et al., 2001). Another tool, the Hot Flash–Related Daily Interference Scale (HFRDIS), a 10-item scale designed to measure the extent to which hot flashes interfere with overall quality of life, has been validated in breast cancer survivors (Carpenter, 2001; Carpenter et al., 2002).

Four categories have been used to describe hot flash severity in men: mild, moderate, severe, and very severe. Each category is based on hot flash duration and symptomatology (Alekshun & Patterson, 2006; Sloan et al., 2001). See Figure 16-3 for a description of hot flash categories for men.

In summary, two hot flash assessment tools or measures are validated to assess subjective hot flash frequency, duration, and intensity: the daily diary method and the HFRDIS, which measures hot flash interference on activities of daily living and quality of life. Sternal skin conductance is a validated instrument to assess objective measures of hot flash frequency in patients with breast and prostate cancer. Table 16-1 lists objective and subjective hot flash measurement tools.

Evidence-Based Interventions

A wide variety of interventions, both pharmacologic and nonpharmacologic, have been recommended for treating patients with cancer who experience hot flashes. These recommendations include the use of hormonal and nonhormonal agents, complementary and alternative interventions, and lifestyle modifications. However, it is important to assess the efficacy of hot flash interventions in patients with cancer based on the best available evidence reported in the literature, ideally from placebo-controlled randomized clinical trials, and to take into account the magnitude of the placebo effect on reported outcomes. In 2009, the Oncology Nursing Society (ONS), as part of its Putting Evidence Into Practice (PEP) program, brought together an expert group of oncology nurses to conduct a systematic review of the literature on hot flash interventions for patients with breast or prostate cancer and a comprehensive analysis of studies published through February 2010 judged appropriate for inclusion. Levels of evidence for each intervention were ranked by group consensus according to an ONS weight-of-evidence scale divided into six categories: Recommended for Practice, Likely to Be Effective, Benefits Balanced With Harms, Effectiveness Not Established, Effectiveness Unlikely, and Not Recommended for Practice (Mitchell & Friese, n.d.). The outcomes of this initial comprehensive review of the evidence were published in 2011 (Kaplan, 2011; Kaplan, Mahon, Cope, Hill, et al., 2011; Kaplan, Mahon, Cope, Keating, et al., 2011). Since then, the PEP team review of the pertinent hot flash literature has been ongoing, and updated and synthesized results were published in 2014 (Kaplan et al., 2014; Kaplan & Mahon, 2014).

The highest evidence rank assigned to studies was Likely to Be Effective and applied only to two interventions for reducing hot flashes, the pharmacologic agents venlafaxine, a se-
## FIGURE 16-2 Patient-Reported Hot Flash Diary

### First Study Week (Baseline)

**Daily Patient Questionnaire: Double-Blind Phase**

No tablets this week

<table>
<thead>
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<th>Date week started:</th>
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<table>
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<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of today’s hot flashes that were mild, moderate, severe, or very severe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>_ Mild - Moderate</td>
<td>_ Mild - Moderate</td>
<td>_ Mild - Moderate</td>
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<td>_ Mild - Moderate</td>
<td>_ Mild - Moderate</td>
</tr>
<tr>
<td>_ Severe - Very severe</td>
<td>_ Severe - Very severe</td>
<td>_ Severe - Very severe</td>
<td>_ Severe - Very severe</td>
<td>_ Severe - Very severe</td>
<td>_ Severe - Very severe</td>
<td>_ Severe - Very severe</td>
</tr>
</tbody>
</table>

| Total number of hot flashes today* | | | | | | |
| | | | | | | |

| * One day should be considered to be a 24 hour period (i.e. 7:00 am to 7:00 am, or midnight to midnight) |

<table>
<thead>
<tr>
<th>Date week stopped:</th>
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</tbody>
</table>

Do you have any of the following symptoms?

- Appetite loss _ no _ yes
- Sleepiness _ no _ yes
- Nausea _ no _ yes
- Dizziness _ no _ yes
- Tiredness (Fatigue) _ no _ yes
- Dry mouth _ no _ yes
- Other _ no _ yes
- Abnormal sweating _ no _ yes
- Constipation _ no _ yes
- Trouble sleeping _ no _ yes
- Nervousness _ no _ yes
- Mood changes _ no _ yes

Please describe:

____________________________________________________________________________
__________________________________________________________________________________________
__________________________________________________________________________________________

Comments:

_______________________________________________________________________________
__________________________________________________________________________________________
__________________________________________________________________________________________
__________________________________________________________________________________________

| Blood pressure___/___ | Date blood pressure obtained: |  |  |  |  |  |  |  |
|-----------------------|--------------------------------|---|---|---|---|---|---|
| __/__/__              | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ |

**Please complete the next three pages on day 7**

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rotonin-norepinephrine reuptake inhibitor (SNRI) used for depression, and gabapentin, a drug approved for epilepsy and neuropathic pain (Kaplan et al., 2014; Kaplan & Mahon, 2014). The majority of all types of interventions reviewed fell into the category of Effectiveness Not Established because of factors such as small sample size, brief length of treatment, and other methodologic limitations. One drug, paroxetine, a selective serotonin reuptake inhibitor (SSRI) antidepressant, was updated to Benefits Balanced With Harms (Kaplan et al., 2014). Although paroxetine was approved by the U.S. Food and Drug Administration (FDA) in 2013 as the first nonhormonal treatment for hot flashes in postmenopausal women (U.S. FDA, 2013), clinicians should be aware that using it to treat tamoxifen-induced hot flashes warrants caution. Paroxetine is a strong inhibitor of the cytochrome P450 2D6 (CYP2D6) enzyme system, through which tamoxifen is metabolized to its active form, and concomitant use of the two drugs may reduce the efficacy of tamoxifen (Kaplan & Mahon, 2013; Kelly et al., 2010; National Comprehensive Cancer Network® [NCCN®], 2014). Tibolone, a synthetic steroid compound with hormone-like effects, was categorized as Not Recommended for Practice because of reports of increased breast cancer recurrence (Kaplan & Mahon, 2014). Two types of dietary/herbal interventions were ranked Effectiveness Unlikely: soy

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**FIGURE 16-3 Hot Flash Definitions for Men**

**Patient Information Sheet: Hot Flash Definitions for the Male Patient**

Please refer to these examples of hot flashes that have been given by cancer survivors in the previous studies when describing their hot flash severity. One or more of these descriptions may help to categorize your hot flash as mild, moderate, severe, or very severe.

**Mild**
- Duration: Lasting less than 3 minutes
- Physical symptoms: Very light perspiration, generalized warmth, or a flushed sensation
- Emotional symptoms: None or rare
- Action needed: Usually no action taken

**Moderate**
- Duration: Lasting up to 5 minutes
- Physical symptoms: Light-to-moderate perspiration, moderate warmth and/or perspiration
- Emotional symptoms: Mild anxiety, some irritability, loss of concentration
- Action needed: Needed to use a fan, needed to loosen clothing, needed to remove clothing, needed to remove bedding

**Severe**
- Duration: Lasting up to 10 minutes
- Physical symptoms: Described as feeling “hotter” or “very hot,” heavy perspiration, dizziness, nausea, shortness of breath, weakness, extreme discomfort
- Emotional symptoms: Moderate anxiety, moderate irritability
- Action needed: Needed to loosen clothing, needed to change clothing, needed to change bedding

**Very Severe**
- Duration: Lasting up to 30 minutes
- Physical symptoms: Described as feeling “very hot,” drenching perspiration, dizziness, nausea, shortness of breath, weakness, chest discomfort, extreme discomfort
- Emotional symptoms: Severe anxiety, severe irritability, restlessness, totally out of control
- Action needed: Needed to change clothing, needed to towel off, needed to change bedding, used wet towels, took a bath or shower, needed a rest

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supplements and homeopathic remedies. All other dietary and complementary and alternative interventions were considered Effectiveness Not Established due to small sample sizes, methodologic issues, and conflicting results (Kaplan et al., 2014; Kaplan & Mahon, 2014). See www.ons.org/practice-resources/pep/hot-flashes for a descriptive list of the evidence for hot flash interventions.

The following discussion provides a synthesis of randomized clinical trials and other studies investigating hot flash interventions in men with prostate cancer and women with breast cancer.

**Pharmacologic Interventions**

Evidence is lacking for the efficacy of most hot flash interventions for patients with cancer, and conflicting information exists for many treatment recommendations. In addition, the magnitude of the placebo effect should be taken into account when reviewing the results of hot flash intervention studies.

**The Placebo Effect**

The placebo effect has been shown to have a significant role in studies of hot flash interventions that have a placebo-control arm. In an analysis of results from 1,174 patients participating in studies that included a placebo or control arm, researchers found that about one-quarter of the patients who were not receiving the active treatment reported at least a 50% reduction in hot flashes and, 15% reported greater than a 75% reduction (Boekhout et al., 2006). Another review of the data from seven placebo-controlled randomized clinical trials (N = 375) found that patients receiving placebo reported an average decrease of 25% in hot flash frequency and intensity at four weeks (Sloan et al., 2001). A placebo-controlled study comparing the effectiveness of venlafaxine and clonidine in reducing hot flashes found that patients receiving placebo reported a 29% decrease in hot flashes.
Nonhormonal Therapies

Two nonhormonal therapies have demonstrated efficacy in reducing hot flashes in women with breast cancer: venlafaxine and gabapentin. Various studies of the SNRI venlafaxine and the SSRIs paroxetine, sertraline, fluoxetine, and citalopram reported greater hot flash reduction compared to placebo (Loprinzi & Wolf, 2010). The SSRI and SNRI agents appeared to produce similar results in all women experiencing hot flashes, including those with or without a history of breast cancer or tamoxifen use (Loprinzi & Wolf, 2010). However, not all SSRIs are recommended for treatment of hot flashes in patients with cancer. Insufficient evidence existed to recommend the use of sertraline, fluoxetine, or citalopram (Kaplan & Mahon, 2014). Concerns have also arisen about using tamoxifen concomitantly with the SSRIs because they may diminish the efficacy of tamoxifen (Kelly et al., 2010), especially in light of the recent approval of the SSRI paroxetine to treat hot flashes in postmenopausal women (U.S. FDA, 2013). Tamoxifen, which is the sole adjuvant hormonal agent available for premenopausal women with estrogen receptor–positive breast cancer, is metabolized to its active form, endoxifen, through the CYP2D6 enzyme system (Kaplan & Mahon, 2013). The SSRIs and several other types of drugs, including tricyclic antidepressants, antipsychotic agents, opioid analgesics, antiarrhythmic agents, and antihistamines, are associated with inhibition of CYP2D6 (see Table 16-2). Although no significant relationship was found between concomitant use of these drugs and efficacy of tamoxifen therapy in the ATAC trial of women with breast cancer (Rae et al., 2012), some clinicians recommend that strong CYP2D6 inhibitors, such as the SSRIs paroxetine and fluoxetine, should be avoided for treating tamoxifen-associated hot flashes (Desmarais & Looper, 2010; Kelly et al., 2010; NCCN, 2014; Sideras et al., 2010). Venlafaxine, an SNRI that does not inhibit CYP2D6, is recommended as a better treatment choice for patients experiencing tamoxifen-induced hot flashes (Boekhout et al., 2011; Sideras et al., 2010).

Data gathered from studies in men with hot flashes associated with ADT for prostate cancer demonstrated that venlafaxine and paroxetine reduced hot flashes (Loprinzi & Wolf, 2010) and were similar to data from studies of these drugs in women, who reported hot flash reductions of 50%–60% (Stearns, 2006). Similar results were reported for both sexes in studies evaluating hot flash reduction with estrogen, progesterone, and gabapentin, leading researchers to suggest that most drugs used to reduce hot flashes in women should be considered equally effective in men, despite the lack of prospective randomized trials for men (Loprinzi & Wolf, 2010).

A systematic review and meta-analysis of studies incorporating gabapentin in the treatment of menopause- or tamoxifen-associated hot flashes in women with breast cancer found that gabapentin reduced the frequency and severity of hot flashes by 20%–30% compared to placebo, although data across the studies were too heterogeneous to generalize. Side effects reported for gabapentin included dizziness/unsteadiness and fatigue/somnolence and were associated with higher dropout rates compared to controls. The researchers recommended further studies to consolidate treatment outcomes (Toulis, Tzellos, Kouvelas, & Goulis, 2009). A Cochrane systematic review of nonhormonal interventions for hot flashes in women with a history of breast cancer found that both gabapentin and venlafaxine demonstrated efficacy in reducing hot flashes (Rada et al., 2010).
Bordeleau et al. (2010) conducted a study to determine which of the two agents found to be effective in treating hot flashes, venlafaxine and gabapentin, was preferred by breast cancer survivors. Fifty-six breast cancer survivors with hot flashes were asked to indicate a treatment preference after being randomly assigned to a crossover clinical trial of venlafaxine versus gabapentin. Each group received four weeks of one drug, and after a two-week washout period, participants were crossed over to the other treatment arm for four weeks. Study results revealed very similar hot flash reductions and comparable toxicities with venlafaxine and gabapentin. Despite these similarities, 68% of the patients preferred venlafaxine over gabapentin (p = 0.01) for managing hot flashes. Reasons included greater reduction in hot flash severity and frequency, fewer adverse events, and ease of administration (venlafax-
ine is taken once daily; gabapentin is taken three times daily). Of the patients expressing a drug preference, most wished to continue that drug (76.3% venlafaxine vs. 55.6% gabapentin), some wanted to take no medication, and some wanted to try another drug (16.7% gabapentin, 5.3% venlafaxine). The authors concluded that the study results support the use of venlafaxine as a first-line therapy for moderate to severe hot flashes in breast cancer survivors. Because venlafaxine is an SNRI drug that does not inhibit the CYP2D6 enzyme system that metabolizes tamoxifen, it is thought to be safe to use in patients receiving tamoxifen therapy. Gabapentin can be used as an alternative treatment if necessary (Bordeleau et al., 2010). In men, a study evaluating gabapentin 600 mg per day in prostate cancer survivors (N = 117) reported moderately decreased hot flash scores without substantial toxicities (Moraska et al., 2010).

Results of randomized trials incorporating clonidine for hot flashes in women with breast cancer have been mixed. Clonidine has been shown to provide a modest benefit in women with tamoxifen-induced hot flashes (Buijs et al., 2009; Goldberg et al., 1994; Pandya et al., 2000). However, the associated side effects (dry mouth, constipation, and drowsiness) were determined to outweigh the benefits, and clonidine was not recommended for treatment (Baber et al., 2005; Goldberg et al., 1994). Another study in which venlafaxine was compared to clonidine found venlafaxine superior to clonidine (p = 0.025) in decreasing the frequency of hot flashes compared to baseline (Loibl et al., 2007). More recently, a trial comparing venlafaxine, clonidine, and placebo was conducted by Boekhout et al. (2011). They designed a randomized, double-blind, placebo-controlled study to compare average daily hot flash scores at 12 weeks among women with a history of breast cancer. Patients were randomized in a 2:2:1 schema to daily venlafaxine 75 mg, clonidine 0.1 mg, or placebo for 12 weeks. Results from 80 patients were evaluable at study completion and showed that hot flash scores were significantly lower in the clonidine group versus the placebo group (p = 0.03); approaching significance for venlafaxine versus placebo (p = 0.07); and equal in the clonidine and venlafaxine groups. Over the course of 12 weeks, the differences between both active treatments and placebo were significant (p < 0.001 for venlafaxine vs. placebo; p = 0.045 for clonidine vs. placebo). The venlafaxine group had a higher incidence of side effects (nausea, constipation, and severe appetite loss) and a more rapid reduction in hot flash scores than those taking clonidine, but at week 12, hot flash scores were lower in the clonidine group (Boekhout et al., 2011). However, an editorial published in the same journal issue (Loprinzi, Barton, & Qin, 2011) highlighted some of the methodologic limitations of the Boekhout study: a small number of participants per study arm (40), an unbalanced randomization scheme (2:2:1) that resulted in twice as many subjects in the active treatment arms compared to the placebo arm, and an uneven dropout rate among the treatment arms. Loprinzi and colleagues calculated that the study sample size was insufficient to provide the statistical power needed to detect real differences between treatment arms. They calculated that 156 patients would need to be entered into each of the two active treatment arms to have at least 80% power to detect up to a 10% difference in hot flash reduction between venlafaxine and clonidine (Loprinzi et al., 2011). Unlike in women, clonidine was not found to produce benefit in men. Results of a randomized study using transdermal clonidine in men treated with orchiectomy for prostate cancer showed no significant decrease in hot flash frequency or severity (Loprinzi et al., 1994).

**Hormonal Therapies**

Historically, estrogen and progesterone supplementation has been the mainstay in reducing hot flashes in both women and men (Neff, 2004). The safety of using hormone re-
placement therapy in women with a previous history of breast cancer was addressed in the HABITS (Hormonal Replacement Therapy After Breast Cancer—Is It Safe?) study, which consisted of two randomized controlled trials conducted in Scandinavia. The studies were stopped early because of a significant increase in the rate of breast cancer recurrence in the patients randomized to estrogen, leading to the conclusion that hormonal therapy is contraindicated in patients with hormone-dependent tumors such as breast cancer (Holmberg & Anderson, 2004).

In 2011, Loprinzi and colleagues published a review article summarizing results from studies evaluating the efficacy of nonestrogenic agents in hot flashes in women with breast cancer. They reported that the most effective nonestrogenic agents for treating hot flashes are progesterone analogs. Low doses of megestrol acetate (20–40 mg/day PO) or medroxyprogesterone acetate (400–500 mg intramuscularly as a single dose) were shown to decrease hot flashes almost as much as estrogen. However, progesterone analogs are hormones, and there are no definitive data that they are safe for use in breast cancer survivors (Loprinzi et al., 2011).

In men with prostate cancer experiencing hot flashes due to ADT with leuprolide, results of a small randomized study found transdermal estrogen replacement therapy to be effective in reducing hot flash symptoms. Two dose levels of transdermal estrogen (0.05 mg vs. 0.5 mg) were evaluated, and both produced significant reductions in the severity of hot flashes (Gerber, Zagaja, Ray, & Rukstalis, 2000). However, estrogen administration in men is associated with an increased incidence of thromboembolic complications and painful gynecomastia (Alekshun & Patterson, 2006). Progesterone analogs, such as megestrol acetate, have been used to manage hot flashes in men treated for prostate cancer, but clinicians are reluctant to use them due to adverse side effects such as weight gain, edema, and headaches and concerns that they may stimulate tumor growth in prostate cancer (Alekshun & Patterson, 2006; Jones et al., 2012).

Frisk (2010) conducted a systematic review of the literature indexed between 1966 and 2009 for managing hot flashes in men treated for prostate cancer or receiving ADT. Few treatments available for men were found, and some were not appropriate in the setting of cancer. Based on the review, the hormonal agents diethylstilbestrol, megestrol acetate, and cyproterone acetate were the most effective treatments; they were reported to decrease hot flashes by at least 75% but produced severe side effects. Cyproterone acetate is associated with fatigue, weight gain, depressed mood, gynecomastia, and hot flashes. Megestrol produced weight gain, edema, and nausea and increased the PSA level in one patient, raising concern about stimulating prostate cancer (Frisk, 2010). The lengths of all studies were too limited to evaluate long-term risks and side effects of treatment. Large, prospective, long-term, randomized controlled clinical trials are needed to arrive at evidence-based recommendations for treating hot flashes and to determine safety in both men and women with cancer (Frisk, 2010).

In 2010, results were published for a double-blind randomized clinical trial comparing the efficacy of venlafaxine, medroxyprogesterone acetate, and cyproterone acetate for the treatment of vasomotor hot flashes in men receiving ADT with leuprolide. Results indicated that the two hormonal agents, medroxyprogesterone acetate and cyproterone acetate, were superior to venlafaxine in reducing hot flashes in men (Irani, Salomon, Oba, Bouchard, & Mottet, 2010). Cyproterone acetate is a progestational antiandrogen agent that is not approved in the United States but is used in Europe for treatment of prostate cancer (Jones et al., 2012). Newer hormonal agents used to treat prostate cancer include abiraterone acetate, which is approved by the U.S. FDA for use with prednisone for metastatic castration-resistant prostate cancer before chemotherapy (National Cancer Institute, 2013). Abiraterone
acetate is a potent inhibitor of CYP2D6, and concomitant administration with drugs activated or deactivated by the CYP2D6 system, such as the SSRI antidepressants that might be used to treat hot flashes, is to be avoided if possible (see Table 16-2 for a list of other CYP2D6 inhibitors). In addition, hormonal agents used to treat hot flashes in men may interfere with the patients’ androgen ablation therapy (Jones et al., 2012).

Tibolone, a synthetic steroid compound that combines the properties of estrogen, progesterone, and androgen, was compared to placebo in a study of women with tamoxifen-induced hot flashes. At three months, no changes were noted in either study arm (Kroiss et al., 2005). Other placebo-controlled studies evaluating tibolone for alleviating vasomotor symptoms in women with breast cancer found a significant placebo effect (Sismondi et al., 2011) and an increased incidence of breast cancer recurrence that precipitated early discontinuation of the study (Kenemans et al., 2009). Thus, tibolone is categorized as Not Recommended for Practice.

In summary, based on the evidence from numerous studies, the only interventions that appeared to be effective in reducing hot flashes in both men and women were two pharmacologic agents, venlafaxine (an SNRI drug) and gabapentin (an antiepileptic drug). A study to determine which of the two agents was preferred by breast cancer survivors for managing hot flashes revealed that almost 70% of the patients preferred venlafaxine over gabapentin. Studies incorporating SSRI drugs, such as paroxetine, sertraline, and fluoxetine, reported reductions in hot flashes in women with and without a history of breast cancer. However, clinicians urge caution in using these agents for women receiving tamoxifen therapy for breast cancer because of concerns about the inhibiting effect of the SSRIs on the CYP2D6 enzyme system needed for tamoxifen metabolism. In men, results similar to studies in women were reported for hot flash reduction using venlafaxine and paroxetine. Clonidine was not recommended for use in either women or men. Although it reduced hot flashes in women, clonidine was associated with adverse side effects and showed no benefit in men.

No hormonal therapy was recommended for managing hot flashes in patients with breast or prostate cancer because of concerns about promotion of tumor growth and adverse side effects. In men, estrogen replacement therapy was found to decrease the incidence of hot flashes but was associated with risk of clot formation and painful breast enlargement. Studies of progestational antiandrogen agents, such as megestrol acetate, medroxyprogesterone acetate, and cyproterone acetate, demonstrated significant decreases in hot flashes. However, concerns about side effects and interference with treatment efficacy or promotion of prostate cancer mitigate against the use of these agents for managing hot flashes in men. Estrogen replacement therapy is the most effective intervention for reducing hot flashes in postmenopausal women with no breast cancer history. Studies have also shown that progesterone analogs reduce hot flashes in women with breast cancer. However, estrogen replacement and progesterone analogs are not used in women who are survivors of breast cancer because of safety concerns about promoting tumor growth. Tibolone, a steroidal agent with hormone-like properties, has been associated with breast cancer recurrence and is also considered unsafe to use.

Nonpharmacologic Interventions

The ONS PEP team of oncology nurses who analyzed the strength of studies of hot flash interventions categorized most types of dietary supplements and complementary and alternative medicine approaches as Effectiveness Not Established. The exceptions were soy supplements and homeopathy, which were categorized as Effectiveness Unlikely.
Nonpharmacologic interventions that were ranked as Effectiveness Not Established include black cohosh, vitamin E supplements, acupuncture, hypnosis, peer counseling, relaxation therapy, and yoga (Kaplan et al., 2014; Kaplan & Mahon, 2014). Most studies had methodologic limitations, small sample sizes, and short duration and follow-up (see ONS, 2014).

Black cohosh is an herbaceous perennial plant thought to have multiple mechanisms of action, including potential phytoestrogenic properties, which have caused some concern about its use by patients with hormone-sensitive cancer (Walji, Boon, Guns, Oneschuk, & Younus, 2007). It commonly is used to treat hot flashes and other symptoms associated with menopause, but results of clinical trials have been mixed. A meta-analysis of clinical (n = 5) and preclinical (n = 21) studies of black cohosh to treat hot flashes in patients with cancer (breast and prostate) found that black cohosh seems not to exhibit phytoestrogenic activity and is possibly an inhibitor of tumor growth (Walji et al., 2007). One study of premenopausal breast cancer survivors receiving tamoxifen therapy randomly assigned 136 patients to tamoxifen alone or tamoxifen plus a black cohosh preparation. Over a 12-month period, the combination of tamoxifen and black cohosh was associated with a significant reduction in tamoxifen-induced vasomotor episodes (Hernández Muñoz & Pluchino, 2003). However, a large randomized placebo-controlled study of black cohosh using a crossover design (N = 132) revealed that black cohosh did not reduce hot flashes any more than placebo (Pockaj et al., 2006), the same results as previous trials (Jacobson et al., 2001). A prospective observational study of 50 women with breast cancer and tamoxifen-induced hot flashes who took black cohosh extract for up to six months reported benefit and good to very good tolerability. There was no comparator placebo arm, so the placebo effect could not be distinguished from the effects of treatment (Rostock et al., 2011).

The efficacy of vitamin E in reducing hot flashes was evaluated in one randomized, crossover, placebo-controlled study. Results from 105 survivors of breast cancer experiencing hot flashes revealed one less hot flash per day compared to placebo and lack of patient preference for vitamin E over the placebo (Barton et al., 1998). One randomized, nonblinded study of the efficacy of gabapentin 900 mg/day for controlling vasomotor symptoms in women with breast cancer (N = 115) included vitamin E 800 IU as a placebo equivalent. Vitamin E had a marginal effect on hot flashes. Hot flash frequency scores were reduced 10.02%, and severity scores decreased by 7.28% (p ≥ 0.05). Gabapentin was significantly more effective in reducing hot flash frequency and severity (57.05% and 66.87%, respectively (p < 0.05) (Biglia et al., 2009). A systematic review by Rada et al. (2010) also found lack of efficacy with vitamin E.

Acupuncture as a method to reduce hot flashes has been tested in several studies, most of which had small sample sizes and other methodologic issues, including concomitant use of medications for hot flashes (Kaplan et al., 2014; Kaplan & Mahon, 2014). Randomized studies comparing the use of true acupuncture to sham acupuncture (sham needles do not puncture the skin and are positioned at non-acupuncture points) in women with breast cancer and hot flashes have reported conflicting results. One study randomized 72 women with breast cancer and hot flashes to receive either true acupuncture or sham acupuncture. Based on self-reports, no significant difference between the true and sham acupuncture groups was found (Deng, Vickers, Yeung, & Cassileth, 2007). Another study randomized women with tamoxifen-induced hot flashes to true acupuncture (n = 38) and to control (sham) acupuncture (n = 36). Both groups reported reduction in hot flash severity and frequency, but more women in the control group reported improvements after six weeks than in the true acupuncture group (47% vs. 42%) (Liljegren et al., 2012). However, a prospective single-arm observational study using true acupuncture without
a placebo comparator reported benefit from the intervention (de Valois, Young, Robinson, McCourt, & Maher, 2010). An earlier study of 31 patients with breast cancer who were randomized to 12 weeks of relaxation therapy or acupuncture found that symptoms were significantly reduced in both groups at 12 weeks and at six-month follow-up. There was no placebo control arm (Nedstrand, Wijma, Wyon, & Hammar, 2005). A randomized study comparing 12 weeks of acupuncture to venlafaxine enrolled 25 women with breast cancer and hormone therapy–induced hot flashes in each treatment arm. Based on self-report diaries, both the acupuncture and venlafaxine groups initially reported reduced hot flashes, but at assessment two weeks after treatment completion, the venlafaxine group reported significantly increased hot flashes while the acupuncture group remained at low levels. Venlafaxine was also associated with adverse effects, including nausea, dry mouth, dizziness, and anxiety (Walker et al., 2010). A systematic review of randomized clinical trials that included menopausal women and/or women with breast cancer who received acupuncture for symptoms other than chemotherapy-induced nausea and vomiting was inconclusive about the efficacy of acupuncture because of the high risk of bias found among the studies (Garcia et al., 2013). A systematic review of 16 studies that compared true acupuncture to sham acupuncture for hot flashes associated with menopause or with breast cancer treatment found the evidence to be of poor quality, and the efficacy of acupuncture for vasomotor symptoms could not be determined. It may be that sham acupuncture is not a real placebo intervention but produces an active effect related to peripheral sensory stimulation (Dodin et al., 2013).

A study of acupuncture in men using a convenience sample of 60 men receiving ADT for prostate cancer found that 95% of the patients reported a decrease in hot flash severity over a 10-week acupuncture treatment period (Harding, Harris, & Chadwick, 2009). A prospective single-arm trial of acupuncture in men with prostate cancer (N = 14) found a short-term decrease in hot flash intensity and frequency (Ashamalla, Jiang, Guirguis, Peluso, & Ashamalla, 2011). Similar findings were reported by Beer et al. (2010) in an acupuncture intervention study of 22 men with hot flashes due to ADT for prostate cancer.

Hypnosis is an intervention that has been hypothesized to help alleviate hot flashes. When subjects are hypnotized, it is suggested that they are relaxed and may be more open to suggestion (Kaplan, Mahon, Cope, Keating, et al., 2011). One pilot study using hypnosis in four weekly sessions in breast cancer survivors (N = 16) showed a 59% decrease in total daily hot flashes (Elkins, Marcus, Stearns, & Rajab, 2007). A subsequent randomized trial of hypnosis versus no treatment in 51 breast cancer survivors followed for a period of five weeks showed a 68% decrease in hot flashes (p < 0.001) in the hypnosis group (Elkins et al., 2008). Both studies had methodologic limitations due to small sample size, brief treatment duration, and lack of long-term follow-up.

Cognitive behavioral therapy (CBT) has been studied as a novel approach to managing hot flashes and night sweats in breast cancer survivors. A recent randomized controlled trial enrolled symptomatic women seen in breast cancer clinics in London, England, into two treatment arms: usual care (n = 49) or usual care plus group CBT (n = 47) (Mann et al., 2012). All patients received “usual care” that included routine follow-up appointments with a healthcare provider and telephone access to breast cancer nurses who provided psychoeducational support and instructions in symptom management and paced breathing technique (slow, controlled diaphragmatic breathing). Patients randomized to receive the group CBT attended six weekly 90-minute support and education sessions led by a clinical psychologist that included group discussion, handouts, a paced breathing and relaxation CD for home use, and weekly homework and self-report hot flash/night sweat diaries. Participants were able to use medications or nonpharmacologic interventions to treat hot flash-
es throughout the study period. Follow-up occurred at 9 weeks and 26 weeks. Compared to those receiving usual care, the women receiving group CBT reported the hot flashes and night sweats as more tolerable at both the 9-week and 26-week assessments. Both groups reported nonsignificant reductions in hot flashes and night sweats at 9 weeks (21% in the CBT group and 24% in the usual care group) and at 26 weeks (38% in both groups). The 24-hour rates of hot flashes/night sweats were recorded by sternal skin conductance or event markers and showed little change at nine weeks. The researchers concluded that CBT provided a benefit and should be incorporated into breast cancer survivorship programs (Mann et al., 2012). However, correspondence from two oncology nurses published in a subsequent issue of *Lancet Oncology* in response to the findings of the CBT study suggested that the placebo effect might have contributed to the hot flash reductions recorded in both groups in the study (Mahon & Kaplan, 2012). The control group had access to high-quality support services and symptom management and relaxation instructions provided by breast care nurses, and the added individual attention could have contributed to the placebo effect in the control group as much as in the intervention group (Mahon & Kaplan, 2012). Another study randomized 422 women with breast cancer and treatment-induced menopausal symptoms to either CBT (n = 109), physical exercise (PE) (n = 104), combined CBT and PE (n = 106), or a waiting list control group (n = 103). Based on self-report questionnaires over six months, the interventions were much more effective in reducing endocrine symptoms than no treatment (control group). The groups that included CBT reported a significant decrease in the perceived burden of hot flashes and night sweats (problem rating scale of the Hot Flush Rating Scale; p < 0.001; effect size, 0.39–0.56) (Duijts et al., 2012).

Two nonpharmacologic interventions were ranked Unlikely to Be Effective: soy supplements and homeopathy remedies. Soy phytoestrogens are weak estrogens found in many plants, vegetables, and fruits. Based on the results of several randomized clinical trials in the early 2000s, no evidence was found that soy is better than placebo in controlling hot flashes in women with breast cancer (Kaplan & Mahon, 2014). Results of one randomized, placebo-controlled pilot study in men undergoing ADT for prostate cancer (N = 33) showed no significant improvement in vasomotor symptoms in men receiving soy isoflavones (Sharma et al., 2009). A placebo-controlled study randomized 120 men with prostate cancer and ADT-induced hot flashes to one of four study arms: venlafaxine alone, venlafaxine plus soy, soy alone, or placebo. No significant effect on hot flash severity was reported with venlafaxine or soy. At week 12, hot flashes had decreased 28% in the venlafaxine plus soy arm, 35% in the venlafaxine arm, and 31% in the soy arm. The placebo arm had the greatest decrease in hot flashes at 55% (Vitolins et al., 2013).

Homeopathy intervention involves a consultation with a homeopathic practitioner who prescribes an individualized regimen based on the patient’s reported symptoms. Randomized controlled trials involving homeopathic interventions are lacking. Most reported studies have methodologic issues, and the prescribed ingredients and doses are unclear (Kaplan & Mahon, 2014). In a systematic review of studies using homeopathic remedies, Rada et al. (2010) found it difficult to evaluate treatment efficacy or to replicate the homeopathic treatment. Review of data from studies of many different types of interventions revealed that no complementary or alternative medicine approach was found to have sufficient evidence establishing efficacy in managing hot flashes, mostly because of small sample sizes and brief study duration and follow-up. Use of soy supplements and homeopathy interventions were found unlikely to be effective. Studies of black cohosh in women with breast cancer had conflicting outcomes, although most clinical trials showed that it was no better than placebo in reducing hot flashes. Acupuncture was studied in both women with breast cancer and men with
prostate cancer with conflicting positive and negative results among studies. Hypnosis appeared to be effective in a study with a small number of subjects. Researchers reported benefit from using CBT; however, it may be that the individual attention influenced reported outcomes. Larger, randomized clinical trials of sufficient duration and follow-up are needed to assess for efficacy and safety of all types of interventions for reducing hot flashes. In addition, the placebo effect may play an important role in the results of studies testing interventions for hot flashes.

**Patient Teaching Points**

Treatment should be individualized to each patient following a thorough assessment of the severity and frequency of hot flashes and considering the potential risks and benefits of each intervention. Hot flashes may occur in a cluster of symptoms, such as sleep-wake disturbances, alterations in cognition, anxiety or depression, or decreased quality of life (Engstrom, 2008). Nurses should encourage patients to report symptom interference with social activities, activities of daily living, rest and sleep, and overall quality of life.

Patient education should begin with behavioral approaches for maintaining a cool core body temperature, such as wearing loose clothing and dressing in removable layers, drinking cold liquids, avoiding alcohol and foods that are hot or spicy, sleeping in a cool room on cotton sheets, and carrying a portable fan (Dalal & Zhukovsky, 2010). Lifestyle modifications that may reduce hot flashes should be discussed, such as reducing BMI, smoking cessation, and limiting alcohol and caffeine intake (Dalal & Zhukovsky, 2006; Richardson, 2013). However, the effects of these measures have not been evaluated in randomized clinical trials.

Several pharmacologic options are available for managing hot flashes in cancer survivors. Patient education should focus on the potential benefits, risks, and scientific uncertainties of each treatment option (Stearns, 2007). Although hormonal therapies are known to provide relief from hot flashes, because of the long-term risks of promoting tumor growth in cancer survivors, nonhormonal therapies should be used. Use of the SSRI agents fluoxetine and paroxetine should be avoided in patients taking tamoxifen; they are potent inhibitors of the CYP2D6 pathway by which tamoxifen is metabolized to its active form. Venlafaxine, an SNRI that does not inhibit CYP2D6, is a better choice for patients receiving tamoxifen (Morrow et al., 2011).

Patient use of personal hot flash diaries or journals to record the number, frequency, severity, and timing of hot flashes will assist both patients and nurses in assessing the efficacy of interventions. Patients should be educated to identify and avoid personal triggers for hot flashes (e.g., ambient room temperature, hot or cold beverages, anxiety, stress, caffeine, alcohol, spicy foods) and to record these in the diary as well. Referral to support groups may help some patients to cope with the side effects of treatment.

**Need for Future Research**

Currently, no standardized guidelines exist for the treatment of hot flashes in the oncology patient population. Few effective treatment options are available for men and women with hot flashes apart from hormonal therapies, which are contraindicated in the oncology setting. Many types of pharmacologic and nonpharmacologic interventions to reduce hot flashes.
flashes have been studied, although not many have shown efficacy. Recent studies of novel interventions, such as bupropion (an atypical antidepressant approved to treat depression and aid with smoking cessation), magnesium supplements, or eating flaxseed bars, have not demonstrated significant differences between the intervention and placebo (Park, Parker, Boardman, Morris, & Smith, 2011; Pruthi et al., 2011; Ribeiro Nuñez et al., 2013). Areas for future research include better understanding of the physiologic mechanisms involved in stimulating hot flashes and of the role of environmental factors on hot flash incidence. Randomized clinical trials with sufficient sample sizes, study duration, and follow-up are needed to provide evidence-based recommendations for the use of pharmacologic and nonpharmacologic interventions and to assess the long-term safety and efficacy of treatments providing a positive response. Some studies with nonsignificant findings that had a small sample size might warrant replication with larger numbers of subjects. Ideally, therapies should be tailored to the individual patient, taking into consideration existing comorbidities and concomitant medications that the patient may be taking.

Conclusion of Case Study

To help understand the etiology and extent of J.B.’s symptoms, the nurse obtains a detailed patient history and review of systems. J.B. denies a history of diabetes, tuberculosis, thyroid disease, cardiac disease, or generalized anxiety disorder and reports that he has had episodes of sweating during the past three months, with each episode lasting from one to five minutes. At night the sweating is so profuse that he wakes to find his pajama top soaking wet. J.B. has noticed that if he drinks coffee, he breaks out in a sweat that drips down his face and neck and is embarrassing when he is with customers. He has tried carrying a small battery-operated fan with him to cool off, but it has had minimal effect. He denies fever, chills, nausea, vomiting, weight loss, or signs and symptoms of an infection or other cancers. J.B. says that when his heart starts “pounding” during the hot flashes he becomes quite anxious. He denies fatigue, chest pain, shortness of breath, dyspnea on exertion, dizziness, cough, peripheral edema, or change in medications.

The most likely diagnosis for J.B. is hot flashes related to the androgen ablation treatment for prostate cancer. Infection, cardiac disease, respiratory disease, diabetes, and thyroid disease most likely can be ruled out by the pertinent negatives in the review of symptoms, physical examination, and diagnostic testing.

The nurse explains to J.B. that his symptoms are most likely the result of side effects from the hormonal therapy he is receiving for prostate cancer. He and his wife have had all of the treatment options explained to them, including possible side effects. His wife is taking venlafaxine for her own hot flashes, and he decides to try it as well to see if it helps. The nurse practitioner writes a prescription for venlafaxine, one 75 mg extended-release tablet per day as a starting dose, which can be increased if needed. The nurse also provides instructions about medication administration and describes possible side effects and adverse events (e.g., avoid use of monoamine oxidase inhibitors, which may cause serious or even fatal reactions for two weeks before, during, and at least one week after taking venlafaxine). The nurse suggests some behavioral approaches that may help to reduce hot flashes, such as limiting caffeine and alcohol consumption, and provides J.B. with written information about local and national prostate cancer support groups, such as Us TOO International Prostate Cancer Education and Support Network, as well as Live Strong Foundation resources.
Conclusion

Hot flashes and vasomotor symptoms are commonly reported side effects of hormonal treatment for men with prostate cancer and women with breast cancer. Reliable evaluation tools are needed to accurately measure both subjective and objective hot flashes. Interventions should match the frequency, distress, and severity of the symptoms. The only therapies found likely to be effective in reducing hot flashes are venlafaxine and gabapentin. No complementary or alternative intervention was associated with sufficiently powerful evidence to make a recommendation (Kaplan et al., 2014; Kaplan & Mahon, 2014). Future research studies of good quality are needed to provide meaningful evidence for hot flash reduction strategies.

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References


CHAPTER 17

Lymphedema

Joyce A. Jackowski, MS, FNP-BC, AOCNP®

Case Study

L.J. is a 56-year-old woman who was diagnosed in 2007 with a stage I intraductal carcinoma of the right breast. She underwent a lumpectomy with a sentinel lymph node biopsy. The tumor was 0.8 cm in size, intermediate grade, with the sentinel lymph node negative for metastasis. Prognostic indicators for estrogen receptors and progesterone receptors were negative. HER2/neu was also negative. Because the sentinel lymph node was negative for metastatic disease, she did not need further axillary dissection.

Following surgery, L.J. received adjuvant chemotherapy that included the use of an anthracycline and a taxane. When chemotherapy was completed, she received radiation therapy. She had been followed on a regular basis without any evidence of disease recurrence. She was in good health and reported no ongoing side effects or complications from prior treatment. She began to note swelling in her right upper arm and a sensation of fullness six years out from her cancer diagnosis.

Overview

Lymphedema in the oncology setting can be a lifelong concern. Lymphedema occurs when the flow of fluid in the lymphatic system is obstructed. The obstruction causes a chronic, persistent swelling in the affected extremity or body part. The presence of lymphedema can result in pain, decreased mobility, altered body image, infection, and diminished quality of life (Beck, Wanchai, Stewart, Cormier, & Armer, 2012; Bernas, 2013). Signs of lymphedema include tightness of the affected limb, swelling, puffiness, pain, or stiffness. Patients and healthcare providers often overlook the first signs of lymphedema because the changes may be subtle (Holcomb, 2006; Lester, 2013). Oncology nurses can affect patient outcomes by having basic knowledge of the condition, monitoring for its presence, educating patients about prevention, and assisting in treatment measures. Lymphedema is classified as either primary or secondary.

Primary Lymphedema

Primary lymphedema is caused by a lack of or an abnormality in the lymphatic tissue (Dell & Doll, 2006; Holcomb, 2006). Three types of primary lymphedema exist: congeni-
tal lymphedema, lymphedema praecox, and lymphedema tarda. One million to two million people in the United States are affected with primary lymphedema (Holcomb, 2006). In primary lymphedema, fluid accumulation generally is bilateral, with lower extremities affected more often than upper extremities, and women are more likely than men to have the disorder (Holcomb, 2006; Story, 2005; Williams, Franks, & Moffatt, 2005). The age at onset determines the type of primary lymphedema. The cause and presentation of each primary lymphedema type differ.

- **Congenital lymphedema** is present at birth and represents 10%–25% of primary lymphedema cases. With congenital lymphedema, the subcutaneous lymphatic trunks are absent (Rossy & Scheinfeld, 2014). Milroy disease, a familial sex-linked inherited disorder, is a classification of congenital lymphedema.

- **Lymphedema praecox**, also known as Meige disease, can present from birth to age 35. Lymphedema praecox is the most common primary type and is accountable for 65%–80% of primary lymphedema cases with 70% of those cases being unilateral and involving the left lower extremity. In lymphedema praecox, the number and diameter of lymphatic channels are reduced (Rossy & Scheinfeld, 2014).

- **Lymphedema tarda** typically does not develop until after the age of 35 and is the rarest form of primary lymphedema. The lymphatic vessels are tortuous and often have incompetent or missing valves (Rossy & Scheinfeld, 2014).

Three known genetic mutations are associated with primary lymphedema: *VEGFR3* is associated with Milroy disease, *FOXC2* with lymphedema-distichiasis, and *SOX18* with hypotrichosis-lymphedema-telangiectasia syndrome (Lymphoedema Framework, 2006).

### Secondary Lymphedema

Secondary lymphedema affects two to three million people in the United States (Holcomb, 2006). It develops when lymphatic structures are damaged, which results in fluid accumulation (Lasinski, 2013; Muscari, 2004). Anatomic changes in the lymph system arise from physical disruption, compression, or closure of the lymphatic channel. For example, a woman who has had lymph nodes removed as part of breast cancer treatment may develop secondary lymphedema when surgery physically disrupts the lymph system. This same woman may develop fibrosis following radiation. The fibrosis then compresses the lymphatic vessels. Finally, the woman may later develop metastatic cancer in the axilla that obstructs or closes the existing lymphatic channels. Figure 17-1 lists specific causes of secondary lymphedema. The most common cause worldwide for secondary lymphedema is filariasis, a parasitic infection of the lymph nodes (Holcomb, 2006; Tiwari, Coriddi, & Lamp, 2012).

With secondary lymphedema, the problem may present in an acute or chronic phase. Four types of acute lymphedema exist (Holcomb, 2006). The following provides a de-
scription of presentation and most effective treatment for each type of acute lymphedema.

- The first type is a mild acute lymphedema that occurs a few days following surgery. The lymphedema develops because lymphatic vessels have been either manipulated or cut during surgery. Symptoms of mild acute lymphedema are swelling, warmth, and erythema. The mild acute type is not usually associated with pain. This form is transient and responds to elevation and muscle contraction to improve blood flow to the extremity.

- A second type occurs six to eight weeks after surgery or radiation therapy. Acute lymphedema occurs as a result of inflammation such as lymphangitis or phlebitis without thrombosis. The limb may be red, warm, and tender. Treatment involves elevation of the extremity and use of anti-inflammatory agents.

- The third type is an erysipeloid form that occurs following a minor trauma or insect bite. The area will be red, hot to touch, and painful. Treatment necessitates antibiotics and elevation.

- The fourth type can occur 18–24 months after surgery yet also may appear many years later. Patients will note an insidious onset of pain that generally is associated with soft tissue stretching or postural changes from limb weight. Pain medication and anti-inflammatory medications may be used to provide symptom relief. See Table 17-1 for a summary of acute-phase lymphedema.

Acute lymphedema may become chronic. Chronic lymphedema develops when the lymphatic system is unable to handle the demands of lymphatic fluid flow. The amount of fluid removed is less than the amount produced, leading to excessive accumulation. Chronic lymphedema can affect both upper and lower extremities, depending on the causative factor (Story, 2005). Figure 17-2 presents the prevalence of distribution patterns in upper- and lower-extremity lymphedema. Patients may complain of heaviness, pain, aching, weakness, fullness, puffiness, and skin changes with chronic lymphedema (Marrs, 2007). Lymphedema has the potential to be a lifelong problem.

<table>
<thead>
<tr>
<th>TABLE 17-1</th>
<th>Acute Phases of Secondary Lymphedema</th>
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<tr>
<td><strong>When Problem Occurs</strong></td>
<td><strong>Description</strong></td>
</tr>
<tr>
<td>Within a few days after surgery</td>
<td>Mild acute lymphedema</td>
</tr>
<tr>
<td>6–8 weeks after surgery or radiation</td>
<td>Lymphangitis or phlebitis without thrombosis</td>
</tr>
<tr>
<td>Following minor trauma or insect bite</td>
<td>Erysipeloid</td>
</tr>
<tr>
<td>18–24 months to many years after surgery</td>
<td>Lymphedema</td>
</tr>
</tbody>
</table>

*Note. Based on information from Holcomb, 2006.*
In the oncology setting, the two most common causes for secondary lymphedema are radiation therapy and lymph node dissection (Lasinski, 2013; Muscari, 2004). Lymphedema may occur in any area of the body, including the face and neck, shoulders, upper extremities, chest, abdomen, groin, and lower extremities, with the highest rates occurring in survivors of head and neck cancer (Ridner, 2013). Figure 17-3 depicts a patient with a history of bilateral upper-extremity lymphedema that was caused by treatment with both radiation therapy and lymph node dissection. The anatomic changes in the lymphatic system from radiation therapy and lymph node dissection lead to an increased lifetime risk of developing secondary lymphedema (Armer & Stewart, 2005; Muscari, 2004). Figure 17-4 identifies risk factors that may affect the development or worsening of secondary lymphedema through impairment of the lymphatic load. While nurses are most aware of upper-extremity edema, 20%–30% of patients who have had lymph nodes removed, trauma, or abdominal or groin irradiation may develop lower-extremity lymphedema. Brown, Chu, Cheville, and Schmitz (2013) surveyed 107 long-term cancer survivors at risk for lower-limb lymphedema, and one-third reported one or more symptoms, including difficulty walking, pain, tightness, or aching in the affected extremity. Among the participants, 78% were unaware of the risk for lymphedema (Brown et al., 2013). Nurses can assist patients in identification of the risk factors and instruct them on preventive measures, such as weight loss for obesity, regular exercise, and tight glucose control for those with diabetes. In addition to the list of risk factors provided, nurses should advise patients to avoid wearing tight-fitting clothing that causes constriction of the extremity and to avoid increasing their body temperature through the use of hot tubs, heating pads, or hot showers, which may contribute to the development of lymphedema (Muscari, 2004). Long-term consequences of lymphedema are listed in Figure 17-5. Consequences of lymphedema may be both physiologic and psychosocial. Oncology nurses need to be aware of the impact that lymphedema can have in order to take appropriate actions in prevention and/or treatment of the disorder.

### Pathophysiology

The lymphatic system is present extensively throughout the body. The purpose of the system is to remove waste and foreign materials that are the byproducts of the body clearing
infection and disease (Marrs, 2007). In embryonic development, the lymphatic system arises from endothelial cells as a product of vasculogenesis and angiogenesis. The process takes place in four stages. Stage 1 is the lymphatic competence, where some of the cells express lymphatic vessel endothelial hyaluronan receptor-1 (LYVE-1) and vascular endothelial growth factor-3 (VEGF-3). Stage 2 involves commitment of the lymphatic system through signaling of the lymphatic-exclusive prospero-related homeobox 1 (Prox1) to be responsive to VEGF-3, which promotes lymphatic vascular development. Stage 3 involves higher levels of cell differentiation leading to lymphatic specialization. Stage 4 is the maturation stage, where cells bud into lymph sacs and migration takes place, leading to development of lymphatic vessels (Ridner, 2013). The network of fine vessels begins just beneath the surface of the skin, and the fine vessels then merge to become larger vessels in the tissue. The system is responsible for removing interstitial fluid that the circulatory system does not eliminate, approximately 3 L per day (McLafferty, Hendry, & Farley, 2012; Muscari, 2004). The fluid exchange occurs at the blood capillary-interstitial-lymphatic vessel surface (see Figure 17-6). The small lymphatic vessels have one-way valves that transport the fluid into larger lymphatic vessels that connect to lymphatic trunks that run through territories or quadrants into lymph node basins and eventually terminate in the venous system (Muscari, 2004; Ridner, 2013). Movement through the lymphatic system is dependent on three mechanisms: contraction of segments between valves when full, compression of vessels from external pressure such as muscle contractions, and intrinsic contractile filaments in the endothelial cells of lymph vessels (Muscari, 2004). Figure 17-7 depicts the normal lymph transport system. Fluid accumulation (lymphedema) occurs because the lymph transport system is unable to handle the capacity of fluid produced (McLafferty et al., 2012; Morrell et al., 2005; Muscari, 2004).

Fluid in the lymphatic system is composed of protein, water, fats, and cellular waste. Lymph vessels are thin, allowing larger proteins to filter through easily. An obstruction in lymphatic flow allows the large proteins to filter through the vessels and invade the surrounding interstitial tissue (Marrs, 2007; McLafferty et al., 2012; Morrell et al., 2005; Muscari, 2004). When this happens, the highly concentrated protein-filled fluid in the interstitial
FIGURE 17-4  Risk Factors for Lymphedema

- Obesity
- Lack of exercise
- Overuse of an affected extremity
- Hematomas
- Seromas
- Cellulitis
- Wounds
- Tight or constrictive clothes
- Airplane travel
- Long-distance travel
- Infection in or trauma to an affected extremity
- Prolonged standing
- Diabetes

Note. Based on information from Dell & Doll, 2006; Story, 2005.

FIGURE 17-5  Consequences of Lymphedema

- Pain
- Altered sensations and function
- Need for nontailored, large-sized clothing and shoes
- Repeated, persistent infections
- Fatigue
- Altered interpersonal relationships
- Functional disability
- Self-image alterations


FIGURE 17-6  Blood Capillary-Interstitial-Lymphatic Vessel Interface

space causes inflammation and subsequent skin changes along with fibrosis. The amount of accumulation determines the severity or stage of lymphedema. Staging is based on physical examination and measurement of the extremity (Lymphoedema Framework, 2006; Morrell et al., 2005; Muscari, 2004). See Table 17-2 for the stages of lymphedema. Fortunately, early stages of lymphedema are reversible. As the disorder progresses into later stages, the condition will become irreversible (Morrell et al., 2005; Muscari, 2004). Survivors with progressive, chronic, irreversible changes are susceptible to cellulitis, lymphangitis, elephantiasis, and rarely, angiosarcoma (Muscari, 2004).

Lymphedema can develop as a result of oncology treatments including surgery, radiation, and chemotherapy (Ridner, 2013). Lymphedema caused by surgery depends on the surgical site, type of treatment, and number of lymph nodes involved. Radiation causes a series of complex processes causing inflammation and fibrosis. Some of the processes involved include proinflammatory cytokines, decreased oxygenation to epithelial cells, and apoptosis with replacement of normal cells with connective tissue. The resulting fibrosis impairs lymph transport capability in the site of radiation. In previous years, chemotherapy was not thought to be associated with development of lymphedema. However, studies have reported that patients who received taxanes for breast cancer have higher reports of lymphedema development (Ridner, 2013). Fontaine et al. (2010) conducted a prospective study monitoring the incidence of lymphedema in 52 patients. The patients had surgical intervention for breast cancer followed by adjuvant chemotherapy and radiation. The adjuvant chemothera-
A Guide to Oncology Symptom Management (Second Edition)

Table 17-2: Stages of Lymphedema

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Patients have no obvious signs or symptoms. Impaired lymph drainage is subclinical. Lymphedema (LE) may be present for months to years before progressing to later stages.</td>
<td>Edema is not evident. Clinical detection of edema does not occur until the normal interstitial volume increases by 30% or more.</td>
</tr>
<tr>
<td>Stage I</td>
<td>Swelling is present. An affected area pits with pressure. Elevation relieves swelling. Skin texture is smooth. LE is spontaneously reversible.</td>
<td>&lt; 3 cm difference between extremities</td>
</tr>
<tr>
<td>Stage II</td>
<td>Skin tissue is firmer. Skin may look tight and shiny. Pitting may or may not occur. Elevation does not completely alleviate the swelling. Hair loss or nail changes may be experienced in an affected extremity. LE is spontaneously irreversible. Assistance will be needed to reduce edema.</td>
<td>3–5 cm difference between extremities</td>
</tr>
<tr>
<td>Stage III</td>
<td>LE has progressed to the elephantiasis stage. An affected area is nonpitting with a permanent edema. Skin is firm and thick. Hyperkeratosis, fat deposits, and acanthosis are present. Skin folds develop. Patients may be at risk for cellulitis, infections, or ulcerations. An affected area may ooze fluid. LE is irreversible. Elevation will not alleviate symptoms.</td>
<td>≥ 5 cm difference between extremities</td>
</tr>
</tbody>
</table>

Note. Based on information from Dell & Doll, 2006; Holcomb, 2006; Quan & Petrek, 2004; Story, 2005.

Therapy consisted of anthracycline-based therapy followed by a taxane. The arms were measured every three weeks during chemotherapy and then every three to six months for two years after surgery. There was a 40% incidence of lymphedema in the group, with 80% of the cases developing during taxane treatment (Fontaine et al., 2010). Further studies need to be done to determine causative mechanisms. In addition to therapy-related pathologic changes that can lead to lymphedema, a genetic predisposition has been theorized. In breast cancer survivors with secondary lymphedema, studies have suggested a genetic susceptibility that may contribute to lymphedema development (Ridner, 2013). Further work in this area will help determine those individuals who may be more at risk.

Assessment

Nursing assessment should include inspection of the affected limb for color, warmth, texture, and presence of any scars, injuries, wounds, or skin changes (Dell & Doll, 2006; Holcomb, 2006; Muscari, 2004). The nurse should verify whether swelling is relieved with elevation. Because lymphedema is not isolated to upper extremities, all limbs need to be assessed. The affected extremity should be measured on a regular basis, comparing the affected limb to the unaffected limb and results documented in the patient’s record (Dell & Doll, 2006; Holcomb, 2006; Story, 2005). Suggested assessment questions for patients and/or caregivers include the following.

- Is this a new problem or have you had this previously? If you have had this previously, has it gotten worse?
• Do you experience swelling?
• Do you experience any tightness, firmness, tenderness, or a heavy sensation?
• Are your movements limited in the extremity?
• Do you have numbness?
• What makes the swelling better or worse?
• How has this affected your daily life?

Several measurement techniques are available to assess the extent of lymphedema. Water displacement uses the amount of water displaced to determine the volume of the limb (Armer & Stewart, 2005; Bernas, 2013; Lymphoedema Framework, 2006). Although water displacement is sensitive and accurate, the process is cumbersome and must not be used if open skin wounds are present. Circumferential measurement is easy to use in the clinical setting. A tape measure is the only tool required. Measurements of the upper extremity should be taken 5 cm and 10 cm above and below the olecranon process (see Figure 17-8), for a total of four measurements per extremity. These four measurements are recorded and compared over time. The lower extremity should be measured at calf level (Story, 2005). Bioelectric impedance uses electrical current to measure the amount of fluid in a limb. This technique may be beneficial in diagnosing early signs of lymphedema (Armer & Stewart, 2005; Bernas, 2013; Lymphoedema Framework, 2006). Perometry measures limb volume with the use of an infrared light that measures the outline of the limb. The testing is not effective in measuring the volume of either a hand or foot. The technique is limited because of the machine’s expense (Lymphoedema Framework, 2006). Limb measurement provides the foundation for diagnosis of lymphedema. However, for those with lymphedema affecting the head and neck, breast, trunk, or groin, there is no way to accurately measure the extent of lymphedema. The Lymphoedema Framework (2006) recommends the use of digital photos to document the presence of lymphedema and response to therapy in these affected areas.

The diagnosis of lymphedema may be based on the patient history and a physical examination; however, further testing might be conducted to eliminate other possible causes (Bernas, 2013; Lymphoedema Framework, 2006; Wanchai, Beck, Stewart, & Armer, 2013). Workup should include evaluation for disease recurrence because of compression from tumor or lymphatic obstruction (Bernas, 2013; Morrell et al., 2005; Muscari, 2004). Tests that can be performed include lymphoscintigraphy, computed tomography (CT) scan, magnetic resonance imaging (MRI), lymphangiography, and evaluation of lymph fluid for protein content.

• Lymphoscintigraphy is a nuclear medicine test that has 100% sensitivity and specificity for the detection of lymphedema. The patient is injected with a radiolabeled protein in the first web space of the affected hand or foot, and the movement of the radiolabeled protein is tracked through the lymph sys-
tem. Alterations in lymph drainage are detected through the tracking process (Lymphoedema Framework, 2006). A CT scan or MRI can be used to check for disease recurrence.

- Lymphangiography may be used if surgery is being considered. The procedure assesses the dermal lymph capillaries using a fluorescein-labeled human albumin.

The lymph fluid may be evaluated for protein content. Determination of protein content differentiates the underlying cause of edema. A protein level of 1–5.5 g/dl indicates lymphedema, and a level of 0.1–0.9 g/dl indicates venous or cardiac edema (Holcomb, 2006). Other testing useful in lymphedema evaluation includes venous Doppler ultrasound to check for thrombus formation and laboratory tests to measure liver function, albumin level, kidney function, or urinalysis (Lymphoedema Framework, 2006). Once the diagnosis is confirmed, treatment measures will be initiated.

### Evidence-Based Interventions

Treatment of lymphedema depends on the stage at presentation. Most management will involve nonpharmacologic measures.

### Recommended for Practice

The gold standard used to treat lymphedema is termed complete decongestive therapy (CDT) (Armer, Beck, Deng, Fu, & Giammicchio, 2014; Chang & Cormier, 2013; Lasinski, 2013; Lymphoedema Framework, 2006; Ridner et al., 2012) and is recommended for use with lymphedema. Components of CDT include (a) manual lymph drainage (MLD), (b) compression bandaging using multilayer short-stretch bandages, (c) exercise, (d) compression garments, (e) skin care, and (f) education in self-management (Armer et al., 2014).

MLD involves the movement of lymph fluid from a nonfunctioning region to an adjacent region that is draining effectively (Lasinski, 2013; Muscari, 2004). Figure 17-9 shows MLD of the thorax, done prior to moving fluid from distal regions. Although the MLD technique appears to be similar to massage, the method uses lighter pressure. Figure 17-10 demonstrates how the hands are placed to stretch the skin during MLD. MLD should not be used on patients with open wounds, skin infections, or thrombosis (Lymphoedema Framework, 2006). Initially, in the acute phase of treatment, MLD involves daily therapy lasting 60–90 minutes for up to 15 sessions (Muscari, 2004). The subsequent maintenance phase involves self-care activities for patients to complete on a regular basis. During the acute phase, the therapist will apply compression bandages following each MLD session. For patients with lymphedema who cannot be treated with compression bandages, such as lymphedema of the head and neck, MLD alone may

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**FIGURE 17-9 Manual Lymph Drainage Pathways**

be the only treatment option (Lasinski, 2013; Lymphoedema Framework, 2006). Hamner and Fleming (2007) studied the effects of MLD on 135 patients with lymphedema. The mean initial lymphedema volume prior to therapy was 709 ml. Following twice-weekly therapy for eight weeks, the mean lymphedema volume was reduced to 473 ml, thus showing the benefit of MLD (Hamner & Fleming, 2007).

Compression bandaging involves the application of multiple layers of short-stretch bandages from distal to proximal regions (Lasinski, 2013; Muscari, 2004). Compression bandaging promotes the movement of fluid along a pressure gradient to reduce the potential for refilling of the nondraining lymphatic tissue. Figure 17-11 depicts a patient wearing compression bandaging. Multilayered compression bandages are intricately wrapped using bandages similar to ACE® bandages. Compression bandaging is worn up to 22 hours a day during the acute phase of treatment. Figure 17-12 shows the effect of MLD and compression bandaging therapy in a patient with lower-extrem-
ity lymphedema. Once the acute phase of treatment has ended and maximum fluid reduction has taken place, patients will be fitted for a garment. Kim, Yi, and Kwon (2007) studied how CDT affected the reduction in limb volume and quality of life one month and six months after therapy for upper-limb lymphedema from breast cancer in 53 patients. The study demonstrated that lymphedema was reduced from baseline at one and six months after therapy. The quality-of-life measures improved in physical function, mental health, and
overall health at six months. The improvement in quality-of-life measures correlated with a reduction in lymphedema volume (Kim et al., 2007).

Compression garments are used for long-term control of lymphedema. Compression garments use the application of pressure at a level of 20–60 mm Hg to prevent recurrence (Lymphoedema Framework, 2006). Compression garments provide a gradient pressure that prevents backflow of lymph fluid into distal tissue. Compression garment construction is either circular knit or flat knit; flat knit garments will have a seam (Cooper, 2013; Lymphoedema Framework, 2006). Nurses should advise patients that they will be measured and fitted for the compression garment by a person properly trained in fitting the garment. Patients wear the compression garment during waking hours to maintain a reduction in chronic lymphedema. A properly fitting compression garment will be close-fit without a tourniquet-like effect, easy to apply, and comfortable to wear during activities of daily life. Garments should be washed regularly and replaced every six months. Proper care of garments will ensure better control of lymphedema. Patients with arterial insufficiency, acute cardiac failure, cellulitis, or weeping wounds should not use compression garments (Lasinski, 2013; Lymphoedema Framework, 2006).

**Likely to Be Effective**

Exercise is recommended in the post-therapy setting for overall health benefits, yet the role of exercise with lymphedema was lacking in supportive evidence (Chang & Cormier, 2013). A systematic review of exercise with breast cancer survivors revealed that exercise was not associated with an increase in arm volume and may have contributed to a reduction in exacerbations of lymphedema and halted further increase in arm size (Ridner et al., 2012).

Resistance exercise has been studied in breast cancer survivors, and no increase was found in exercise-related lymphedema when it was started at any point after surgery (Chang & Cormier, 2013). When resistance exercise is combined with aerobic exercises, the benefit of the intervention needs to be balanced with the potential for harm. The studies evaluating resistance and aerobic exercise involved small sample sizes and low adherence to study interventions (Chang & Cormier, 2013). For example, Courneya et al. (2007) conducted a randomized controlled study evaluating the effects of resistance and aerobic exercise on 242 patients undergoing adjuvant chemotherapy for breast cancer. The patients were randomized to either usual care (n = 82), supervised resistance exercise (n = 82), or supervised aerobic exercise (n = 78). The patients were treated for a mean duration of 17 weeks. Participants had a 70% adherence rate to the supervised exercise interventions. The effect of exercise on lymphedema was a secondary endpoint for the study. The researchers concluded that resistance or aerobic exercises are not a cause for lymphedema (Courneya et al., 2007).

**Effectiveness Not Established**

Closed-controlled subcutaneous drainage was first reported in 2004 and has been reserved for use in those with advanced cancer (Beck et al., 2012). The technique involves insertion of subcutaneous needles or catheters to drain fluid. The studies have involved small sample sizes with a reduction in limb volume. None of the participants developed any side effects such as infections (Beck et al., 2012).

Intermittent pneumatic compression (IPC) therapy is designed to be used in conjunction with CDT and compression garments (Chang & Cormier, 2013; Ridner et al., 2012). The use
of mechanical pumps involves an air compression pump that applies pressure along an extremity. The intervention can be used in place of MLD for those not able to undergo MLD. While studies have shown volume reduction, there have been inconsistencies with frequency of treatment, duration of treatment, optimal pressure of the treatment, and cost for therapy. IPC should not be used for patients with cellulitis or deep vein thrombosis or those on blood thinners (Chang & Cormier, 2013). For patients who are receiving IPC therapy, healthcare providers need to monitor for signs of increased edema or fibrosis at the level just above where the sleeve is applied.

Surgery can involve excisional procedures such as liposuction; microsurgical techniques such as lymphedema bypass, tissue transfer, and lymphatic reconstruction; or lymph node transplantation (Becker, Assouad, Riquet, & Hidden, 2006; Chang & Cormier, 2013; Salcido, 2013). Surgery does not cure lymphedema. It provides a reduction in tissue and weight of the affected limb. At this time, surgery should not be considered for first-line therapy. Surgery should only be considered when CDT has failed (Becker et al., 2006; Chang & Cormier, 2013; Salcido, 2013; Williams, 2012).

Wearing compression garments during exercise needs to be further studied to establish benefit. The studies done were limited, and results have not established effectiveness (Chang & Cormier, 2013). However, the National Lymphedema Network (NLN) position statement supports use of 20–30 mm Hg garments for upper extremities during exercise (NLN, 2012). Until further studies are completed that establish effectiveness, compression garment use during exercise is supported by NLN for those with lymphedema and as an individual choice for those at risk for lymphedema (Chang & Cormier, 2013).

**Not Recommended for Practice**

**Compression Garment Use When Flying**

NLN has developed position statements designed to inform the public on risk-reduction measures concerning the development of lymphedema in those without a history of lymphedema. The position statements are based more on expert opinion than on evidence-based studies. One update from NLN that has changed in recent years concerns the recommendation of wearing a compression sleeve when flying. The current NLN position statement is that evidence is lacking to support the use of a compression garment for prevention of lymphedema when flying (NLN, 2012). Compression garment use when flying is still categorized as Expert Opinion in the Oncology Nursing Society (ONS) Putting Evidence Into Practice (PEP) recommendations for those with a history of lymphedema (Armer et al., 2014).

**Massage and Aromatherapy**

A study of self-massage and skin care with massage cream with and without aromatic oil added found no significant differences between limb volumes when massage cream had aromatic oil versus cream with no oil. The self-massage and skin care alone decreased limb volume and improved overall well-being (Barclay, Vestey, Lambert, & Balmer, 2006).

**Diuretics**

Diuretics have been used historically on a short-term basis for other causes of edema in the affected limb, not necessarily for lymphedema itself. However, the use of diuretics is not recommended on a long-term basis because the treatment does nothing to remove the underlying cause of protein accumulation in the interstitial tissue (Lymphoedema Frame-
work, 2006). Fluid and electrolyte imbalances may occur as a result of inappropriate diuretic use.

**Natural Products**

Benzopyrones, specifically coumarin, are available in Europe and are used to treat lymphedema (Lymphoedema Framework, 2006; Morrell et al., 2005; Wanchai, Armer, & Stewart, 2013). However, the use of benzopyrones is not approved in the United States. The drug’s mechanism of action is attributed to an ability to break down proteins, which then helps to decrease the fluid accumulation. Two studies were reported in the 1990s. Casley-Smith, Morgan, and Piller (1993) randomized 52 patients to either benzopyrone or placebo. The patients received the medication for six months. When patients were on placebo, the lymphedema worsened. While patients were on benzopyrone, their limb volume measurements decreased. A second study was conducted by Loprinzi et al. (1999) with 140 women with lymphedema after treatment for breast cancer. The patients were randomized to either benzopyrone or placebo. Each group was on the medication for six months followed by another six months of the other treatment. The limb volume measurements were not reduced at either the 6- or 12-month intervals (Loprinzi et al., 1999). These studies failed to demonstrate significant benefit, and coumarin (not to be confused with Coumadin®) causes liver toxicities.

Selenium has been studied as a treatment for radiation-induced lymphedema and secondary lymphedema from breast cancer surgery. Radiation causes fibrosis of the tissue surrounding the lymph vessels, producing compression with subsequent fluid accumulation (Morrell et al., 2005). The hypothesis is that selenium will consume oxygen radicals, which will subsequently decrease the lymph system damage (Holcomb, 2006). The drug has only been evaluated in a small population of survivors. Although the study showed a reduction in arm circumference in 83% (10 of 12) of patients, the evidence is not strong enough to recommend the use of selenium for lymphedema at this time (Morrell et al., 2005). Although selenium often is considered nontoxic, it may cause side effects of nausea, vomiting, diarrhea, and elevated heart rate (Holcomb, 2006; Morrell et al., 2005).

Ginkor Fort® was studied in a randomized, placebo-controlled trial conducted with 48 participants with a history of breast cancer. The study looked at twice-daily dosing versus three-times-a-day dosing for two months. There were some reports that limb heaviness was less in the twice-daily dosing group. Lymphoscintigraphic measurements were used in addition to the report of limb heaviness. In both the treatment and placebo arms, the lymphoscintigraphic measurements improved. The study did not adequately demonstrate the benefit of use, and further trials need to be conducted (Cluzan, Pecking, Mathiex-Fortunet, & Picherit, 2004).

Horse chestnut seed extract, butcher’s broom, and ginkgo are products used in patients with chronic venous insufficiency. Their precise mechanisms of action are not known. A study was conducted measuring lymphatic flow before and after a three-month period of time on the horse chestnut complex supplement in 15 participants without lymphedema. The complex administered contained horse chestnut seed extract, butcher’s broom, and ginkgo. Although flow of lymphatic fluid was increased following administration of the horse chestnut complex, the study had flaws that do not support use of these agents without further randomized controlled trials in patients affected by lymphedema (Wheat, Currie, Kiat, & Bone, 2009).

Vitamin E was used in combination with pentoxifylline for 6- and 12-month periods in 68 patients with lymphedema of the arm following treatment for breast cancer. The evaluation of arm volume, presence of fibrosis, and quality-of-life measures did not demonstrate any benefit with the use of vitamin E and pentoxifylline (Gothard et al., 2004).
Patient Teaching Points

Education is essential to the prevention and treatment of lymphedema. Interventions include the following (Dell & Doll, 2006; Holcomb, 2006; Muscar, 2004; Story, 2005).

• Exercise regularly and maintain proper weight.
• Avoid injury to the affected extremity by averting cuts, abrasions, and insect bites.
• Avoid tight clothing, jewelry, or elastic bands on the affected extremity.
• Avoid blood pressure measurements, blood draws, and IV insertions in the affected extremity.
• Report signs of redness, warmth, pain, swelling, or change in fit of clothes in the affected extremity.
• Report feelings of heaviness or aching in the affected extremity.
• Avoid carrying a purse or briefcase on the affected side.
• Wear a compression garment when traveling by plane for those with a history of lymphedema.
• Use an electric razor to shave an affected limb or axilla.
• Keep nails clean and short. Avoid cutting the skin when trimming nails, and avoid use of artificial nails.
• Avoid use of sharp objects, such as knives, needles, or scissors, on the affected side.
• If lymphedema is in the lower extremities, avoid standing or sitting for long periods and do not cross legs.
• Use compression garments, stockings, and devices as directed by a healthcare provider trained in lymphedema management.

The following patient and provider resources may be helpful.

• Breastcancer.org: www.breastcancer.org/tips/lymphedema/index.jsp
• Lymphology Association of North America: www.clt-lana.org
• MayoClinic.com: www.mayoclinic.com/health/lymphedema/DS00609
• NLN: www.lymphnet.org
• Oncology Nursing Society Lymphedema Management Special Interest Group: http://lymphedema.vc.ons.org
• American Lymphedema Framework Project: www.alfp.org; has also developed the Look-4LE smartphone app to enable searching for lymphedema specialists by geographic area.

Expected Patient Outcomes

The outcomes with lymphedema are based on whether the condition has developed. The primary goal is to prevent the development of lymphedema. Nurses should complete measurements of the extremities on a regular basis to identify the effectiveness of risk-reduction interventions. When measurements of the extremity are taken regularly, the development of lymphedema will be detected early, and treatment can be initiated quickly and can influence long-term outcomes that reduce further progression. Prevention and early detection are the keys to lessen the effects of lymphedema and improve quality of life.

Need for Future Research

Although great strides have been achieved in the prevention and management of lymphedema, much work remains. Research is needed in a variety of aspects (Morrell et al., 2005;
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Muscari, 2004). Lymphedema remains an underidentified problem. Epidemiology studies need to be conducted to identify the extent of the problem. Preventive measures, although based on sound physiologic thought, lack evidence-based studies to support their effectiveness. Specific measurement techniques and imaging studies that are clinically useful and accurate and that require minimal time and expense are needed. Research into best practices for interventions such as exercise and surgery is needed to establish effectiveness. Healthcare providers need to support all efforts that will have an impact on this chronic, debilitating disorder.

Conclusion of Case Study

L.J. called the office to report a week-long history of right-arm edema. At the time, she was six years out from diagnosis and treatment. She described the arm as feeling tight and heavy. She denied any redness, tenderness, or warmth. She had not had any recent airline travel, blood pressure measurement, or needlesticks. Her hobbies include gardening. She denied any cuts, insect bites, or injuries. An appointment was made for evaluation with a healthcare provider.

At the evaluation, the nurse completes a review of her medical history, social history, and family history. The subjective review of systems is negative except for the new onset of right-sided arm swelling. On physical examination, the breasts are supple bilaterally, a lumpectomy scar is present in the right breast, and no lumps or masses are palpable. No palpable adenopathy is present. The right arm is visibly edematous; the skin feels smooth. No evidence of pitting is present. Measurements reveal a 2.5 cm difference in size between the right and left arms. Swelling decreased some with elevation. L.J. is suspected of having stage 1 lymphedema. Further workup is required.

L.J. undergoes a breast MRI, which is negative for disease recurrence. A Doppler ultrasound does not show thrombosis. Because there is no evidence of underlying disease recurrence, she is referred to a certified lymphedema specialist for follow-up evaluation and treatment. L.J. is shown how to massage the limb to decrease the swelling and is provided education about how to care for her extremity. Components of future treatment likely will include MLD, compression bandaging, light exercise, and self-management. As she is seen in follow-up, the nurse will review her current interventions and provide further individualized planning to optimize lymphedema reduction.

Conclusion

Lymphedema is an often debilitating condition in cancer survivors. Nurses can make a tremendous impact on survivors’ quality of life through comprehensive knowledge of the condition and recommendations for interventions based on sound science. Nurses need to provide education in the prevention of lymphedema, conduct ongoing assessment for the presence of lymphedema, and refer patients promptly for current lymphedema management interventions.

References


CHAPTER 18

Mucositis

Carlton G. Brown, PhD, RN, AOCN®, FAAN

Case Study

G.B. is a 64-year-old man diagnosed with adenocarcinoma of the colon. Next week he is scheduled to begin four to six cycles of leucovorin and bolus 5-fluorouracil (5-FU), which will be administered over five days every four weeks. G.B. and his wife ask the nurse who is providing chemotherapy teaching what will likely be the most significant symptom for him during the treatment. The nurse knows that oral mucositis (OM) will be a severe problem for G.B.

Overview

OM is one of the most incapacitating, painful, and menacing side effects of cancer therapies such as chemotherapy and radiation. It is an inflammatory and ulcerative process affecting the mucous membranes of the oropharynx, mouth, and gastrointestinal (GI) tract that can result in lesions (Eilers & Million, 2011), and these lesions are sometimes so painful for patients that opioid analgesics are necessary. OM is a somewhat common and treatment-limiting side effect of cancer therapy. Of interest, OM generally begins to disappear a few days or weeks after the chemotherapy or radiation is discontinued.

Varying degrees of mucositis exist, ranging from mild changes in sensation to more major changes including acute oral pain, infection, xerostomia (dry mouth), and ulcerative, bleeding lesions (Eilers & Million, 2011). Patients who encounter OM complain of a “sore mouth” and are sometimes subjected to a variety of physical sequelae along with pain, including difficulty eating and drinking, difficulty talking, depression, sleep disturbances, weight loss, and hospitalization (Eilers & Million, 2011; Rose-Ped et al., 2002). Because it can be painful for patients with OM to eat and drink, they may suffer from dehydration, dysgeusia, and malnutrition (National Cancer Institute [NCI], 2014). Not all mucositis is confined to the oral cavity, but it presents very similarly throughout the entire GI tract and is commonly referred to as alimentary mucositis (Keefe, Peterson, & Schubert, 2006).

Patients may find OM so painful and unbearable that they may prematurely terminate their cancer therapy. Sonis et al. (2004) estimated that well over half of patients with OM had temporary delays in treatment, and more than one-third of patients with OM discontinu-
ued treatment altogether. According to Elting et al. (2003), for patients with OM, the potential for having a chemotherapy dose reduction almost doubled.

While OM is certainly a detriment to patients’ quality of life, this debilitating side effect can be financially costly as well. An episode of OM may increase patients’ chances for hospitalization, and the length of stay may be extended because of fever, infection, or the necessity for pain management and parenteral nutrition (Rubenstein et al., 2004). Sonis et al. (2004) estimated that 62% of patients with OM are hospitalized and 70% require tube feedings to maintain acceptable hydration and nutrition. Peterman, Cella, Glandon, Dobrez, and Yount (2001) found in their retrospective study of costs associated with an episode of OM that patients with head and neck cancer with OM had statistically higher medical costs and that these were associated with OM severity. Nonzee et al. (2008) noted that patients with head and neck cancer who developed severe OM had a median incremental additional cost of approximately $17,000, whereas patients with non-small cell lung cancer who developed OM had an additional cost of $25,000. Additional care costs associated with patients with OM included inpatient hospitalization, supportive care pharmaceuticals (antibiotics and pain medications), and procedures (such as the placement of a gastrostomy tube for nutritional support) (Nonzee et al., 2008; Sonis, 2011).

Risk Factors and Associated Incidence

OM incidence and severity vary depending on patient-related and treatment-related risk factors. Patient-related factors are listed in Figure 18-1. Vokurka et al. (2006) reported a higher incidence of chemotherapy-induced OM in women when compared with men. Raber-Durlacher et al. (2000) suggested that patients older than 50 develop OM that is more severe and has a longer duration. They proposed that this more intense and prolonged OM might be related to a decline in renal function. In the past decade, there has been an increased curiosity in the role of genetic factors, which might play an important role in OM and its treatment (Al-Dasooqi et al., 2013; Eilers & Million, 2011).

Examples of treatment-related risk factors (see Table 18-1) include the particular chemotherapy agents and dosage, the frequency of the treatment, the use of radiation therapy, and neutropenia (Avritscher, Cooksley, & Elting, 2004; Barasch & Peterson, 2003; Eilers & Million, 2011; Peterson & Cariello, 2004). The treatment-associated risk factors will now be discussed in further detail.

<table>
<thead>
<tr>
<th>FIGURE 18-1</th>
<th>Patient-Related Risk Factors for Oral Mucositis</th>
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<tbody>
<tr>
<td>• Age: Children/elderly</td>
<td></td>
</tr>
<tr>
<td>• Oral health/hygiene: Poor oral health/hygiene</td>
<td></td>
</tr>
<tr>
<td>• Salivary secretion function: Reduced salivary flow</td>
<td></td>
</tr>
<tr>
<td>• Genetic factors: Expression of high levels of cytokines</td>
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</tr>
<tr>
<td>• Body mass index: Low body mass (&lt; 20 kg/m² for males and &lt; 19 kg/m² for females)</td>
<td></td>
</tr>
<tr>
<td>• Renal function: Decreased renal function</td>
<td></td>
</tr>
<tr>
<td>• Tobacco: Patients who use tobacco products</td>
<td></td>
</tr>
<tr>
<td>• Previous cancer treatment with chemotherapy or radiation therapy</td>
<td></td>
</tr>
<tr>
<td>• Nutritional status: Patients with low body weight</td>
<td></td>
</tr>
<tr>
<td>• Oral microflora: Higher levels of oral microflora</td>
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<tr>
<td>• Inflammation: Role is unclear, but suspected.</td>
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Note. Based on information from Avritscher et al., 2004; Barasch & Peterson, 2003; Eilers & Million, 2011.
Chapter 18  Mucositis

**Radiation**

The occurrence of OM fluctuates noticeably depending on the different types of treatments for cancer (Peterson & Cariello, 2004). The incidence of radiation-induced OM is particularly high in (a) patients with primary tumors of the oral cavity, oropharynx, or nasopharynx, (b) those who have received concomitant chemotherapy, (c) those who have received greater than 5,000 cGy of radiation, and (d) those treated with more than one radiation treatment per day (Lalla, Sonis, & Peterson, 2008). In patients receiving radiation, especially those treated with 30 Gy or more of radiation for head and neck cancer, the incidence of OM is almost 100% (Sonis, 2011). Thereafter, the severity of OM generally worsens over the following weeks of radiation treatment and does not subside until the treatment is terminated. For patients receiving radiation, ulcerative lesions usually persist for approximately two to four weeks after the termination of treatment (Sonis, 2011). Unfortunately, radiation causes permanent tissue damage not only to the oral mucosa but also to the salivary glands, muscles, and bone, resulting in permanent chronic problems such as xerostomia and trismus (NCI, 2014). For patients receiving chemotherapy and radiation together, the potential to develop OM is greater (Eilers & Million, 2011).

**Chemotherapy**

Receiving a particular chemotherapy regimen may put patients at particular risk for OM. Certain chemotherapy agents have a higher potential to cause OM than others; not all chemotherapy agents cause OM. NCI (2014) estimated that 10% of patients receiving adjunctive and 40% of patients receiving primary chemotherapy experience OM. Although all chemotherapy agents should be suspect of causing OM, the following are more likely to be responsible: antimetabolites such as 5-FU, methotrexate, and cytosine arabinoside; alkylating agents such as melphalan and busulfan; antitumor antibiotics such as dactinomycin, doxorubicin, and epirubicin; and taxanes, such as docetaxel and paclitaxel (Polovich, Olsen, & LeFebvre, 2014). 5-FU, a common drug used in the treatment of colon cancer, can cause higher levels of OM, especially when given by bolus (Eilers & Million, 2011). Chemotherapy-induced OM can be detected 2–14 days following drug administration. Mucositis in-

<table>
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<th>TABLE 18-1 Treatment-Related Factors for Oral Mucositis</th>
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<tr>
<td><strong>Factor</strong></td>
</tr>
<tr>
<td>Chemotherapy agent</td>
</tr>
<tr>
<td>Chemotherapy dose</td>
</tr>
<tr>
<td>Type of transplant</td>
</tr>
<tr>
<td>Radiation site</td>
</tr>
<tr>
<td>Combined modality</td>
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*N*ote. Based on information from Avritscher et al., 2004; Barasch & Peterson, 2003; Eilers & Million, 2011.
duced by chemotherapy usually lasts for about one week and heals approximately 21 days after infusion of chemotherapy (Rodríguez-Caballero et al., 2012).

**Stem Cell Transplantation**

OM in hematopoietic stem cell transplant (HSCT) recipients is a significant problem and is usually caused by the much higher doses of chemotherapy used in the conditioning regimens. Allogeneic transplants are associated with higher levels of OM than autologous transplants (Eilers & Million, 2011). Three historical trials supported the presence of OM in patients undergoing HSCT (McGuire et al., 1993; Wardley et al., 2000; Woo, Sonis, Monopoli, & Sonis, 1993). McGuire et al. (1993) reported that approximately 89% of patients receiving either an allogeneic or autologous transplant had OM, and 36% of the same sample reported OM-associated pain. In a longitudinal study of 59 transplant recipients undergoing HSCT, 76% of participants had ulcerative lesions that developed approximately five days after conditioning with a duration of approximately six days (Woo et al., 1993). Wardley et al. (2000) found that of those patients undergoing some form of HSCT, 99% reported some level of OM, and 67% reported grade 3 or 4 OM. HSCT recipients are at an even higher risk for OM when total body irradiation (TBI) is given concurrently with consolidating chemotherapy. Sonis et al. (2004) reported that when patients receive TBI as part of the conditioning regimen for HSCT, the incidence of grade 3 and 4 OM exceeded 60%. Conversely, the same researchers reported lower levels (30%–50%) of OM without TBI.

**Pathophysiology**

Historically, it was believed that the primary cause of OM was epithelial damage to the oral mucosa. However, it is more than a result of epithelial injury, and the existence of other mediators and circumstances must be accounted for to include damage to the important connective tissues (Sonis, 2011). Sonis (2011) proposed a pathophysiologic model (see Figure 18-2) for mucositis, which encompasses five distinct phases: (a) initiation, (b) upregulation and message generation, (c) signaling and amplification, (d) ulceration, and (e) healing. It is important to note that although there are five distinct phases, more than one phase can occur simultaneously.

**Initiation**

The first phase of the process is the initiation phase, which occurs very quickly after chemotherapy or radiation is administered. During the initiation phase, chemotherapy and radiation treatments cause DNA and non-DNA (blood vessel, tissue) damage resulting in cell death and ensuing injury of the basal and epithelium cells in the submucosa and damage to connective tissue. This process is mediated by the generation of reactive oxygen species, which damage DNA and can create further biologic problems later (Sonis, 2011).

**Upregulation and Message Generation**

Following initiation, a series of individual biologic events happen that create further damage. One such event is activation of transcription nuclear factor-kappa B (NF-κB), which controls nearly 200 genes connected with mucositis (Sonis, 2004, 2011). Amplification of in-
jury occurs as these genes present in the endothelium, fibroblasts, macrophages, and epithelium and become activated. It is at this point that proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-\(\alpha\)), interleukin-1-beta, and interleukin-6, are released and cause tissue damage and apoptosis (Sonis, 2011). Patients are not likely to feel the effects of damage during this phase.

**Signaling and Amplification**

The third phase is signaling and amplification. Via a positive feedback loop, proteins and cytokines continue to damage tissue, as well as increase the primary damage from chemotherapy or radiation. The continued bombardment of positive signals accelerates and amplifies the biologic effect of a dose of chemotherapy, thus causing continuous injury to the oral mucosa. In this phase, patients may still not feel the effects of the ongoing mucosal damage (Sonis, 2004).

**Ulceration**

The clinical highpoint of mucositis occurs during ulceration, which is the fourth phase of the model and is considered the most complex and symptomatic for patients and caregivers (Sonis, 2004). As the biologic barrage begins to take its harmful toll on the mucosa, injury is manifested in the form of ulceration. Fibrinous exudates may cover the oral lesions, which become inundated with high levels of bacteria. In patients already neutropenic, the accumulation of bacteria may leave them at significant risk for invasion of microorganisms that may lead to bacteremia and sepsis (Sonis, 2011). It is during the ulcerative phase that OM greatly affects patients’ well-being by causing very painful lesions (Sonis, 2011). Patients may begin to experience considerable pain and have difficulty swallow-
ing, leading to a decrease in nutritional intake, coupled with decreased talking and an increased potential for bleeding.

Healing

The final phase of the pathobiology model is healing (Sonis, 2011). Fortunately, the oral mucosa eventually heals (after about four weeks), which happens when treatments such as chemotherapy or radiation are terminated. New messenger molecules direct the epithelium to heal through regeneration. During the healing phase, there is an augmented creation of white blood cells, which help to fight and disable infection from bacteria and other harmful microorganisms. However, it is essential to understand that cells and tissue of the mucosa may not immediately return to their original state. In instances when several cycles of chemotherapy or radiation are delivered, there may not be enough time for complete healing, which often positions patients for more severe OM in future cycles of treatment.

Assessment

A thorough and systematic assessment is significantly important in the prevention and treatment of OM of the oral cavity. In fact, Eilers and Million (2011) recently noted that for oncology nurses caring for patients with OM, assessment is the paramount clinical intervention. A systemic assessment conducted by oncology nurses should include a pretreatment assessment that takes into consideration those patient-related and treatment-related risk factors presented in Tables 18-1 and 18-2. Additionally, during the pretreatment assessment, nurses should inquire about patients’ usual daily oral care techniques (brushing and flossing) and ability to perform oral care during their respective cancer treatment (Eilers & Million, 2011). If time permits, it is recommended that patients who are about to initiate chemotherapy or radiation treatment have a complete oral assessment by a dental professional with the goal of alleviating any dental caries or other dental problems prior to treatment.

Numerous assessment tools are available to oncology nurses to help record the extent and severity of OM, including the Oral Assessment Guide (Eilers, Berger, & Petersen, 1988), the Oral Mucositis Index (McGuire et al., 2002), the Oral Mucositis Assessment Scale (Sonis et al., 1999), and the Western Consortium for Cancer Nursing Research tool (Western Consortium for Cancer Nursing Research, 1987). Each of these respective assessment tools has both benefits and weaknesses related to ease of use and reliability.

Beck (2004) recommended that all patients with cancer receive a systematic assessment of their respective oral cavity. Nurses should ask patients if they are experiencing any rubbing or tissue damage from an ill-fitting appliance. Patients should be asked about current oral pain, changes in saliva and swallowing, obvious lesions, or any other changes to the oral mucosa. Patients are usually very aware of any alterations or differences in their own oral cavity and should be considered an excellent source of overall change.

Nurses should conduct the oral assessment in a room or area with a good source of natural light. Prior to the assessment, they should ask patients to remove any dental appliances, such as partials or full dentures. Nurses should gather any needed equipment to conduct the oral assessment, including nonsterile gloves, tongue blade, dental mirror, and gauze. Nurses should wash their hands and apply the gloves prior to the assessment. During the visual inspection, they should look at the outer lips, teeth, gums, tongue, inside cheek area, and hard and soft palate. It may be important to wrap the tongue in a piece of gauze to help move the tongue for inspection of the floor of the oral cavity under the tongue. Additionally, nurses
should gently pull the upper and lower cheeks away to inspect the tissue close to the gums. The oral assessment will likely take only a minute or two, and patients should be referred to a dentist or hygienist if a more thorough examination is warranted.

The oral cavity in a healthy individual is usually moist, clean, pink, and intact. Abnormal assessment findings in the oral mucosa include bleeding or changes in color (pallor, erythema, white patches), changes in moisture (dryness and decreased amounts of saliva), changes in cleanliness (accumulation of debris and odor), changes in integrity (ulcers, cracks, lesions, or erosions or indentations of the tongue), and changes in perception (hoarseness, difficulty swallowing, pain) and taste ability (Beck, 2004). Following the oral assessment, nurses should document their findings in the patient record. Nurses would then use both the patient report and physical findings from the oral examination to develop or guide interventions, especially for patients who are experiencing OM.

Evidence-Based Interventions

The management of OM has been primarily palliative in nature (Lalla et al., 2008). The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO), two multidisciplinary groups, has published several evidence-based clinical practice guidelines for the prevention and treatment of OM (Keefe et al., 2007; Rubenstein et al., 2004). In 2014, MASCC and ISOO updated their guidelines for mucositis (Lalla et al., 2014), which can be reviewed at www.mascc.org/mucositis-guidelines. Additionally, recent Cochrane reviews have focused on interventions for the treatment (Clarkson et al., 2010) and prevention (Worthington et al., 2011) of OM.

From a more nursing-focused approach, the Oncology Nursing Society (ONS) Putting Evidence Into Practice (PEP) resources have presented evidence-based practice recommendations for OM (Eilers et al., 2014). The PEP resource presented the research in several categories, which included Recommended for Practice, Likely to Be Effective, Benefits Balanced With Harms, Not Recommended for Practice, and Expert Opinion. This chapter will now focus on these interventions, as it is important for oncology nurses to be knowledgeable of the interventions both supported and not supported for use in patients with OM.

Recommended for Practice

Oral Care Protocols

Interventions are placed in the Recommended for Practice category when there is strong evidence of support from rigorously designed studies. Of all the interventions that have been developed to either lessen or prevent OM, oral care is widely considered the foundation of mucosal health (McGuire et al., 2013). It is hypothesized that oral care reduces pain, bleeding, and high levels of microbial flora; prevents infection; and reduces the risk of dental complications (Harris et al., 2008; Rubenstein et al., 2004). Thus, the ONS PEP resource places oral care protocols, or formalized and standardized plans that have been developed by a multidisciplinary team, in the Recommended for Practice category. According to Harris et al. (2008), basic components of an oral care protocol include an assessment, patient education, tooth brushing, flossing, and use of an oral rinse.

In a recent systematic review conducted by the Basic Oral Care Section of the Mucositis Study Group of MASCC/ISOO, the group made no recommendations for the prevention or treatment of OM related to dental care, normal saline rinse, sodium bicarbonate, mixed
medication mouthwash, calcium phosphate, or chlorhexidine (McGuire et al., 2013). Still, MASCC/ISOO suggests “using oral care protocols in the prevention of OM in all age groups and across treatment modalities” (McGuire et al., 2013, p. 3176).

For oral care protocols, it is recommended that clinicians (a) collaborate with a multidisciplinary team in all phases of treatment, (b) conduct a systematic oral assessment at least daily or upon each patient visit, (c) teach patients when to report self-assessment findings to the clinician, and (d) provide written instructions and education to patients regarding oral care and verify patient understanding with return demonstrations and explanations (Harris et al., 2008).

Patients are recommended to (Eilers & Million, 2011)
• Brush all tooth surfaces for at least 90 seconds twice daily using a soft toothbrush.
• Allow the toothbrush to air dry before storing, and replace the toothbrush on a regular basis.
• Floss at least once daily or as advised by the clinician.
• Rinse the mouth four times daily (with a bland mouth rinse like normal saline) or as advised by the clinician.
• Avoid tobacco, alcohol, and irritating foods.
• Use water-based moisturizers to protect lips.
• Maintain adequate hydration.

Cryotherapy

Cryotherapy is the use of ice chips during chemotherapy administration to prevent OM. It is hypothesized that sucking on ice chips during the administration of chemotherapy causes local vasoconstriction and reduces blood flow to the tissue of the oral mucosa, thus resulting in a decreased delivery of chemotherapy (Lalla et al., 2008). Studies have suggested that cryotherapy actually reduces the severity of oral mucositis in patients receiving bolus doses of chemotherapy (5-FU, melphalan) (Cascinu, Fedeli, Fedeli, & Catalano, 1994; Mahood et al., 1991). The MASCC/ISOO Mucositis Study Group recommended the use of 30 minutes of oral cryotherapy to prevent OM in patients receiving bolus 5-FU chemotherapy (Peterson et al., 2013). The ONS PEP resource for OM noted that the use of cryotherapy was beneficial in the prevention of all categories of OM in those with hematologic malignancies or stem cell transplant (Eilers et al., 2014).

Palifermin

Palifermin, a recombinant human keratinocyte growth factor that stimulates the production of epithelial cells of the oral mucosa, has been shown to reduce the severity and duration of OM in patients receiving high-dose chemotherapy and TBI with autologous stem cell transplant (Spielberger et al., 2004). The MASCC/ISOO Mucositis Study Group recommended that palifermin be given at 60 mcg/kg/day IV for three days prior to the beginning of the conditioning regimen and for three days post-transplant to prevent OM in patients receiving high-dose chemotherapy and TBI followed by autologous stem cell transplantation for hematologic malignancies (Raber-Durlacher et al., 2013). It is important to note that palifermin administration is associated with mild rash and taste changes (Wujcik, 2014).

Low-Level Laser Therapy

Low-level laser therapy (LLLT) is the local application of a monochromatic, narrow band, coherent light source to tissue to promote healing and reduce pain and inflammation. Specifically, it is hypothesized that LLLT activates a rapid generation of myofibroblasts, which play a role in epithelial repair of damaged tissue (Genot & Klastersky, 2005).
The MASCC/ISOO Mucositis Study Group recommended that LLLT be used to prevent OM in patients receiving HSCT conditioned with high-dose chemotherapy, with or without TBI (Migliorati et al., 2013). In addition, the group recommended that LLLT be used for the prevention of OM in patients undergoing radiation therapy, without concomitant chemotherapy, for head and neck cancer (Migliorati et al., 2013). Of note, the MASCC/ISOO Mucositis Study Group did not recommend the use of LLLT in any other patients with cancer.

**Pain Management**

Oral pain is a significant problem for patients with OM (Eilers & Million, 2011; Polovich et al., 2014). The MASCC/ISOO Mucositis Study Group recommended that patient-controlled analgesia with morphine be used to treat pain due to OM in patients undergoing HSCT (Lalla et al., 2014). Please refer to Chapter 20 for more information on pain management.

**Likely to Be Effective**

Benzydamine hydrochloride is a cryoprotectant medication (nonsteroidal anti-inflammatory drug) that inhibits proinflammatory cytokines including TNF-α. The MASCC/ISOO Mucositis Study Group recommends that benzydamine mouthwash be used to prevent oral mucositis in patients with head and neck cancer receiving moderate dose of radiation therapy (up to 50 Gy), without concomitant chemotherapy (Lalla et al., 2014). It is important to note that the U.S. Food and Drug Administration has not approved the use of benzydamine at the time of publication. Further, MASCC/ISOO is an international organization; thus, their recommendations go beyond those of the United States. In some other countries, benzydamine is sold over the counter.

**Effectiveness Not Established**

The ONS PEP resource for OM (Eilers et al., 2014) recognized numerous medications and interventions where effectiveness has not been established by research. This recommendation does not necessarily mean that the interventions are not effective but rather they need more thorough, well-conducted randomized clinical trials to establish effectiveness.

**Not Recommended for Practice**

Just as it is important to recognize interventions that are effective for the prevention or management of OM, it is equally as important to discuss those interventions that are not recommended for practice. Both ONS and MASCC/ISOO recommend against certain interventions that should not be used for the prevention or treatment of OM. This classification is defined as an intervention where ineffectiveness or harm clearly has been demonstrated or when the cost burden exceeds potential benefit (Eilers et al., 2014). Interventions included the following.

- Chlorhexidine used as a mouthwash is not effective in reducing chemotherapy or radiation induced OM (Eilers et al., 2014; Lalla et al., 2014).
- Granulocyte macrophage–colony-stimulating factor mouthwash is not recommend for practice in the prevention of OM in patients undergoing HSCT (Lalla et al., 2014).
- Sucralfate has not been recommended for use in patients to prevent radiation-induced OM (Eilers et al., 2014; Lalla et al., 2014). Sucralfate is a mucosal coating agent, which
showed a lack of tolerability related to nausea and vomiting in patients. Further, some patients who received sucralfate also experienced rectal bleeding.

MASCC/ISOO (Lalla et al., 2014) advises against the following other interventions: (a) PTA (polymyxin, tobramycin, amphotericin B) and BCoG (bacitracin, clotrimazole, gentamicin) antimicrobial lozenges, (b) iseiganan antimicrobial mouthwashes, (c) IV glutamine, (d) misoprostol mouthwash, (e) orally administered pentoxifylline, and (f) systemic pilocarpine. For reasons why these interventions are not suggested for use, please refer to the MASCC/ISOO mucositis summary guidelines table (see www.mascc.org/mucositis-guidelines for the link to the current version).

Patient Teaching Points

Perhaps the most significant intervention that oncology nurses can provide for patients who will potentially experience OM is an oral care protocol with emphasis on consistent use. In this author’s experience, patients receiving chemotherapy or radiation treatment want to help with their individual care in some way. Teaching patients to assess and care for their oral cavity is an excellent intervention that likely lessens the experience of OM and involves patients in their own care.

Oral Self-Assessment

Patients can be taught to assess their oral cavity for any erythema, edema, white lesions, bleeding, or feelings of pain, soreness, or anything that “feels” different. The self-assessment should be conducted once daily in front of a mirror. This assessment is particularly important for patients receiving outpatient chemotherapy, who might only see their health-care provider every two to three weeks between cycles of chemotherapy. Patients conducting their own oral assessment should wash their hands prior and should use good lighting to help see all areas of the oral mucosa.

Oral Care

The ONS PEP resource (Eilers et al., 2014) recommends that patients follow an oral care protocol that focuses on proper tooth brushing, flossing, and rinsing of the oral cavity. Patients should be taught to brush all the surfaces of their teeth with a soft-bristled toothbrush for 90 seconds at least two times per day. If patients cannot tolerate a toothbrush, a sponge or “toothette” can be used, or patients can even clean their teeth with a piece of gauze wrapped around their finger. To deter growth of microorganisms, the toothbrush should be allowed to dry before storing. Patients should floss their teeth once daily or as advised by a clinician. Patients should rinse their mouth four times a day with a bland mouth rinse. It is believed that this rinsing helps to remove loose debris as well as hydrate the oral cavity. Over-the-counter mouthwashes containing alcohol should be avoided because they can burn the oral cavity or any lesions that are present. Patients should moisturize the lips with a water-based product.

Patients should be taught to avoid tobacco products, which may exacerbate OM. They are encouraged to avoid alcohol and certain foods and liquids (i.e., those that are spicy, acidic, rough, or hot). It is important for patients to maintain proper adequate oral hydration (nonalcoholic) to help keep the oral mucosa moist. Finally, patients should be taught when to report adverse findings or oral pain to their healthcare provider (Harris et al., 2008).
Expected Patient Outcomes

The clinical burden of OM is evident, and there is a serious need for interventions to reduce this burden. Occasionally OM is so severe that patients require modifications of anticancer therapy such as breaks in the treatment regimen or dose reduction of chemotherapy (Scully, Sonis, & Diz, 2006). Dose reduction or complete termination could potentially be avoided if proper pain management or other interventions to help lessen OM are used. Oncology nurses are in a great position to assist in controlling the symptom of OM so that patients can obtain the ultimate outcomes, with goals of controlling OM during treatment so that patients have a tolerable quality of life and controlling OM so that all patients can receive the best treatment, absent of dose reduction, delay, or termination of treatment, in hopes of receiving a complete cure of their cancer.

Need for Future Research

Given that OM is such a debilitating and detrimental side effect associated with cancer treatment, it is frustrating that only a handful of interventions are approved for use. Numerous interventions were placed in the Effectiveness Not Established category of the ONS PEP resource for OM. This categorization does not mean that the intervention is ineffective but rather that there is a need for more randomized clinical trials to test previously identified interventions. Further research should evaluate whether agents can be used in combination for better clinical effectiveness (Lalla et al., 2008). There is an important need for research that tests whether portions of oral care protocols (e.g., brushing and flossing) truly decrease the severity and duration of OM. More investigation should be conducted to help explain why some of the most high-risk patients who should present with OM do not ever present with it or why they experience the symptom with less severity and distress. Finally, it would be very beneficial to test an algorithm that could be used to predict the risk for development of clinically significant OM so that patients at highest risk could get needed preventive interventions in advance.

Conclusion of Case Study

Recall that G.B. was scheduled to begin chemotherapy treatment of leucovorin and 5-FU the following week for a diagnosis of colon cancer. Because he would receive a bolus therapy of 5-FU daily for five days, it might be beneficial for him to suck on ice 5 minutes prior and 30 minutes after chemotherapy infusion during each day of treatment. Before beginning the first chemotherapy treatment, the nurse advises G.B. to see his dentist for a thorough oral assessment and correction of caries.

Because G.B. is likely to experience some level of OM, the nurse teaches him how to conduct his own oral assessment and encourages him to report any pain or other findings to his healthcare team. The nurse teaches him a particular oral care protocol, to include brushing, flossing, and rinsing his mouth at the same time daily to establish a routine. Finally, because his wife was present for chemotherapy teaching, the nurse takes the opportunity to teach not only the patient but also his family members who may be called upon to assist him with oral care during his treatment.
Conclusion

Oral mucositis is a clinically significant side effect that can cause pain, infection, dysfunction, and detriment to quality of life and place patients receiving cancer treatment for cancer at high risk for infection. Progress in the understanding of oral mucosal pathobiology, coupled with new preventive interventions and oral care protocols, has improved the care of patients with OM. However, interventions are still needed that can lessen or eliminate OM, which causes some patients to request a decrease in the dosage or termination of their cancer therapy altogether. Oncology nurses are in an excellent position to assist patients in the care of OM so that patients can receive the ultimate treatment for their respective cancer.

References


Neutropenia and Infection

Colleen O’Leary, MSN, RN, AOCNS

Case Study

R.M., a 68-year-old woman with lung cancer, is admitted for her third cycle of docetaxel and cisplatin. Her past medical history includes hypertension, coronary artery disease, and hyperlipidemia. After her first cycle of chemotherapy, she experienced neutropenia with an absolute neutrophil count (ANC) of 100/mm$^3$ for two weeks. During this time she also had oral candidiasis. She is currently feeling well and ready to start her treatment. The nurse recognizes that the patient is at increased risk for neutropenia with this cycle because of her gender, age, comorbidities, and history of fungal infection and neutropenia. The nurse verifies that colony-stimulating factors (CSFs) are ordered as part of the chemotherapy regimen. The patient’s neutrophil count begins to drop during her therapy, and at the conclusion of her treatment cycle, her ANC is 500/mm$^3$. Based on R.M.’s ANC, the nurse initiates neutropenic precautions. R.M. states that she is not feeling well and is starting to feel “achy.” The nurse checks her vital signs, and she has a low-grade fever of 100.4°F (38°C). All of her other vital signs are within normal limits.

Overview

Neutropenia is a decrease in circulating neutrophils that can be caused by problems with neutrophil production or distribution, infection, cancer treatment, or certain drugs (Rogers, 2014). Regardless of the etiology, neutropenia has significant negative clinical outcomes for patients with cancer, including being one of the greatest predictors of life-threatening infection in patients. Other serious patient outcomes of neutropenia include hospitalization; increased IV antibiotic use; effect on quality of life for patients and caregivers; loss of productivity; economic costs to patients, families, and the healthcare system; and suboptimal delivery of treatment regimens (Nirenberg et al., 2006). In patients with lung cancer, ovarian cancer, breast cancer, and lymphoma, chemotherapy dose reductions and dose delays due to neutropenia have shown to produce poor outcomes (Bosly et al., 2008; Chirivella et al., 2009; Radosavljevic, Golubicic, Gavrilovic, Kezic, & Jelic, 2009; Sarosy et al., 2010). Chemotherapy-induced neutropenia (CIN) is the major dose-limiting toxicity of systemic cancer chemotherapy and is associated with significant morbidity, mortality, and costs (Lyman, Lyman, & Agboola, 2005).
Definitions

ANC is an essential tool used to determine potential risk for neutropenia. The ANC represents the number of mature white blood cells (WBCs) in circulation. Both the Infectious Diseases Society of America (IDSA) and the National Comprehensive Cancer Network® (NCCN®) define neutropenia as an ANC of less than 500/mm³ or an ANC that is expected to decrease to less than 500/mm³ within the next 48 hours (Freifeld et al., 2011; NCCN, 2014a). ANC is calculated by multiplying the WBC count by the percentage of bands and segmented neutrophils (see Figure 19-1).

The degree and duration of neutropenia can help to determine the risk of infection. Patients with an ANC less than 100/mm³ are often referred to as having profound neutropenia (Freifeld et al., 2011). Short-term neutropenia is defined as lasting less than seven days, whereas long-term neutropenia exceeds seven days (Freifeld et al., 2011). Following administration, each chemotherapy agent has a relatively predictable period of neutropenia. The nadir, which is the point of lowest WBCs following treatment, occurs on average 10–14 days following treatment, with 7–10 days being most frequent (Polovich, Olsen, & LeFebvre, 2014). However, some cell cycle–nonspecific agents such as the nitrosoureas can produce delayed and prolonged neutropenia with nadirs occurring 21–46 days post-treatment with recovery in 35–60 days in adults and 21–35 days with recovery at 42–50 days in children (Hennessy & Scott, 2008; Wilkes & Barton-Burke, 2012). Figure 19-2 depicts a general overview of nadir length. A greater degree and longer duration of neutropenia can put patients at a greater risk for complications.

A consequence of neutropenia, febrile neutropenia is defined by the National Cancer Institute Cancer Therapy Evaluation Program (NCI CTEP) as an ANC less than 1,000/mm³ and a single temperature higher than 101°F (38.3°C) or a sustained temperature of 100.4°F (38°C) or higher for more than one hour (NCI CTEP, 2010). A commonly used scale for grading the severity of febrile neutropenia associated with cancer chemotherapy is NCI CTEP’s (2010) Common Terminology Criteria for Adverse Events (CTCAE). This scale categorizes febrile neutropenia from grades 1–5 (see Table 19-1). However, the grade of toxicity does not always correlate directly with the incidence of infection. Although the CTCAE is used most often for grading the response to chemotherapy in clinical trials, it also can be a valuable tool for practitioners when describing the degree of neutropenia.

---

**FIGURE 19-1 Calculating Absolute Neutrophil Count**

The absolute neutrophil count (ANC) is calculated as follows.

\[ \text{ANC} = \frac{\text{Segmented neutrophils} + \text{bands}}{\text{white blood cell (WBC) count}} \times 100 \]

An example of calculating the ANC of a patient with the counts of:

- Segmented neutrophils = 50
- Bands = 4
- WBC = 2700

\[ \text{ANC} = \frac{(50 + 4)}{2700} = 0.54 \]

\[ = 0.54 \times 2700 = 1458 \]

\[ = 1458 \]
Risk Factors

Despite the assumption that the longer a patient is receiving chemotherapy, the greater the risk for developing neutropenia, patients undergoing their first cycle of chemotherapy actually are at greater risk for developing neutropenia. NCCN (2014a) identifies risk factors for neutropenia that can be classified as patient specific, disease specific, or treatment specific. Figure 19-3 lists examples of each of these types of risk factors.

Patient-Specific Risk Factors

Patient-specific risk factors include advanced age, female gender, poor performance status, poor nutritional status, comorbid conditions, and poor pretreatment health. In a study of 18 published risk models developed to assess neutropenia, advanced age (older than 65) and poor performance status were validated in at least two of the models chosen. Further-
more, 10 studies found older age to be a general risk factor for the development of severe neutropenia (Lyman et al., 2005). Older patients often are treated with lower chemotherapy doses to minimize the occurrence of neutropenic complications; however, several studies have shown that older patients are able to tolerate full doses of chemotherapy without increased complications (Kuderer, Dale, Crawford, Cosler, & Lyman, 2006; Lyman, 2009; Shayne et al., 2007, 2009; Zitella, 2014). Because older patients with cancer can obtain the

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>ANC &lt; 1,000/mm³ with a single temperature of &gt; 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>


FIGURE 19-3 Risk Factors for Neutropenia

**Patient-Related Factors**
- Age > 65
- Female
- Poor performance status
- Albumin < 35 g/L
- Comorbid conditions
  - With non-Hodgkin lymphoma
    - Renal disease
    - Cardiovascular disease
  - With breast cancer
    - Liver disease
    - Renal disease
    - Cardiovascular disease
  - Diabetes
  - Sepsis
  - Pneumonia
  - Hypertension
  - Prior fungal infections
  - Chronic obstructive pulmonary disease
- Previous neutropenia
- Decreased white blood cell count
- Hemoglobin < 12 g/dl
- Open wounds
- Active tissue infections

**Disease-Related Factors**
- Hematologic malignancies
- Advanced disease
- Uncontrolled cancer
- Lung cancer
- Elevated lactate dehydrogenase in lymphoma

**Treatment-Related Factors**
- Chemotherapy regimen
- High-dose cyclophosphamide
- Etoposide
- High-dose anthracyclines
- Relative dose intensity > 80%
- Extensive prior chemotherapy
- Concurrent or prior radiation therapy
- Previous history of severe neutropenia with similar chemotherapy

same benefit from aggressive chemotherapy as younger patients, effective management of the risk of neutropenia is crucial in order to administer full-dose chemotherapy to this patient population. Studies have shown that poor performance status is a significant risk for neutropenia and that in older adults, physiologic age, comorbidities, or frailty may be a more accurate predictor of risk than chronologic age (Zitella, 2014). Several tools can be used to measure a patient’s performance status. One such tool is the Eastern Cooperative Oncology Group (ECOG) scale (Oken et al., 1982) (see Table 19-2). Once the patient’s performance status is graded, the grade can be used to help identify whether the individual is at greater risk for neutropenia.

The presence of comorbid conditions also increases the risk of neutropenia in patients with cancer. Renal disease and cardiovascular disease increase the risk for developing febrile neutropenia in patients with non-Hodgkin lymphoma (Lyman et al., 2011). The presence of liver, renal, and cardiovascular disease increases the risk of neutropenia in patients with breast cancer. Comorbid conditions such as sepsis, pneumonia, hypertension, prior fungal infections, and chronic obstructive pulmonary disease have been shown to increase the risk for serious neutropenic complications, including prolonged hospitalizations for febrile neutropenia and death (Lyman et al., 2011). NCCN (2014a) also identified the presence of diabetes mellitus as increasing the risk for developing febrile neutropenia.

Other patient-specific predictors of neutropenia include previous neutropenia, decreased WBC count, hemoglobin levels less than 12 g/dl and serum albumin concentrations of 3.5 g/L or less, open wounds, and active tissue infections (Lyman et al., 2011).

### Disease-Specific Factors

Patients with hematologic malignancies are at a greater risk for the development of CIN than patients with solid tumors. This is most likely because of bone marrow involvement of the tumor, as well as the intensity of treatment required for hematologic diseases. Because of this involvement of bone marrow, neutropenia may be the initial presenting symptom in patients with hematologic malignancies. In all cancer types, both advanced disease and uncon-
trolled cancer are significant predictors of hospitalization for neutropenia and serious complications, including death (Lyman et al., 2011). NCCN (2014a) also identified patients with lung cancer and elevated lactate dehydrogenase, such as in lymphoma and leukemia, as having a higher risk for neutropenia.

**Treatment-Specific Risk Factors**

Some chemotherapy regimens are more myelosuppressive than others, which puts patients at a higher risk for neutropenia. High-dose cyclophosphamide, the use of etoposide, and high doses of anthracyclines have all been identified as significant predictors of severe neutropenia. Other treatment-related predictors include relative dose intensity greater than 80%, extensive prior chemotherapy, concurrent or prior radiation therapy, and previous history of severe neutropenia with similar chemotherapy (Lyman et al., 2005, 2011).

**Pathophysiology**

A number of WBC subtypes are referred to as *granulocytes*. The foremost are *neutrophils*, also called *polymorphonuclear segmented cells*, *segs*, or *polys*. The neutrophils account for 60% of circulating WBCs and are the first responders to infection by bacteria, viruses, and other pathogens.

Production of mature neutrophils in the bone marrow takes 10–14 days, but once released into the circulation, they live for only four to eight hours. Because the life span of circulating neutrophils is so short, the bone marrow must continually produce neutrophils. This continuous replenishing supply of neutrophils moves from the marrow space through the blood to sites of infection. Neutrophils are drawn to pathogens by either random movement through the circulation or via chemotaxis. When chemotherapy is administered, the bone marrow is suppressed and stem cells may be damaged. The neutrophil count is lowered as the mature cells die and are not replaced, which in turn impairs the body’s ability to fight infection (Camp-Sorrell, 2011).

The risk of death related to infection is paramount when the body’s ability to fight infection is impaired. Patients with hematologic cancers, specifically acute leukemia and lymphoma, are at a greater risk, with approximately 70% of deaths occurring due to infection secondary to neutropenia (Legrand et al., 2012).

**Assessment**

Nurses are ideally positioned and qualified to conduct appropriate risk assessments and play an integral role in directing the quality of patient care by implementing guidelines for the consistent management of neutropenic complications. A thorough patient history is important in assessing for the presence or risk of neutropenia. This history should include a review of previous cancer therapy. Previous chemotherapy, biotherapy, radiation therapy, or multimodal therapies can put a patient at increased risk for neutropenia. A patient’s medication regimen, including hematopoietic growth factors and antibiotics, also should be reviewed. Common medications that may cause neutropenia include procarbazine, phenytoin, amoxicillin, cimetidine, captopril, enalapril, ibuprofen, levamisole, and ranitidine (Godwin, Braden, & Sachdeva, 2014). Continued use of these medications
will need to be addressed, especially in light of any additional comorbid conditions. The use of agents such as trimethoprim-sulfamethoxazole or amphotericin B can decrease the neutrophil count (Coates, 2014).

Physical examination of patients should focus on assessing for signs of infection. With infection, neutrophils are sent to the site of infection to produce the common signs of redness, swelling, and pus formation. However, in patients with decreased neutrophils, the number of mature neutrophils may not be sufficient to mount this response. Therefore, the usual objective signs of infection may not be present with a decreased neutrophil count. In neutropenic patients, fever is the most common and perhaps the only response to infection. Febrile neutropenia can be a significant finding in patients because of the high risk of sepsis in these individuals (Courtney et al., 2007; O'Leary, 2011).

Twenty to thirty percent of patients with febrile neutropenia have clinically documented infections (Almyroudis, Battiwalla, & Segal, 2010). The most common sites of infection in patients with neutropenia are the respiratory tract, gastrointestinal (GI) tract, genitourinary tract including the perineum and anus, skin, and mucous membranes (see Table 19-3). The respiratory tract should be assessed for abnormal breath sounds, cough, and characteristics of expectorations. Abdominal tenderness, stiffness, guarding, and diarrhea should be evaluated as potential infections of the GI tract. Subtle signs of infection, including any breaks in integrity in the perineum and anus, should be noted. All catheter exit sites should be assessed for edema, drainage, erythema, and tenderness. Tenderness and erythema along the subcutaneous tunnel of an indwelling catheter may indicate a tunnel infection. Tenderness and ulceration of the mucous membranes should be noted, and the oral cavity should be inspected for thrush and plaques. Oral cultures for fungus and virus should be obtained because mucositis can easily progress to secondary infections (Zitella, 2014). (For more information on mucositis, see Chapter 18.) Assessment for changes in mental status and nutritional status should be included. Protein-calorie malnutrition can cause decreased lymphocytes, diminished levels of the complement system, and a decrease of immunoglobulins (Ig) IgA, IgE, IgG, and IgM (Camp-Sorrell, 2005; Rust, Simpson, & Lister, 2000). Although an estimated 50% of patients with febrile neutropenia have an infection, in the majority of cases of febrile neutropenia, no identifiable infection will be found (Almyroudis et al., 2010).

Important diagnostic tools for assessing neutropenia include obtaining a complete blood count with differential and the respective ANC. To diagnose bloodstream infections, though, blood cultures should be taken before administration of antibiotics. Blood

<table>
<thead>
<tr>
<th>TABLE 19-3</th>
<th>Common Sites of Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>System</strong></td>
<td><strong>Assess for</strong></td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>Abnormal breath sounds</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
</tr>
<tr>
<td></td>
<td>Color, amount, and viscosity of expectorations</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Abdominal tenderness</td>
</tr>
<tr>
<td></td>
<td>Stiffness</td>
</tr>
<tr>
<td></td>
<td>Guarding</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Genitourinary tract</td>
<td>Breaks in integrity of perineum and/or anus</td>
</tr>
<tr>
<td></td>
<td>Subtle signs of infection</td>
</tr>
<tr>
<td>Skin (including catheter sites)</td>
<td>Edema</td>
</tr>
<tr>
<td></td>
<td>Drainage</td>
</tr>
<tr>
<td></td>
<td>Erythema</td>
</tr>
<tr>
<td></td>
<td>Tenderness</td>
</tr>
<tr>
<td>Mucous membranes</td>
<td>Redness</td>
</tr>
<tr>
<td></td>
<td>Tenderness</td>
</tr>
<tr>
<td></td>
<td>Ulceration</td>
</tr>
</tbody>
</table>

cultures should be obtained at the first fever and may continue daily as long as the patient remains febrile, until the source of infection is identified and antibiotic sensitivity is determined, or the neutrophil count returns to normal. The current standard for obtaining blood cultures requires a minimum of 20 ml per culture set and two sets per episode of fever. The IDSA recommends using two sites for blood cultures with a set collected from each lumen on central venous catheter (CVC) if one is present and from a peripheral vein or from two separate venipuncture sites when no CVC is present (Freifeld et al., 2011). However, NCCN advises that obtaining an adequate volume of blood is more important and therefore recommends the use of a CVC when available (NCCN, 2014a). It is common practice to use the CVC until a positive culture is received. Then cultures can be drawn from both the peripheral blood and the CVC to differentiate bacteremia from an infected catheter (Safdar, Fine, & Maki, 2005; Zitella, 2014). Clearly, additional research is needed to develop a practice consensus on this issue.

Another diagnostic tool used in the assessment of neutropenia is the chest radiograph (CXR), which may reveal widespread infiltrates or darkened areas on the lung. Serial CXRs have been useful in showing subtle changes in patients with prolonged neutropenia. However, no studies have been completed on the risks or effects of the use of serial CXRs or on how long they should be done. To determine lower respiratory infections, invasive bronchoscopic procedures often are used.

In patients with diarrhea, testing for *Clostridium difficile* is indicated. *Clostridium difficile* is a bacterium that causes toxin release and is treated with an antifungal medication. Also, patients with prolonged neutropenia are at risk for typhlitis, an inflammation of the small intestine or colon that can progress to bowel perforation.

**Evidence-Based Interventions**

A focus of nursing care for neutropenic patients is the prevention of complications and the maintenance of optimal functioning. The Oncology Nursing Society (ONS) has described *nursing-sensitive patient outcomes* (NSPOs) as those outcomes affecting patients and their health problems that are directly affected by nursing interventions (Given et al., 2004). NSPOs must be within the scope of nursing practice and evidence based. The results of nursing interventions within NSPOs include changes in patients’ functional status, symptom experience, safety, psychological distress, and/or costs (Given et al., 2004). ONS, NCCN, NCI, IDSA, and the American Society of Clinical Oncology (ASCO) have current guidelines regarding NSPOs and other recommended interventions to protect neutropenic patients from negative outcomes. These guidelines address interventions related to infection control, CSFs, vaccinations, antimicrobial therapies, oxygen and respiratory care, and oral care.

**Infection Control**

One of the simplest and most effective interventions for reducing the risk of infection is hand hygiene and is rated as Recommended for Practice by the ONS Putting Evidence Into Practice (PEP) resource on prevention of infection. Hand hygiene has been shown to decrease the risk of transmitting infection from person to person (Centers for Disease Control and Prevention, 2014; Kilpatrick, Hosie, & Storr, 2013; World Health Organization, 2009). As early as 1861, physician Ignaz Semmelweis discussed the importance of hand hygiene for healthcare workers. He was the first person to demonstrate the role of hand hygiene in the
prevention of person-to-person transmission of infection (Larson, 1999). Studies continued throughout the 1960s when a group of investigators studied the transmission of *Staphylococcus (S.) aureus* to infants in an intensive care unit. This bacteria resides in the normal flora of the anterior nares and is rarely airborne. It usually is transmitted by direct contact. In these early studies, Mortimer, Lipsitz, Wolinsky, Gonzaga, and Rammelkamp (1962) found that *S. aureus* was transmitted by the airborne route only 6%–10% of the time. However, 54% of the babies handled by nurses with unwashed hands were colonized with *S. aureus*. When noncarrier nurses handled a baby colonized with *S. aureus* and then handled another baby without hand washing, the transmission rate from the nurses’ hands was 43%. Hand washing subsequently reduced the transmission rate to 14%. This study provided clear evidence that when compared to no hand washing, cleansing of hands between patient contacts reduces the transmission of healthcare-associated pathogens. Larson and Nirenberg (2004) also looked at the effectiveness of various types of antiseptic hand hygiene. They defined effective hand hygiene as including washing hands with soap and water or the use of antiseptic hand rub if hands are not visibly contaminated. Current literature supports the use of hand sanitizer as an effective method of decreasing infection (O’Grady et al., 2011).

Historically, neutropenic patients were isolated in private reverse-flow rooms when hospitalized. The practice of placing a neutropenic patient in strict isolation is beginning to decrease. Strict protective isolation has not been shown to decrease infections, febrile episodes, or antibiotic use for neutropenic patients (Mank & van der Lelie, 2003; Nauseef & Maki, 1981). However, these studies were small and should be interpreted with caution. Because of the lack of high-level evidence, the ONS PEP resource on prevention of infection designates protective isolation as being in the category of Effectiveness Not Established (Wilson et al., 2014).

Many practitioners and institutions still implement strict dietary restrictions for patients with neutropenia (Nirenberg et al., 2006). However, no recent studies have shown that the use of dietary restrictions reduces the risk of infection in general in neutropenic patients (Larson & Nirenberg, 2004; Moody, Charlson, & Finlay, 2002; Nauseef & Maki, 1981; Wilson, 2002). The ONS PEP resource lists dietary restrictions in the Effectiveness Unlikely category (Wilson et al., 2014). Commonsense efforts when preparing and consuming food still need to be taken. The joint recommendations of the Center for International Blood and Marrow Transplant Research, the National Marrow Donor Program, the European Blood and Marrow Transplant Group, the American Society of Blood and Marrow Transplantation, the Canadian Blood and Marrow Transplant Group, IDSA, the Society for Healthcare Epidemiology of America, the Association of Medical Microbiology and Infectious Diseases Canada, and the Centers for Disease Control and Prevention specify that all foods be well cooked and that raw foods, including seafood, mayonnaise, and eggs, be avoided during the neutropenic period in patients following hematopoietic stem cell transplantation (HSCT) (Tomblyn et al., 2009). General dietary restrictions for patients with neutropenia have not shown to be any more effective than the U.S. Food and Drug Administration’s safe food-handling practices (DeMille, Deming, Lupinacci, & Jacobs, 2006; Nirenberg et al., 2006; U.S. Food and Drug Administration, n.d.).

### Colony-Stimulating Factors

The prophylactic use of CSFs can reduce the risk, severity, and duration of both severe neutropenia and febrile neutropenia in adult and pediatric patients. Rather than stimulating the immune system to produce increased neutrophils, CSFs accelerate the maturation of immature neutrophils that are already present. Although it was previously thought that the use of CSFs did not reduce infection-related mortality or improve overall sur-
vival, recent studies have established a substantial reduction in infection-related mortality and early deaths due to chemotherapy with the use of CSFs (Kuderer, Dale, Crawford, & Lyman, 2007). A systematic review conducted by Lyman et al. (2010) reviewed 25 randomized controlled trials involving more than 12,000 patients who either did or did not receive CSFs. This review confirmed the survival advantage of the use of CSFs (Lyman et al., 2010). The NCCN guidelines address the use of CSFs based on the risk for febrile neutropenia (see Table 19-4) (NCCN, 2014a). Both ASCO and NCCN guidelines recommend the use of CSFs for all patients undergoing chemotherapy who have a greater than 20% risk for febrile neutropenia (NCCN, 2014a; Smith et al., 2006). In addition, the ONS PEP resource designates the use of CSFs for patients with cancer who are undergoing chemotherapy with greater than 20% risk of febrile neutropenia as Recommended for Practice (Wilson et al., 2014).

**Vaccination**

Annual influenza vaccination for all people who are at high risk for complications from influenza, including patients with cancer, is recommended beginning in September and

| TABLE 19-4 | Guidelines for Prophylactic Use of Colony-Stimulating Factors for Febrile Neutropenia |

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throughout the influenza season (Freifeld et al., 2011; Tablan, Anderson, Besser, Bridges, & Hajjeh, 2004). People who are at risk for transmitting influenza to high-risk individuals, including healthcare workers and family members of high-risk individuals, also should be vaccinated. Patients who are not receiving chemotherapy have a superior response to vaccination compared to those patients who are receiving chemotherapy (Ring, Marx, Steer, & Harper, 2002). Therefore, patients with cancer should be vaccinated before beginning chemotherapy treatments. The ONS PEP resource lists annual influenza vaccine in the Recommended for Practice category (Wilson et al., 2014).

Vaccination for pneumococcal disease is recommended for most patients with cancer (Tablan et al., 2004). Patients with cancer who should be vaccinated include all patients age 65 and older, patients living in long-term care facilities, and patients ages 5–64 who are receiving immunosuppressive therapy or who have generalized malignancies, multiple myeloma, leukemia, lymphoma, or chronic conditions. Patients should receive the vaccination once every five years. Another formulation of a pneumococcal vaccination exists for children younger than two years old. It is recommended that this vaccination is administered to all children younger than two and children ages 24–59 months who are at an increased risk for pneumococcal disease, including those with cancer (Tablan et al., 2004). The ONS PEP resource on prevention of infection designates pneumococcal vaccination as well as meningococcal vaccination as Recommended for Practice (Wilson et al., 2014).

**Antimicrobial Therapy**

Table 19-5 depicts the IDSA guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Because a variety of microorganisms are responsible for infection in patients with neutropenia, a discussion of antimicrobial therapies is imperative. The first step in determining the use of antimicrobial therapy is to assess the patient’s risk level for infection. This will help to guide the type of antimicrobial therapy, the appropriate venue for administration of the antimicrobial, and the duration of therapy. A formal risk assessment can be conducted using a tool such as the Multinational Association of Supportive Care in Cancer (MASCC) scoring system. This valid and reliable tool uses criteria such as burden of illness, hemodynamics, type of cancer, and comorbidities to determine the risk of neutropenia as being either low or high (Klastersky & Paesmans, 2013). According to the MASCC system, patients with a score of less than 21 are considered high risk, whereas those with a score of 21 or higher are considered low risk. In addition to the MASCC tool, most experts, including NCCN, consider high-risk patients to be those who experience neutropenia for seven or more days and with an ANC of 100/mm$^3$ or lower (NCCN, 2014b). The prophylactic use of fluoroquinolones such as levofloxacin and ciprofloxacin is recommended for high-risk patients with an expected ANC of 100/mm$^3$ or less for more than seven days (Freifeld et al., 2011; NCCN, 2014b). Neither the addition of a gram-positive active agent to the fluoroquinolone prophylaxis nor prophylaxis for low-risk patients is recommended. Because of a lack of evidence for effectiveness, antifungal prophylaxis is not recommended for all patients with cancer. However, it is recommended for patients who are at high risk, including those with acute leukemia or those undergoing HSCT (Freifeld et al., 2011; NCCN, 2014b).

The use of antifungal therapy for the prevention of oral candidiasis is common (Pappas et al., 2004). It is important to note that antifungal drugs that are absorbed or partially absorbed from the GI tract, such as fluconazole, ketoconazole, itraconazole, miconazole, and clotrimazole, have been shown to be effective in preventing oral candidiasis. However, antifungal drugs that are not absorbed from the GI tract, such as amphotericin B, nystatin, thy-
<table>
<thead>
<tr>
<th>Treatment Characteristic</th>
<th>Patient Characteristics</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis</td>
<td>Low-risk with anticipated neutropenia $&lt; 7$ days</td>
<td>No routine prophylaxis is recommended.</td>
</tr>
</tbody>
</table>
|                          | High-risk with expected duration of profound and prolonged neutropenia $> 7$ days | Consider treatment with  
  - Fluoroquinolone  
  - Levofloxacin  
  - Ciprofloxacin. |
| Initial empiric antibiotic therapy | Low-risk adults | Patient may be ambulatory or hospitalized.  
Treat with oral ciprofloxacin plus amoxicillin-clavulanate. |
|                          | High-risk adults | Admit to hospital.  
Administer IV monotherapy with  
- $\beta$-lactam such as cefepime  
- Carbapenem  
- Piperacillin-tazobactam.  
If complications or resistance suspected: Administer aminoglycosides or fluoroquinolones. |
|                          | Patients with antibiotic-resistant organisms | Methicillin-resistant *Staphylococcus aureus*: Consider early addition of vancomycin, linezolid, or daptomycin.  
Vancomycin-resistant *Enterococcus*: Consider early addition of linezolid or daptomycin.  
Extended-spectrum $\beta$-lactamases: Consider early use of a carbapenem.  
*Klebsiella pneumoniae* carbapenemase: Consider early use of polymyxin/colistin or tigecycline. |
| Afebrile for 3–5 days     | Etiologic agent identified: Adjust therapy to appropriate drug.  
No etiologic agent identified: Continue use of same drug.  
Low-risk patient on oral therapy: Continue use of same drug.  
Low-risk patient on IV therapy. Continue use of same drug. |
| First week of therapy    | Persistent fever | No clinical worsening: Continue same antibiotic. Stop vancomycin if cultures do not yield organism.  
Disease progression: Change antibiotic to include coverage for resistant gram-negative, gram-positive, and anaerobic bacteria and fungi. |
| Afebrile by day 3         | Absolute neutrophil count (ANC) is $> 500/mm^3$ for two consecutive days, no definite site of infection, and cultures do not yield positive results: Stop antibiotic therapy when patient is afebrile for $> 48$ hours.  
ANC $< 500/mm^3$ by day 7, the patient was low risk, and no subsequent complications occur: Stop therapy when the patient is afebrile for 5–7 days. |
| Duration of antibiotic therapy | Persistent fever $> day 3$ | Obtain new set of blood cultures.  
Perform symptom-directed collection of other diagnostic tests.  
Analyze stool for *Clostridium difficile*.  
Obtain CT of chest and sinuses. |

(Continued on next page)
mostimulin, polyenes, natamycin, and norfloxacin, did not prevent oral candidiasis (Clarkson, Worthington, & Eden, 2007; Worthington & Clarkson, 2002).

Patients who have had a prior active herpes infection that required treatment are more susceptible to a recurrence of the active infection while their immune system is compromised (Tomblyn et al., 2009). The preferred treatment for an active herpes infection includes the use of acyclovir or valacyclovir. Because of this, the use of acyclovir or valacyclovir for herpes prophylaxis is recommended during CIN in patients who have had prior active herpes infections that required treatment (NCCN, 2014b). NCCN also recommends herpes prophylaxis for patients receiving T-cell–depleting agents such as fludarabine during HSCT until 30 days after transplantation and during induction or reinduction therapy for acute leukemia through the neutropenic period (NCCN, 2014b).

The ONS PEP resource on prevention of infection also addresses the use of antimicrobial therapy. It lists under Recommended for Practice the use of antifungal, antibiotic, and antiviral drug prophylaxis for patients at high risk for neutropenia (Flowers et al., 2013; Freifeld et al., 2011; Gafter-Gvili et al., 2012; NCCN, 2014b; Rahman & Khan, 2009).

### Oxygen and Respiratory Care

People with symptoms of respiratory infections should be restricted from visiting immunosuppressed patients (Tablan et al., 2004). Patients with documented or suspected airborne respiratory infections should be placed in a negative airflow room with an anteroom to maintain proper air balance. If an anteroom is not available, then a high-efficiency particulate air

---

**TABLE 19-5 Infectious Diseases Society of America Guidelines for Use of Antimicrobial Agents in Neutropenic Patients With Cancer (Continued)**

<table>
<thead>
<tr>
<th>Treatment Characteristic</th>
<th>Patient Characteristics</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of antifungal drugs</td>
<td>Low-risk</td>
<td>Not recommended</td>
</tr>
<tr>
<td></td>
<td>High-risk</td>
<td><em>Candida</em> prophylaxis is recommended for hematopoietic stem cell transplant recipients or those receiving intensive induction chemotherapy for acute leukemia. Options include fluconazole, itraconazole, voriconazole, posaconazole, micafungin, and caspofungin. <em>Aspergillus</em> prophylaxis with posaconazole is recommended for patients ≥13 years of age undergoing intensive chemotherapy for acute myeloid leukemia or myelodysplastic syndrome.</td>
</tr>
<tr>
<td>Use of antiviral drugs</td>
<td>All patients</td>
<td>Antiviral drugs are not recommended for routine use unless clinical or laboratory evidence of viral infection is evident. Yearly influenza vaccination with inactivated vaccine is recommended for all patients being treated for cancer.</td>
</tr>
<tr>
<td>Hematopoietic growth factors</td>
<td>All patients</td>
<td>Prophylactic use should be considered for patients in whom the anticipated risk of fever and neutropenia is ≥20%. Not recommended for treatment of established fever and neutropenia.</td>
</tr>
</tbody>
</table>

*Note. Based on information from Freifeld et al., 2011.*
(HEPA) filter should be used. Patients who utilize oxygen or other respiratory medications need to be diligent in the care of their equipment to prevent infection. Oxygen humidifier tubing, nasal prongs, and masks should be changed when they malfunction or become visibly contaminated, and medication nebulizers should be cleaned and disinfected between uses on the same patient (Tablan et al., 2004).

**Oral Care**

Oral care is an important aspect of caring for patients with neutropenia (Freifeld et al., 2011; Rogers, 2014). Refer to Chapter 18 on oral mucositis for information on this topic.

**Sepsis**

Neutropenia is the single most significant risk factor in the development of sepsis and septic shock in patients with cancer (Camp-Sorrell, 2005; Myers, 2007). When signs of infection are not recognized, patients are at risk for severe infection, which if left untreated may lead to bacteremia, sepsis, end-organ damage, and death.

Sepsis is a cluster of symptoms that represent a systemic response to infection (Bone, 1996). In the United States, more than 751,000 patients (3 per 1,000 people) per year develop sepsis with a mortality rate of 30%–35% (Martens et al., 2007). Sepsis, which can lead to septic shock if not recognized and treated, is a potentially life-threatening oncologic complication (Gobel, Peterson, & Hoffner, 2013). First defined by Roger Bone and associates of the American College of Chest Physicians and the Society of Critical Care Medicine in 1992, the classic spectrum of sepsis occurs along a continuum of infection, bacteremia, systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, and multiple organ dysfunction syndrome (MODS) (Bone, 1996; Levy et al., 2003). Table 19-6 describes the continuum of sepsis.

Risk factors for septic shock include neutropenia; age older than 65 or younger than 1; corticosteroids and immunosuppressive therapies; malignancy, especially lymphoma, leukemia, and multiple myeloma; splenectomy; chemotherapy; radiation therapy; malnutrition; hospitalization; antibiotic use; breakdown of the skin or mucous membranes; and invasive procedures or devices (Girard, Opal, & Ely, 2005; Hachem & Raad, 2002; O’Leary, 2011). A thorough patient history is therefore essential to identifying at-risk patients. A physical examination focused on areas with a high risk for infection in imperative. These include the respiratory tract, GI tract, genitourinary tract, skin including the perineal area, and mucous membranes (Gobel & O’Leary, 2007). Diagnostic tests discussed earlier for febrile neutropenia should be included.

Two well-known tools have been developed to help detect potential sepsis. The Acute Physiology and Chronic Health Evaluation (APACHE) system is used widely in intensive care units (ICUs) throughout the United States and is based on 17 physiologic variables. Points are also added for age and comorbidities. These scores are used to predict mortality within the first 24 hours of admission to the ICU. The higher the score, the greater the chance of mortality, so this tool is used to help determine the aggressiveness of therapy. The APACHE, first developed in the 1980s, has undergone three major revisions with the most recent being the APACHE IV in 2006. However, the APACHE II is still the most commonly used due to ease of access and use (Keegan et al., 2007; Knaus, Draper, Wagner, & Zimmerman, 1985).

The Modified Early Warning Score (MEWS) was developed in 1999 as a means of supporting communication between nursing and medicine when the nurse first assesses deterioration
in a patient’s condition. The purpose of the tool is to facilitate earlier interventions to prevent transfer to critical care areas or promote transfer without undue delay. Based on physical parameters such as vital signs and level of consciousness, a MEWS score greater than 4 is associated with an increased risk of death and indicates an urgent need for intensive care (see Table 19-7) (Audit Commission, 1999; Kellett & Deane, 2006).

The Surviving Sepsis Campaign (SSC) along with the Institute for Healthcare Improvement (IHI) first developed management guidelines for sepsis in 2008 (IHI, 2009) with a recent update in 2012 (Dellinger et al., 2013). As part of the management strategies, care bundles were developed. These bundles direct what care should be provided in specific time frames to obtain the best outcomes (see Figure 19-4). Interventions that must be completed within three hours of the diagnosis of sepsis include measuring lactate level, obtaining blood cultures prior to antibiotic administration, administering broad-spectrum antibiotics, and administering 30 ml/kg of crystalloid for hypotension or increased lactate (Dellinger et al., 2013). Lactate is measured because a lactate level greater than 4 mmol/L is a good indicator of tissue hypoperfusion. Even in patients who demonstrate normal blood pressure, the lactate level can be one of the first indicators of hypoperfusion, impending sepsis, and organ dysfunction (O’Leary, 2011). It is important to obtain blood cultures prior to starting antibiotic therapy in order to increase the chance of identifying the causative pathogen. Prompt administration of broad-spectrum antibiotics improves outcomes for patients with sepsis by reducing mortality (Dellinger et al., 2013; IHI, 2009). For patients who are hypotensive or have an increased lactate level greater than 4 mmol/L, fluid resuscitation is necessary to restore intravascular volume. Whereas increasing the maintenance fluids would take hours to increase intravascular volume, administering 30 ml/kg of fluid over 10–15 minutes can cause a quick response. In addition to these initial steps, the SSC identifies interventions to be completed within six hours when ini-

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Inflammatory response of normally sterile area to presence of pathogen</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>Presence of pathogen in blood evidenced by positive blood culture</td>
</tr>
</tbody>
</table>
| Systemic inflammatory response syndrome (SIRS) | Inflammatory response with 2 or more of the following:  
  • Temperature > 100.4°F (38°C) or < 96.8°F (36°C)  
  • Heart rate > 90 beats/min  
  • Respiratory rate > 20 breaths/min or PaCO₂ < 32 mm Hg  
  • White blood cell count > 12,000/mm³ or < 4,000/mm³ or > 10% bands |
| Sepsis                       | Systemic response to infection identical to SIRS except with documented infection |
| Severe sepsis                | Sepsis complicated by organ dysfunction, hypoperfusion, or hypotension; can be manifested as lactic acidosis, oliguria, or acute changes in mental status |
| Septic shock                 | Sepsis where unstable hemodynamics persist regardless of aggressive fluid challenge where no other causes are obvious |
| Multiple organ dysfunction syndrome | Continuation of sepsis where the function of one or more organs is altered to the point of needing immediate intervention to maintain homeostasis |

Note. Based on information from Bone, 1996; Levy et al., 2003.
TABLE 19-7  Modified Early Warning Score

<table>
<thead>
<tr>
<th>Score</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>&lt; 70</td>
<td>71–80</td>
<td>81–100</td>
<td>101–199</td>
<td>–</td>
<td>≥ 200</td>
<td>–</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>–</td>
<td>&lt; 40</td>
<td>41–50</td>
<td>51–100</td>
<td>101–110</td>
<td>111–130</td>
<td>≥ 130</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>–</td>
<td>&lt; 9</td>
<td>–</td>
<td>9–14</td>
<td>15–20</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Temperature</td>
<td>–</td>
<td>&lt; 95°F</td>
<td>–</td>
<td>95°F–101.3°F</td>
<td>–</td>
<td>≥ 101.3°F</td>
<td>–</td>
</tr>
<tr>
<td>Level of consciousness</td>
<td>–</td>
<td>Decreased</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Note. Based on information from Audit Commission, 1999; Kellett & Deane, 2006.*

FIGURE 19-4  Sepsis Care Bundles

<table>
<thead>
<tr>
<th>Start Immediately and Complete Within 3 Hours</th>
<th>Complete Within 24 Hours</th>
<th>Additional Supportive Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine lactate level.</td>
<td>Administer low-dose corticosteroids if vasopressors unsuccessful.</td>
<td>Maintain adequate nutrition.</td>
</tr>
<tr>
<td>Obtain blood cultures before starting antibiotics.</td>
<td>Maintain glucose &lt; 150 mg/dl.</td>
<td>Implement prevention of deep vein thrombosis.</td>
</tr>
<tr>
<td>Administer broad-spectrum antibiotics.</td>
<td>Maintain inspiratory plateau pressure of &lt; 30 cm H₂O for mechanically ventilated patients.</td>
<td>Implement prevention of stress and pressure ulcers.</td>
</tr>
<tr>
<td>Administer crystalloid.</td>
<td></td>
<td>Implement prevention of additional infection.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complete Within 6 Hours</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Administer vasopressors if fluid resuscitation unsuccessful.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measure central venous pressure and venous oxygen saturation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remeasure lactate.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note. Based on information from Dellinger et al., 2013; Institute for Healthcare Improvement, 2009.*

tial fluid resuscitation is unsuccessful in alleviating hypotension. These include administering vasopressors, measuring central venous pressure (CVP) and central venous oxygen saturation (ScvO₂), and remeasuring lactate level (Dellinger et al., 2013). In continued hypotension, vasopressors are used to maintain a mean arterial pressure greater than 65 mm Hg. When arterial hypotension is persistent or initial lactate is greater than 4 mmol/L, a central venous catheter is placed and fluid resuscitation is repeated until a CVP of greater than 8 mm Hg and ScvO₂ greater than 70% are maintained (Dellinger et al., 2013). Finally, if the initial lactate was elevated, it should be remeasured within six hours. In addition to these initial bundles, the SSC and IHI have identified a management bundle that can be started immediately but should be completed within 24 hours (Dellinger et al., 2013; IHI, 2009). These interventions include administering a low-dose corticosteroid when the addition of vasopressors is insufficient to maintain adequate blood pressure, maintaining blood glucose between the lower limit of normal and 180 mg/dl, and, for mechanically ventilated patients, maintaining an inspiratory plateau pressure of 30 cm H₂O or less (Dellinger et al., 2013; IHI, 2009). Additionally, supportive therapy to reduce the incidence of complications is well within the realm of nursing. Such therapies
include maintaining adequate nutrition and prevention of deep vein thrombosis, stress and pressure ulcers, and further infections.

**Expected Patient Outcomes**

Early identification of neutropenia in patients with cancer is critical. With close monitoring and treatment of neutropenia, the neutropenic period can be decreased, thus maintaining the patient’s treatment schedule and improving quality of life. Patients with cancer who experience sepsis or septic shock may experience irreversible consequences. Therefore, early identification of infection and prompt administration of effective treatments are imperative to improving patient outcomes, especially related to sepsis and septic shock. When patients and families are aware of the signs and symptoms of infection and ways to avoid exposure to pathogens, infection can often be avoided and minimal complications related to neutropenia will be realized.

**Patient Teaching Points**

Many NSPOs have been studied and identified. One of the most important aspects of NSPOs is teaching patients what they can do to effect positive outcomes as well. A vital role of oncology nurses is teaching patients and their caregivers about the side effects of the cancer treatment. This education should include the potential for and consequences of neutropenia, including sepsis; interventions to decrease the risk of infection; signs and symptoms of infection; and what to do if the patient experiences any of the signs and symptoms of infection or those associated with the sepsis continuum. Patients should be taught to report signs of infection, including fever, chills and sweating, sore throat, shortness of breath, difficulty urinating, diarrhea, mouth sores, rectal discomfort, abdominal pain, sinus tenderness, and redness or swelling at the site of any catheter or injury. Instructions on what constitutes a fever (a temperature greater than 100.4°F [38°C]) and how often to monitor temperature should also be included in teaching (Nirenberg et al., 2006). Informing patients on the risk factors for sepsis, including the potential causes and manifestations, may promote better patient care (O’Leary, 2011). Families’ relationships with nurses can become more significant during periods of neutropenia (Eggenberger, Krumwiede, Meiers, Bliesmer, & Earle, 2004). Nurses can support family caring throughout the neutropenic experience. Providing patients and caregivers with interventions to reduce the risk of infection that could lead to irreversible sepsis is critical to achieving positive patient outcomes.

**Need for Future Research**

Research in cancer and cancer therapies is ever-changing and evolving. Research efforts will continue to include the area of neutropenia and infection. Although established guidelines exist for the use of CSFs, the use of CSFs as a preventive measure should continue to be studied. Risk factors for neutropenia are well documented, and risk assessment tools have been developed. However, no standard risk assessment tool is commonly used by nurses. Developing such a tool that addresses issues within the realm of nursing will help nurses to identify interventions to protect patients from developing potentially life-threatening infections. Evidence-based protocols have been discussed in the management of sepsis and sep-
tic shock. Education in the use of these protocols, as well as tools for early detection of sepsis, is critical for nurses to be able to promote positive patient outcomes.

**Conclusion of Case Study**

The doctor orders acetaminophen 650 mg PO, a set of blood cultures to be drawn, cefepime IV to be started after the cultures are drawn, vital signs every four hours, and a diet without any fresh fruits or vegetables, and starts R.M. on nystatin three times a day. Knowing that drugs not absorbed by the GI tract are not effective in the treatment of oral candidiasis (Clarkson et al., 2007), the nurse discusses the use of nystatin with the doctor. They decide to change the medication to fluconazole, which is absorbed by the GI tract. In addition, the nurse reviews the literature to find that no indications exist for preventing R.M. from eating fruits and vegetables as long as they are cleaned well. The nurse is diligent in her physical assessment of R.M., paying special attention to breath sounds, abdominal discomfort, skin, and mucous membranes. R.M. continues to complain of not feeling well. During the night, her vital signs indicate a temperature of 102.4°F (39.1°C), blood pressure of 108/78 mm Hg, pulse of 80 beats per minute, and respiratory rate of 12 breaths per minute. The nurse calls the physician who is the resident on call for the evening. She questions whether she should draw another set of blood cultures and add urine cultures. The resident decides to wait for the team, who should be there within two to three hours. R.M. becomes hard to arouse, and the nurse takes another set of vital signs, which now shows a temperature of 102.2°F (39°C), blood pressure of 81/50, pulse of 100, and respiratory rate of 18. Based on these vital signs, the nurse sees that her MEWS score is 4, which indicates a need for more intensive therapy. The nurse calls the physician and the emergency response team. Upon arrival, the team understands that R.M. is most likely septic and they need to act quickly. A lactate level is drawn, additional blood cultures and urine cultures are obtained, and a bolus of fluids is given. An aminoglycoside is added to her antibiotic therapy, and she is moved to an intermediate care unit. Within hours, her vital signs return to normal and she is more alert. Her blood cultures return with an identified organism, and the appropriate antibiotic is started. After three days, R.M.’s ANC is 1,200/mm$^3$. She remains afebrile and is being discharged home. The nurse prepares discharge instructions. She reviews with R.M. and her family the importance of hand washing. She instructs R.M. on the importance of good oral care and proper nutrition. She cautions against eating any raw or undercooked foods and emphasizes that fruits and vegetables should be cleaned thoroughly. She reviews the potential signs of infection, including fever, that R.M. should report to the physician. Although R.M. experienced CIN that led to sepsis with this chemotherapy cycle, the healthcare team was quick to respond and act. She was discharged home without further complications.

**Conclusion**

Neutropenia has the potential for significant negative clinical outcomes for patients with cancer, including potentially life-threatening infection, increased hospitalizations, and decreased quality of life. Preventing infection in patients with cancer is crucial. Nurses are
critical in implementing infection prevention strategies themselves, as well as teaching these strategies to patients and families. Understanding the risk factors for developing neutropenia along with the recommended treatments allows healthcare providers to offer the most effective care to patients, thus preventing possible negative outcomes for the patients.

References


Case Study

B.V. is a 55-year-old woman with stage IV renal cell carcinoma. She has metastatic disease to the pelvis, ribs, and spine. She completed third-line therapy and radiation to her lower thoracic spine approximately two months prior, and last week she enrolled in a phase I clinical trial as recent scans showed hepatic involvement. She presents to the clinic with severe low back and right hip pain. She reports that her back and hip have become increasingly painful over the past two weeks, but she was trying to ignore it because her daughter is getting married in one month. She decided to come to the clinic, however, because she can no longer tolerate the pain. She is unable to sleep at night, and the pain is causing her to be anxious and exhausted. She is unable to walk. She reports the intensity of the pain at a constant 7 on a 0–10 scale, with acute exacerbations to 10 with some movements, and she is unable to lie on her right side. She describes the pain as a deep ache in her right hip along with a burning and radiating sensation down her right leg.

Medications for pain include morphine sulfate controlled-release 60 mg TID and morphine sulfate immediate-release 15–30 mg every two hours as needed for breakthrough pain. Although she was taking her controlled-release morphine consistently, she was reluctant to take the immediate-release morphine except during the evenings because it caused excessive drowsiness, and she was unable to assist her daughter with the wedding plans. Coanalgesics include acetaminophen 4,000 mg daily, gabapentin 900 mg daily, and lorazepam 1 mg every six hours as needed for anxiety. She shares that she knows her life is limited, but her goal is to control her pain to an intensity of less than 5 so she can enjoy her daughter’s upcoming wedding.

Overview

Pain is a significant problem in patients with cancer and can occur throughout the disease trajectory: at diagnosis, during treatment, in cancer survivors, and in patients with advanced disease. According to the International Association for the Study of Pain, pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (International Association for the Study of Pain, 2012). While pain is a physiologic experience, this definition validates pain as a holistic experience involving physical, psychological, social, and spiritual factors. Emphasis is often placed on physical pain, but nurses should recognize and be reminded that total pain involves much more
(Brant, 2010a). Psychologically, patients can experience anxiety or fear related to pain (Porter & Keefe, 2011). Social isolation can occur for patients who experience pain with increased activity (Haozous, Knobf, & Brant, 2011). Other patients may refuse analgesics because of their belief that suffering results in a greater spiritual reward. Because pain involves physical, psychological, social, and spiritual components, the management of pain should encompass all four domains (Ferrell, Levy, & Paice, 2008; Ferrell, Paice, & Koczywas, 2008; Ferrell & Virani, 2008).

Unfortunately, cancer pain remains undertreated because of multiple barriers. For example, pain assessment is often inconsistent and not well understood (Brant, 2010b). Healthcare professionals, in general, lack adequate knowledge regarding pain pharmacotherapy and management strategies. In a recent study (N = 324), fewer than half of the nurses achieved a passing score on a pain knowledge and attitudes survey (Lewthwaite et al., 2011). Fears about addiction lead to further problems, such as judgmental assessment and underprescribing of opioids. Regulatory standards also create barriers for prescribers (Brant, 2014). Risk evaluation and mitigation strategies (REMS) for some opioids were introduced to safeguard patients receiving opioids and to educate prescribers, but they have added another layer to the prescribing of opioids for patients in need (U.S. Food and Drug Administration [FDA], 2014). For example, for a patient receiving transmucosal fentanyl, the prescriber must review an online tutorial, provide the patient with a medication guide, complete and sign an access agreement with each new patient, submit documentation to the REMS program, and enroll in the drug-specific program every two years (TIRF REMS Access, 2014). In addition to the healthcare and systems barriers, patients and families often fear opioid addiction, lack adherence, and even deny pain for fear that it is a signal of progressing cancer (Borneman et al., 2010). Overall, the undertreatment of cancer pain has profound negative effects on patients’ mood, functional status, and quality of life (Black et al., 2011). Therefore, assessment and aggressive management of cancer pain are priorities for all oncology nurses.

**Risk Factors and Associated Incidence**

The incidence of pain is variable and dependent upon patients’ diagnosis, treatment, and extent of disease. A systematic review that examined pain prevalence revealed that approximately 53% of patients with cancer experience pain at some point along the disease trajectory: up to 59% during anticancer treatment, 33% following curative therapy, and 64% in advanced or terminal stages of the disease. One-third of patients graded the pain as moderate to severe (van den Beuken-van Everdingen et al., 2007). Pain also can become chronic and extend throughout the cancer survivor’s life span (Brant, 2011).

The systematic review by van den Beuken-van Everdingen et al. (2007) also examined the cancer diagnoses associated with the most pain. Patients with head and neck cancer are shown to experience the most pain (70%), followed by those with gynecologic malignancies (60%), gastrointestinal cancers (colon, esophageal, pancreatic) (59%), lung cancer (55%), breast cancer (54%), and urogenital cancers (prostate, bladder) (52%). For patients who had pain, more than one-third estimated the pain as moderate to severe, up to 43% rated it as moderate, and up to 26% rated it as severe (van den Beuken-van Everdingen et al., 2007). Breakthrough pain is also common among patients with cancer and is often inadequately assessed and mismanaged. Depending on how breakthrough pain is defined in a study, 23%–90% of patients with cancer experience this deleterious type of pain, which compromises function and quality of life (Caraceni, Martiní, Zecca, Portenoy, & Working Group of an IASP Task Force on Cancer Pain, 2004; Davies et al., 2011).

Some patients are at greater risk for untreated pain as a result of communication, assessment, and cultural barriers and societal attitudes. Older adults, women, patients from a minor-
ity race, patients who have a current or previous history of drug abuse, and those with less education and a lower socioeconomic status are at greater risk for inadequate pain assessment and management (Delgado-Guay & Bruera, 2008; Fairchild, 2010; Jacobsen et al., 2009; Sun, Borneman, Piper, Koczywas, & Ferrell, 2008).

Pathophysiology

Cancer-Related Pain

Patients can experience acute and chronic pain from cancer, diagnostic procedures, treatments, or preexisting painful conditions (e.g., osteoarthritis, painful diabetic peripheral neuroopathy, lower back pain). Oncology nurses need to be able to recognize the most common pain conditions and syndromes associated with cancer and its treatment. Definitions of pain terms are included in Figure 20-1.

The most common types of acute pain associated with cancer treatment are postoperative pain, oral mucositis, and peripheral neuropathy (Aiello-Laws et al., 2009; Irwin, Brant,

<table>
<thead>
<tr>
<th>FIGURE 20-1</th>
<th>Glossary of Pain-Related Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute pain</strong></td>
<td>Short-term pain usually lasting less than 3–6 months that dissipates with normal tissue healing. This type of pain is considered a normal physiologic response to tissue damage. Some causes of acute pain are surgery and infection. Acute pain is considered a symptom of an underlying disease or condition. Patients may have acute on top of chronic pain.</td>
</tr>
<tr>
<td><strong>Addiction</strong></td>
<td>A primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. <strong>Physical dependence</strong> and <strong>tolerance</strong> are not synonymous with addiction.</td>
</tr>
<tr>
<td><strong>Breakthrough pain</strong></td>
<td>A sudden increase in pain, typically unexpected and usually in the setting of background persistent pain.</td>
</tr>
<tr>
<td><strong>Chronic pain</strong></td>
<td>Longer-term pain lasting longer than 3–6 months that persists beyond the expected period of tissue healing. Chronic pain is considered a condition or disease in and of itself.</td>
</tr>
<tr>
<td><strong>Coanalgesic</strong></td>
<td>Also referred to as <strong>adjuvant analgesic</strong>. A medication that has a primary indication other than pain but is used for its analgesic properties in various pain states. For example, an anticonvulsant can be used to treat neuropathic pain.</td>
</tr>
<tr>
<td><strong>Dysesthesia</strong></td>
<td>An abnormal, unpleasant sensation usually associated with neuropathic pain.</td>
</tr>
<tr>
<td><strong>Hyporeflexia</strong></td>
<td>A decrease in the deep tendon reflexes.</td>
</tr>
<tr>
<td><strong>Narcotic</strong></td>
<td>See <strong>opioid analgesic</strong>. An archaic term for an opioid analgesic. In general, a narcotic is a substance that causes narcosis or stupor. In law enforcement, the term is used to describe a variety of substances with a potential for abuse such as heroin, cocaine, or methamphetamine.</td>
</tr>
<tr>
<td><strong>Nonopioid analgesic</strong></td>
<td>A medication that exerts its analgesic effect by a mechanism other than binding to the opioid receptors in the central nervous system. Examples include acetaminophen and nonsteroidal anti-inflammatory drugs. This term is preferred to the term <strong>non-narcotic</strong>.</td>
</tr>
<tr>
<td><strong>Opioid analgesic</strong></td>
<td>A medication that exerts its primary pharmacologic response by binding to the opioid receptors in the central nervous system. This term is preferred to the term <strong>narcotic</strong>.</td>
</tr>
<tr>
<td><strong>Paresthesia</strong></td>
<td>An abnormal sensation, usually not unpleasant, that manifests as numbness, tingling, or increased sensitivity.</td>
</tr>
<tr>
<td><strong>Physical dependence</strong></td>
<td>A state of adaptation manifested by a drug class–specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.</td>
</tr>
<tr>
<td><strong>Tolerance</strong></td>
<td>A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug’s effects over time.</td>
</tr>
</tbody>
</table>

A Guide to Oncology Symptom Management (Second Edition) by & Eaton, 2012). Because surgery is the most common initial treatment for most cancers, patients with cancer will experience postoperative pain. In most cases, acute postoperative pain decreases over time as healing occurs.

The most common cause of chronic pain associated with cancer is bone metastasis. Patients at high risk for the development of bone metastasis are those with breast, prostate, or lung cancer or multiple myeloma. The most common sites of metastasis are the vertebrae, pelvis, femur, and skull. This somatic pain syndrome is described by patients as severe and localized to the metastatic site. Patients with bone metastases commonly experience incident breakthrough pain, which is pain associated with activity. In addition, bone metastases may cause fractures and spinal cord compression, compounding the painful experience (Shaiova, 2006; van den Beuken-van Everdingen et al., 2007).

Treatment-Related Pain

Patients with cancer commonly experience neuropathic pain related to surgery, chemotherapy, or viral infection such as herpes zoster (shingles) (Lema, Foley, & Hausheer, 2010; Reyes-Gibby, Morrow, Buzdar, & Shete, 2009). The surgical procedures associated with the development of neuropathic pain include radical neck dissection, mastectomy, thoracotomy, nephrectomy, and limb amputation. Patients often describe the pain as burning, tingling, and dysesthetic sensations with or without the loss of sensation at the site of the surgical incision. The pain may be exacerbated with movement (Brant, 2011).

Chemotherapy is the most common cause of neuropathic pain in patients with cancer, causing neuropathy in up to 80% of patients, depending on the regimen (Bennett et al., 2012). The drugs associated with chemotherapy-induced neuropathy include plant alkaloids, taxanes, platinum compounds, epothilones, and immunomodulatory agents such as thalidomide and bortezomib (Bennett et al., 2012). Usually, the severity and duration of the neuropathy are dose related. The specific symptoms patients experience may be related to the specific drug administered as well as its dose. Dose-related neuropathies associated with chemotherapy are characterized by dysesthesias in the feet and hands and may be associated with hyporeflexia (decreased deep tendon reflexes) (Tofthagen & McMillan, 2010). Cold sensitivity is also a common neuropathic sensation in patients receiving oxaliplatin (Tofthagen, McAllister, & McMillan, 2011).

Patients with cancer, particularly during times of immunosuppression, may experience an acute herpes zoster infection followed by chronic postherpetic neuralgia (PHN) pain. PHN is estimated to occur in 10%–20% of immunocompetent individuals and more commonly in immunocompromised patients (Klompas, Kulldorff, Vilk, Bialek, & Harpaz, 2011). Risks related to the occurrence and severity of PHN include advancing age, female gender, and presence of pain and/or abnormal sensations before rash onset (Tontodonati et al., 2012).

Noncancer-Related Pain

Cancer and its treatment can cause a number of pain syndromes, but many patients have chronic pain syndromes unrelated to their cancer diagnosis. The Institute of Medicine estimates approximately 100 million U.S. adults are burdened by chronic pain (Institute of Medicine, 2011). Chronic pain is recognized as a disease itself and, combined with cancer pain, contributes to morbidity, functional decline, and poor quality of life. It is imperative that nurses assess for the presence of chronic pain unrelated to the cancer diagnosis along with cancer-related pain. Chronic pain often goes unrecognized and can confuse or mask the cancer-
related pain, and the pain may be treated differently. For example, if a patient with colorectal cancer has a history of lower back pain, the constant back pain may confuse the clinician when assessing pain related specifically to the colorectal cancer. In addition, the patient may have a pain goal of 5 out of 10 intensity for the chronic pain, but the cancer-related pain should be assessed separately in terms of personal goals and response to treatment. Diligent assessment and multimodal management can address both problems simultaneously.

**Assessment**

Assessment of cancer pain is a continuous process that includes universal screening for the presence of pain, a comprehensive pain assessment, and ongoing reassessments. All patients with cancer, regardless of disease, should be screened for the presence of pain at each outpatient visit or hospital admission. If pain is present, a comprehensive pain assessment should be performed. For hospitalized patients, pain should be reassessed at regular intervals during the stay, with new reports of pain, and at appropriate intervals following pain interventions (American Pain Society, 2008; Brant, 2010b).

A detailed pain assessment should focus on the location, intensity, quality, and temporal factors (e.g., onset, duration, how the pain changes over time) of the pain. Each location of pain should be documented, along with characteristics of each site. Pain intensity should be assessed, using patient report as the gold standard. Patients should be asked to rate pain on a 0–10 scale with 0 being no pain and 10 being the worst possible pain. Patients should also be asked to describe the pain, as characteristics aid in diagnosing the cancer pain syndrome (see Figure 20-2 and Table 20-1). The temporal aspects of pain aid in the management plan. Persistent pain should be differentiated from breakthrough pain. *Persistent cancer pain* is continuous pain present throughout most of the day and usually is managed with around-the-clock medication. *Breakthrough pain* is a transitory exacerbation or flare of moderate to severe pain that occurs in patients with otherwise stable persistent pain. Breakthrough pain can be sudden and severe and is intermittent (Davies et al., 2011; Mercadante, 2011). Figure 20-2 outlines an interview guide that oncology nurses can use to obtain a comprehensive assessment of persistent cancer pain and breakthrough pain.

Cancer pain is a multidimensional experience; therefore, assessment should include the psychological, social, and spiritual factors influencing the perception of and response to pain. Specific areas to assess include the meaning of the pain to patients and their family caregivers; significant past experiences with pain and pain management; how patients and family caregivers have coped with pain in the past, as well as their current level of coping; and any concerns about the use of opioid analgesics. The economic impact of pain on patients and family caregivers should be investigated along with the impact of pain on patients’ ability to function. In addition to a pain intensity score, nurses can use patient function to evaluate the effectiveness of the pain management plan (Brant, 2010a).

The physical examination and diagnostic tests focus on determining the cause of the pain and the extent of the patient’s disease. While patient report should always be the first indication of pain, diagnostic tests can reveal advanced disease. For example, an abdominal computed tomography scan can reveal a bowel obstruction in a patient with ovarian cancer who has increased abdominal pain. As with this example, pain may be the first indication of tumor recurrence or progression. Therefore, new complaints of pain require an appropriate and comprehensive evaluation.

Some patients can be reluctant to report pain for several reasons: they desire to be good patients, fear that the cancer has progressed, or do not want to take opioid medications
because of their potential side effects (Borneman et al., 2010). In patients who are reluctant to report pain, nurses can use nonverbal cues as an indication that the patient is not comfortable. Patients who reposition themselves frequently or who are restless may be experi-

<table>
<thead>
<tr>
<th>FIGURE 20-2</th>
<th>Components of a Comprehensive Pain Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical</strong></td>
<td><strong>Breakthrough Pain (BTP) Assessment</strong></td>
</tr>
</tbody>
</table>
| O | Onset  
*When did the pain start? When the pain comes on, is it sudden or gradual?* |
| L | Location  
*Where is the pain located? Is it deep or on the surface? Is there more than one area of pain?* |
| D | Duration  
*How long have you had pain? How long does it last when it comes on?* |
| C | Character  
*How would you describe the pain in your own words? (Stabbing, throbbing, gnawing, aching?)* |
| A | Aggravating factors  
*What makes the pain worse? What makes the pain better? What has worked or not worked in the past?* |
| R | Radiation  
*Does the pain move anywhere? Does it start in one area and end in another?* |
| T | Timing  
*When do you notice the pain? Is the pain constant or does it come on suddenly? Do you notice any patterns?* |
| S | Severity  
*How is your pain right now? What is the worst it has been today? Best? Average?* |

<table>
<thead>
<tr>
<th><strong>Psychological</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• The meaning of pain to the patient and family</td>
<td></td>
</tr>
<tr>
<td>• History or presence of anxiety, depression, or other psychological illness</td>
<td></td>
</tr>
<tr>
<td>• Cognitive ability, including the presence of confusion or delirium</td>
<td></td>
</tr>
<tr>
<td>• Usual coping strategies in response to pain</td>
<td></td>
</tr>
<tr>
<td>• Beliefs about opioids, addiction, and other concerns</td>
<td></td>
</tr>
<tr>
<td>• Willingness to try complementary modalities such as cognitive behavioral therapy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Social</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Interference of pain on daily living including physical or social withdrawal from activity</td>
<td></td>
</tr>
<tr>
<td>• Family communication and response to illness</td>
<td></td>
</tr>
<tr>
<td>• Support system</td>
<td></td>
</tr>
<tr>
<td>• Economic impact of the pain and its treatment (e.g., ability to afford analgesics)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Spiritual</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Spiritual beliefs related to pain and illness</td>
<td></td>
</tr>
<tr>
<td>• Presence of a spiritual community and its role related to pain and illness</td>
<td></td>
</tr>
<tr>
<td>• Influence of religion or spirituality on coping with pain</td>
<td></td>
</tr>
</tbody>
</table>

**Note.** Based on information from Brant, 2010a, 2012.  
For those unable to communicate, nonverbal tools that examine patient behavior should be used (Herr, Coyne, McCaffery, Manworren, & Merkel, 2011). When patients are reluctant to report pain, nurses should discuss the benefits of comfort such as increased function and quality of life.

### Evidence-Based Interventions

The effective management of cancer pain requires oncology nurses and other members of the healthcare team to work with patients and family caregivers to ensure pain is assessed, a

---

**TABLE 20-1 Cancer-Related Pain Syndromes**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Examples of Related Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct tumor involvement</td>
<td>• Somatic pain</td>
</tr>
<tr>
<td></td>
<td>– Bone pain—primary or metastatic</td>
</tr>
<tr>
<td></td>
<td>• Visceral pain</td>
</tr>
<tr>
<td></td>
<td>– Ascites</td>
</tr>
<tr>
<td></td>
<td>– Lymphedema</td>
</tr>
<tr>
<td></td>
<td>– Intestinal obstruction</td>
</tr>
<tr>
<td></td>
<td>– Organ-related pain—pancreas, liver, abdomen</td>
</tr>
<tr>
<td></td>
<td>• Neuropathic</td>
</tr>
<tr>
<td></td>
<td>– Brachial or lumbosacral plexopathies</td>
</tr>
<tr>
<td></td>
<td>• Headache</td>
</tr>
<tr>
<td>Therapeutic and diagnostic procedures</td>
<td>• Therapeutic procedure–related</td>
</tr>
<tr>
<td></td>
<td>– Pleurodesis</td>
</tr>
<tr>
<td></td>
<td>– Postsurgical pain</td>
</tr>
<tr>
<td></td>
<td>• Diagnostic procedure–related</td>
</tr>
<tr>
<td></td>
<td>– Bone marrow aspiration</td>
</tr>
<tr>
<td></td>
<td>– Lumbar puncture</td>
</tr>
<tr>
<td>Cancer treatment</td>
<td>• Surgery</td>
</tr>
<tr>
<td></td>
<td>– Postsurgical pain</td>
</tr>
<tr>
<td></td>
<td>– Pain following access device placement</td>
</tr>
<tr>
<td></td>
<td>• Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>– Arthralgia from flare reactions</td>
</tr>
<tr>
<td></td>
<td>– Avascular necrosis from medication administration</td>
</tr>
<tr>
<td></td>
<td>– Hemorrhagic cystitis</td>
</tr>
<tr>
<td></td>
<td>– Mucositis</td>
</tr>
<tr>
<td></td>
<td>– Peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td>• Hormone therapy</td>
</tr>
<tr>
<td></td>
<td>– Arthralgia</td>
</tr>
<tr>
<td></td>
<td>– Gynecomastia</td>
</tr>
<tr>
<td></td>
<td>• Biotherapy/targeted therapy</td>
</tr>
<tr>
<td></td>
<td>– Acneform rash</td>
</tr>
<tr>
<td></td>
<td>– Bone pain related to growth factor administration</td>
</tr>
<tr>
<td></td>
<td>• Radiation therapy</td>
</tr>
<tr>
<td></td>
<td>– Dermatitis</td>
</tr>
<tr>
<td></td>
<td>– Enteritis</td>
</tr>
<tr>
<td></td>
<td>– Mucositis</td>
</tr>
<tr>
<td></td>
<td>– Plexopathies</td>
</tr>
</tbody>
</table>

treatment plan is initiated, the effectiveness of the treatment plan is reassessed on an ongoing basis, and appropriate modifications occur to the treatment plan whenever needed. Pain management requires that patients and family caregivers be incorporated as essential participants in the development and implementation of the pain management plan. Without ongoing patient assessment and education, the optimal management of cancer pain will not occur.

The American Pain Society (2008) and the National Comprehensive Cancer Network® (NCCN®, 2014) have published clinical practice guidelines on the management of cancer pain. In addition, the Oncology Nursing Society (ONS) Putting Evidence Into Practice (PEP) team has published recommendations on pharmacotherapeutic interventions for nociceptive and neuropathic pain in adults (Irwin et al., 2012). These recommendations are similar, and the PEP guideline recommendations are summarized in the next sections of this chapter. Nurses should be reminded that the PEP guidelines contain evidence from studies conducted to control pain in patients with cancer, but a lack of evidence exists for many treatment modalities; therefore, further research is needed.

**Acute Cancer Pain**

**Recommended for Practice**

**Opioids:** Oral and IV opioids are commonly employed for the management of acute pain. IV opioids bypass the first-pass effect in the liver and work within 5–15 minutes of administration. Immediate-release oral opioids, which begin working within an hour and generally last approximately four hours, are most commonly used. Recent evidence shows that long-acting or continuous-release opioids, which deliver a controlled release of opioid over approximately 12 hours, also demonstrate efficacy for acute postoperative pain. Women undergoing breast cancer surgery achieved adequate pain control with either controlled-release oxycodone 20 mg or controlled-release tramadol 200 mg (Kampe et al., 2009). Because pain is constant after surgery, consideration should be given to the continuous-release preparations.

**Epidural anesthesia:** Acute pain (see Figure 20-1) can occur at any point during the cancer trajectory and is most often associated with diagnostic, surgical, or other treatment procedures. Epidural anesthetics are recommended for postoperative pain due to cancer surgery, with most evidence in patients undergoing surgery for gynecologic malignancies (Ferguson et al., 2009). In one randomized trial, patients undergoing gynecologic cancer were randomized to receive IV patient-controlled analgesia (PCA, n = 68) or patient-controlled epidural analgesia (PCEA, n = 67). Patients in the PCEA arm experienced significantly lower pain intensity at rest and with cough six days postoperatively (p < 0.003) and were more satisfied than those receiving PCA. One side effect to consider with this route is the potential for urinary retention (Ferguson et al., 2009).

**Coanalgesics:** Some coanalgesics have demonstrated efficacy for acute postoperative pain. Gabapentin is an anticonvulsant used in the treatment of neuropathic pain, but evidence exists that a single dose of 600–1,200 mg given before surgery can decrease postoperative opioid requirements and lower median pain scores (Grover, Mathew, Yaddanapudi, & Sehgal, 2009; Türe et al., 2009). Postoperative sedation is the primary side effect. Local anesthetics such as bupivacaine and ropivacaine, administered into the postsurgical site, have also been shown to decrease postoperative pain in patients undergoing thoracoscopy (Demmy et al., 2009), mastectomy (Heller, Kowalski, Wei, & Butler, 2008), breast reconstruction (Legeby, Jurell, Beausang-Linder, & Olofsson, 2009), or open nephrectomy (Forastiere, Sofra, Giannarelli, Fabrizi, & Simone, 2008). The ability to anatomically place the catheter in the correct position may influence overall results.
Complementary: Hypnosis is a nonpharmacologic intervention that is recommended as an adjunct in the management of procedure-related pain such as lumbar puncture (Richardson, Smith, McCall, & Pilkington, 2006) and following surgery (Montgomery, Weltz, Seltz, & Bovbjerg, 2002). NCCN also includes hypnosis in its pain guidelines. A trained hypnotherapist is essential to incorporate this modality into practice.

Effectiveness Not Established

Large randomized controlled trials are lacking for some interventions for acute cancer-related pain. For example, lidocaine patch for incisional pain is shown by some evidence to decrease neuropathic pain and is recommended in the NCCN guidelines (NCCN, 2014), but the one small study (N = 28) used for this recommendation limits generalizability (Cheville et al., 2009). Perioperative drug regimens using different combinations of coanalgesics have also received attention. Corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and anticonvulsants were tried, but results have been inconsistent. Finally, effectiveness for nonpharmacologic interventions such as foot reflexology or acupuncture for postoperative pain has not been established (Irwin et al., 2012).

Chronic Cancer Pain

The management of chronic cancer pain is foundational to patient comfort and overall quality of life. Numerous guidelines on cancer pain management exist and contain algorithm-based approaches that can guide the initial and ongoing management of cancer pain (American Pain Society, 2008; NCCN, 2014). The World Health Organization’s analgesic ladder is an internationally recognized tool that can be used as a guide for cancer pain management (World Health Organization, n.d.). In general, mild pain (i.e., worst pain intensity between 1 and 4) usually is relieved with a nonopioid analgesic or a combination of a nonopioid and an opioid analgesic (e.g., codeine and acetaminophen, hydrocodone and acetaminophen). Moderate (i.e., worst pain intensity between 5 and 6) and severe (i.e., worst pain intensity between 7 and 10) pain usually require an opioid analgesic.

The interdisciplinary team should keep in mind that pain management is not the same for all patients, but rather it is tailored according to individual patient characteristics. For example, factors to consider when initiating an analgesic regimen for cancer pain are the severity of the patient’s pain, the etiology of the pain, the setting in which the regimen is initiated (e.g., hospital, clinician’s office, patient’s home), whether the patient is opioid naïve or currently taking an opioid analgesic, and the patient’s previous experience with analgesic medications, including their efficacy and side effects. Individual characteristics such as renal status, concomitant medications, and history of addiction also are important factors to incorporate into the pain management plan. The evidence described in this section can aid in the development of the pharmacologic plan to control pain.

Recommended for Practice

Effective chronic cancer pain management requires the use of nonopioid analgesics, opioid analgesics, and coanalgesics. The choice of analgesic medication most often is based on the cause and severity of pain. For example, if the patient has neuropathic pain, a coanalgesic (e.g., gabapentin, nortriptyline) may be a more effective treatment than an opioid. In many cases, patients with chronic cancer pain will require combinations of analgesics to achieve optimal analgesia (American Pain Society, 2008). The specific analgesic medications used should be based on their mechanisms of action and the etiology of the patient’s pain.
Nonopioid analgesics: Nonopioid analgesics, which include acetaminophen, aspirin, and NSAIDs, are the most commonly used analgesics for the management of mild to moderate pain (American Pain Society, 2008). These drugs exert their analgesic effects primarily within the peripheral nervous system. A large amount of interindividual variability exists in response to nonopioid analgesics. In addition, this class of drugs exhibits the pharmacologic property of a ceiling effect (i.e., a maximum therapeutic dose exists, above which no additional analgesic effect occurs and an increased risk of toxicity results if the dose is escalated).

Acetaminophen is an analgesic and antipyretic that does not have an anti-inflammatory effect, but it is recommended for cancer pain management. The addition of acetaminophen to an opioid analgesic may allow for a reduction in the dose of the opioid analgesic. Chronic daily dosing of more than 4 g/day of acetaminophen is not recommended because of the increased risk of hepatotoxicity, and a maximum dose of 3 g/day should be used in frail older patients (Aiello-Laws et al., 2009). Oncology nurses need to assess the amount of acetaminophen the patient is taking on a daily basis. To avoid the development of hepatotoxicity in patients, this assessment needs to include all combination products containing acetaminophen (e.g., over-the-counter analgesics and cold preparations, combination products of an opioid with acetaminophen).

NSAIDs are effective for the treatment of mild or inflammatory pain and have an opioid-sparing effect in the treatment of moderate to severe pain (American Pain Society, 2008). As a class of analgesics, NSAIDs inhibit isoforms of the cyclooxygenase (COX) enzyme either selectively (COX-2) or nonselectively (COX-1 and -2). In both forms, COX catalyzes the synthesis of endoperoxides from arachidonic acid to produce proinflammatory and other types of prostaglandins. Inhibition of this enzyme by nonselective NSAIDs results in analgesia. It additionally results in decreased production of prostaglandins and other substances that protect the gastric mucosa and renal parenchyma, which can result in dyspepsia, gastrointestinal bleeding, and renal failure. Selective COX-2 agents have less affinity for prostaglandins that protect gastric mucosa, thereby causing fewer gastrointestinal (GI) effects. Celecoxib is the only COX-2 agent approved by the FDA and may cause less gastric ulceration than the COX-1 agents. Other adverse events include central nervous system dysfunction such as confusion and cardiovascular effects, especially with the COX-2 inhibitors. NSAIDs are most useful in the treatment of cancer pain when the pain is associated with inflammation (e.g., patients with pain from bone metastasis or lymphedema). However, analgesics in this class may need to be used with caution in patients with cancer who have thrombocytopenia because of their inhibition of platelet aggregation (American Pain Society, 2008; McNicol, Strassels, Goudas, Lau, & Carr, 2005).

Opioid analgesics: Opioid analgesics are the mainstay of chronic cancer pain management and are effective for moderate to severe pain (Aiello-Laws et al., 2009; American Pain Society, 2008; Colson, Koyyalagunta, Falco, & Manchikanti, 2011; Green et al., 2010; NCCN, 2014; Qaseem et al., 2008). Opioids produce analgesia by binding to opioid receptors within and outside the central nervous system. Most of the opioid analgesics that are available for clinical use (e.g., morphine, hydromorphone, oxycodone, oxymorphone, fentanyl) bind to the mu-opioid receptor to exert their analgesic effects. See Table 20-2 for a comparison of commonly used opioids.

Methadone deserves specific attention, as it should be used only by clinicians who understand its unique pharmacology. Methadone is a potent opioid and N-methyl-D-aspartate (NMDA) antagonist that is tightly bound to protein, resulting in a relatively long-acting analgesic effect but also a long half-life with potential for accumulation and adverse effects. Because the plasma concentration of methadone slowly rises to steady-state levels over four
<table>
<thead>
<tr>
<th>Opioid</th>
<th>Oral</th>
<th>Parenteral (IV)</th>
<th>Availability in United States</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30</td>
<td>10</td>
<td>Injection</td>
<td>Standard for opioid comparison</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral IR product</td>
<td>Potential for accumulation of active metabolites in renal impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral ER product</td>
<td>Can cause significant pruritus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rectal suppository Oral liquid</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>–</td>
<td>0.1</td>
<td>Injection</td>
<td>Avoid direct heat to patch.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Transdermal</td>
<td>Onset of action dependent on formulation (patch ~12 hrs, nasal ~ 5 min)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral transmucosal Nasal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.1 mg = 100 mcg</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30</td>
<td>–</td>
<td>Oral IR product</td>
<td>Only available in combination with acetaminophen, aspirin, or ibuprofen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Combination product</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral liquid</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5</td>
<td>1.5</td>
<td>Injection</td>
<td>Option for patients with renal impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral IR product</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral ER product</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rectal suppository Oral liquid</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Less pruritus</td>
</tr>
<tr>
<td>Methadone</td>
<td>See Table 20-3.</td>
<td>Injection</td>
<td>Oral IR product</td>
<td>Requires significant knowledge and experience to use safely</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral liquid</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
<td>–</td>
<td>Oral IR product</td>
<td>Metabolized by the liver into oxymorphone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral ER product</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Combination product</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral liquid</td>
<td></td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>10</td>
<td>1</td>
<td>Injection</td>
<td>Should be taken on an empty stomach</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral IR product</td>
<td>Requires dose reduction in renal or hepatic impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral ER product</td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>200</td>
<td>–</td>
<td>Oral IR product</td>
<td>Converted to morphine by the liver</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Combination product</td>
<td>Can cause significant nausea and vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral liquid</td>
<td>Interindividual variability in metabolism</td>
</tr>
<tr>
<td>Meperidine</td>
<td>No longer recommended for pain management: shorter duration of action compared to morphine, and metabolized into toxic metabolite that can accumulate and cause CNS excitation.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>120</td>
<td>–</td>
<td>Oral IR product</td>
<td>Weak opioid activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral ER product</td>
<td>Also inhibits 5-HT/NE reuptake</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Combination product</td>
<td>Maximum dose 400 mg/day (300 mg in patients &gt; 75 years old; 200 mg in patients with CrCl &lt; 30 ml/min)</td>
</tr>
</tbody>
</table>

CNS—central nervous system; CrCl—creatinine clearance; ER—extended release; 5-HT—serotonin; IR—immediate-release; mcg—microgram; NE—norepinephrine

Note. Based on information from American Pain Society, 2008; McPherson, 2010.
to five half-lives (i.e., almost one week in most patients), titration should be done slowly with close patient monitoring. Due to methadone’s NMDA activity that results in decreased tolerance, rotating to methadone from another opioid requires careful calculation based on previous opioid use (American Pain Society, 2008; Mercadante & Caraceni, 2011; Nicholson, 2007) (see Table 20-3 for considerations with methadone use).

Opioid doses should be individually tailored for each patient to achieve pain relief with an acceptable level of side effects, starting with the least invasive route of administration (Aiello-Laws et al., 2009; Davies et al., 2011; NCCN, 2014). For chronic cancer pain, use of long-acting preparations (oral or transdermal) should be given around the clock (NCCN, 2014).

Because many patients with chronic cancer pain will have persistent pain as well as breakthrough pain, management plans need to address both types of pain. An optimal analgesic regimen for a patient with both persistent and breakthrough pain is one that contains a controlled-release or long-acting opioid (e.g., controlled-release morphine, oxycodone, or oxymorphone; transdermal fentanyl) that is administered around-the-clock and an immediate-release (e.g., morphine, hydromorphone, oxycodone, oxymorphone) or rapid-onset (e.g., oral transmucosal fentanyl citrate, fentanyl buccal tablet) opioid analgesic. If the patient experiences incident pain (i.e., pain is most often associated with movement or activity), the most effective management approach is to premedicate with an immediate-release opioid analgesic approximately 45 minutes before the planned activity. Management of the spontaneous type of breakthrough pain (i.e., pain that occurs without warning) requires an opioid preparation that can be absorbed quickly, such as rapid-onset fentanyl (Caraceni et al., 2013).

As-needed immediate-release opioids should be dosed proportionally at 5%–15% of the 24-hour total daily dose. For example, if a patient is taking 200 mg controlled-release oxycodone per day, the breakthrough pain dose should be set at 10–30 mg as needed (Green et al.,

### TABLE 20-3 Considerations for Safe and Effective Use of Methadone

<table>
<thead>
<tr>
<th>Principle</th>
<th>Property of Methadone</th>
<th>Consequence(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacology</td>
<td>Unique pharmacology</td>
<td>“Nonlinear” opioid conversion (analgesic equivalence varies based on methadone dose)</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Long half-life (range of 5–120 hours)</td>
<td>Lengthy time to steady state (drug equilibrium in the body)</td>
</tr>
<tr>
<td>Metabolized by the liver</td>
<td></td>
<td>Lower utility in patients with limited prognosis</td>
</tr>
<tr>
<td>Inactive metabolites</td>
<td></td>
<td>Multiple significant drug interactions</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>QT interval prolongation</td>
<td>Potential for torsades de pointes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac safety monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Issues with drug interactions</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Inexpensive</td>
<td>Cost effective</td>
</tr>
<tr>
<td></td>
<td>Intrinsic long action</td>
<td>Oral solution is long acting; can be dosed every 8–12 hours</td>
</tr>
<tr>
<td></td>
<td>Unique characteristics</td>
<td>Requires considerable knowledge for safe and effective prescribing and monitoring</td>
</tr>
</tbody>
</table>

*Note. Based on information from McPherson, 2010.*
Rapid-onset fentanyl administered via the transmucosal, buccal, sublingual, or intranasal route is recommended for the management of breakthrough cancer pain. Because of the lipophilicity of fentanyl, it quickly travels across mucous membranes to reach systemic circulation, resulting in an onset within 15 minutes of administration. In the case of rapid-onset fentanyl products, dosing is not proportional to the 24-hour total daily dose but rather based on an individualized titration schedule according to comfort. Instructions should be followed carefully with each product (Aiello-Laws et al., 2009; Davies et al., 2011; Wiffen, Wee, & Moore, 2013; Zeppetella, 2008).

For persistent pain that is not well controlled, the dose of the controlled-release opioid can be increased by 25%–50% or to a dose equal to the amount of supplemental medication the patient is taking for breakthrough pain. Larger dose increases can be considered if the patient is in severe pain and is able to tolerate the increase. Dose increases are safest if performed after steady-state levels of the analgesic medication are achieved (i.e., usually in five to six half-lives) (American Pain Society, 2008).

A “worst pain score” of 7–10 should be considered an oncologic emergency. This level of pain warrants prompt titration using rapid-onset, immediate-release, or IV/subcutaneous opioid analgesics. The advantages of IV administration are that peak analgesic effect is achieved within 15 minutes, repeated doses can be administered more frequently, analgesia may be achieved more rapidly, and adverse effects can be monitored more easily. However, this approach requires patients to be monitored carefully either in an emergency department, inpatient setting, or chemotherapy infusion center with appropriate emergency equipment or at home with oversight from hospice or home health. Fentanyl administered via the intranasal, buccal, sublingual, or transmucosal route has the advantage of rapid onset and can easily be given in the home setting (Caraceni et al., 2013).

If patients experience inadequate pain relief or an unacceptable level of side effects from a specific opioid analgesic, they can also be switched to a different opioid analgesic (i.e., opioid rotation) (Mercadante & Bruera, 2006) or a different route of administration (i.e., route rotation). When switching from one opioid to another, equianalgesic doses of the new drug are calculated (see Figure 20-3) and used as a starting point. The dose of the new drug must be adjusted to reflect the possibility of incomplete cross-tolerance to opioid analgesics, individual variation in response to different opioid analgesics, available dosage forms of the opioid, and the impact of uncontrolled pain and comorbidities on the patient’s response to the new drug (Fine & Portenoy, 2009). Although these practices are routine, effectiveness of these interventions is not established because of the lack of research conducted in this area (Irwin et al., 2012). Table 20-4 details opioid-induced side effects and various prevention and treatment strategies.

Intraspinal analgesia (i.e., epidural and intrathecal) is recommended for practice in patients with refractory and intractable pain. Opioids and local anesthetics can be used to directly bathe pain receptors intraspinally, allowing for lower doses of opioids and fewer systemic side effects as well. In studies related to intraspinal analgesia, pain was significantly reduced and systemic opioid use decreased (Deer et al., 2011; Hayek, Deer, Pope, Panchal, & Patel, 2011; Myers, Chan, Jarvis, & Walker-Dilks, 2010). Side effects were also more manageable. Intrathecal analgesia usually involves an implantable pump, whereas epidural analgesia involves a tunneled catheter that exits at the waistline and is connected to an infusion pump. Both options can be programmed to include basal and breakthrough pain dosing (Deer et al., 2011; Hayek et al., 2011; Myers et al., 2010).

**Coanalgesics:** This class of analgesic medications is composed of drugs that have pain-relieving effects in certain conditions but whose primary or initial indication is not for the treatment of pain. The most common drugs in this class are anticonvulsants, antidepres-
Basic Tenets of Opioid Titration
1. Individualize treatment based on patient characteristics and prior opioid exposure.
2. Titrate opioids until the patient experiences relief or intolerable side effects.
   • For moderate pain, increase doses by 25% or more.
   • For intractable pain, may increase doses by up to 100%.
3. For persistent pain present most of the day, give around-the-clock analgesia.
4. Provide short-acting analgesics for breakthrough pain on an as-needed basis.
   • Breakthrough doses should be 5%–15% of the total daily opioid dose, except in the case of short-acting fentanyl products.
5. Perform regular assessment, especially when initiating or changing analgesics.
6. Predict, prevent, and treat side effects.
7. Use the simplest route of administration possible.

Opioid Conversion (does not apply to transdermal fentanyl or methadone)
1. Perform a comprehensive pain assessment (see Figure 20-2).
2. Calculate the total daily dose of the current opioid used in the previous 24 hours.
3. Determine the equianalgesic dose of the new opioid.
   Example 1: Convert 120 mg oral morphine to oral oxycodone (note the conversion factor from Table 20-2; 30 mg morphine equals 20 mg oxycodone).

\[
\frac{120 \text{ mg PO morphine} \times \frac{20 \text{ mg PO oxycodone}}{30 \text{ mg PO morphine}}}{30 \text{ mg PO oxycodone}} = 80 \text{ mg PO oxycodone}
\]

Example 2: Convert 10 mg IV hydromorphone to oral morphine (note the conversion factor from Table 20-2; 1.5 mg IV hydromorphone equals 30 mg oral morphine).

\[
\frac{10 \text{ mg IV hydromorphone} \times \frac{30 \text{ mg PO morphine}}{1.5 \text{ mg IV hydromorphone}}}{1.5 \text{ mg IV hydromorphone}} = 200 \text{ mg PO morphine}
\]

4. Consider a 25%–50% dose reduction in the new opioid dose to account for incomplete cross-tolerance between the previous opioid and the new opioid. (Dose reduce by less for uncontrolled pain and more for patients experiencing side effects.)
   Example 1: 25%–50% reduction of 80 mg PO oxycodone = 40–60 mg oxycodone.
   Example 2: 25%–50% reduction of 200 mg PO morphine = 100–150 mg morphine.
5. Divide the new calculated dose into the new dosing interval (i.e., q 12 hr), taking into account the available dosage forms of the new opioid.
   Example 1: 60 mg oxycodone daily given as 30 mg extended release (ER) PO q 12 hr
   Example 2: 100 mg morphine daily given as 60 mg ER PO q 12 hr
6. Provide an appropriate breakthrough regimen.
   Example 1: 5%–15% of 60 mg oxycodone = 3–9 mg oxycodone given as 2.5–10 mg PO q 3 hr PRN BTP.
   Example 2: 5%–15% of 120 mg morphine = 6–18 mg morphine given as 5–15 mg PO q 3 hr PRN BTP.
7. Reassess at regular intervals and as needed.
8. Titrate the total daily dose by 25%–100% if needed.
   Example 1: Moderate pain without side effects—increase dose by 25%; 60 mg increased to 75 mg oxycodone daily given as 40 mg ER tablet q 12 hr (new total rounded up to 80 mg for equal dosing every 12 hours).
   Example 2: Intractable pain without side effects—increase dose by 100%; 120 mg increased to 240 mg morphine daily given as 100 mg ER tablet + 20 mg ER tablet q 12 hr.
9. As the total daily dose increases, increase the dose of the breakthrough agent.
   Example 1: 5%–15% of 70 mg oxycodone daily = 3.5–10.5 mg given as oxycodone 5–12.5 mg PO q 3 hr PRN BTP.
   Example 2: 5%–15% of 240 mg morphine daily = 12–36 mg given as morphine 15–30 mg PO q 3 hr PRN BTP.

Note. Based on information from American Pain Society, 2008; McPherson, 2010.
## TABLE 20-4 Opioid-Induced Adverse Events

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Management Example(s)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Constipation</strong></td>
<td>• Stimulant laxative ± stool softener scheduled&lt;br&gt;– Senna ± docusate, bisacodyl&lt;br&gt;• Osmotic laxative scheduled or as-needed&lt;br&gt;– Polyethylene glycol, magnesium citrate, lactulose&lt;br&gt;• Opioid antagonist as-needed&lt;br&gt;– Methylnaltrexone</td>
<td><strong>Pathophysiology:</strong> Decreased peristalsis, decreased secretions, increased sphincter tone&lt;br&gt;Prevention is key.&lt;br&gt;All patients on regular doses of opioids should receive a bowel regimen.&lt;br&gt;Tolerance to opioid-induced constipation does not develop.</td>
</tr>
<tr>
<td><strong>Nausea and vomiting</strong></td>
<td>• Serotonin receptor antagonist&lt;br&gt;– Ondansetron&lt;br&gt;• Dopamine receptor antagonist&lt;br&gt;– Prochlorperazine</td>
<td><strong>Pathophysiology:</strong> Stimulation of the chemoreceptor trigger zone&lt;br&gt;Tolerance usually develops within one week.&lt;br&gt;Rotate opioids if tolerance does not develop.</td>
</tr>
<tr>
<td><strong>Pruritus</strong></td>
<td>• Antihistamines&lt;br&gt;– Hydroxyzine, diphenhydramine&lt;br&gt;• Mixed opioid agonist-antagonist&lt;br&gt;– Nalbuphine (for pruritus due to intraspinal opioids)</td>
<td><strong>Pathophysiology:</strong> Release of histamine&lt;br&gt;Pruritus is more common with morphine and intraspinal opioids.&lt;br&gt;Rotate opioids if pruritus persists.</td>
</tr>
<tr>
<td><strong>Excessive sedation</strong></td>
<td>• Psychostimulant&lt;br&gt;– Methylphenidate</td>
<td><strong>Pathophysiology:</strong> Central nervous system (CNS) depression&lt;br&gt;Reduce opioid dose or dosing interval.&lt;br&gt;Investigate other causes of CNS depression.</td>
</tr>
<tr>
<td><strong>Myoclonus</strong></td>
<td>• Benzodiazepine&lt;br&gt;– Lorazepam, midazolam&lt;br&gt;• Muscle relaxant&lt;br&gt;– Dantrolene</td>
<td><strong>Pathophysiology:</strong> Can result from accumulation of morphine metabolites&lt;br&gt;Opioid rotation or dose reduction may help.</td>
</tr>
<tr>
<td><strong>Respiratory depression</strong></td>
<td>• Opioid antagonist&lt;br&gt;– Naloxone 0.04 mg IV every 2–5 minutes as needed to reverse respiratory depression</td>
<td><strong>Pathophysiology:</strong> Decrease in ventilatory drive&lt;br&gt;Side effect is most common during opioid initiation and titration.&lt;br&gt;Do not administer naloxone too quickly because this can precipitate pain and lead to pain crisis.</td>
</tr>
</tbody>
</table>


sants, and corticosteroids. Most of these medications are used in the management of neuropathic pain (see Table 20-5). Much of the evidence on the safety and efficacy of these medications comes from studies of postherpetic neuralgia and diabetic neuropathy rather than cancer pain.

As with other analgesic medications, a large amount of interindividual variability exists in the effectiveness of the various coanalgesics. In addition, pain relief may take several weeks to occur. Most of these medications need to be titrated slowly to achieve an optimal dose and to reduce the occurrence of intolerable side effects (American Pain Society, 2008). Patients with neuropathic pain need to receive nonopioid or opioid analgesics to control their pain while the coanalgesic medication is titrated to an effective dose.
Tricyclic antidepressants are the best-studied coanalgesics for the management of neuropathic pain (American Pain Society, 2008; Saarto & Wiffen, 2010). These medications block the presynaptic reuptake of serotonin, norepinephrine, and dopamine in the central nervous system. A recent systematic review concluded that tricyclic antidepressants are effective for multiple types of neuropathic pain (e.g., postherpetic neuralgia, diabetic neuropathy) whether or not patients have concurrent depression (Saarto & Wiffen, 2010).

Because tricyclic antidepressants are effective, inexpensive, and usually given once daily, they may be used as initial treatment for neuropathic pain in patients without contraindications to their use (e.g., ischemic heart disease, heart failure, conduction disorders, arrhythmias) (Saarto & Wiffen, 2010). In addition, patients who receive tricyclic antidepressants need to be monitored for adverse events (e.g., cardiotoxicity, confusion, urinary retention, ortho-

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Indication(s)</th>
<th>Example(s)</th>
<th>Potential Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-2 agonists</td>
<td>Neuropathic pain</td>
<td>Clonidine</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>Neuropathic pain</td>
<td>Mexiletine, Lidocaine</td>
<td>Light-headedness, dysrhythmias</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Neuropathic pain</td>
<td>Carbamazepine, Gabapentin, Pregabalin</td>
<td>Sedation, dizziness, ataxia, impaired concentration, peripheral edema, weight gain</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Anxiety; pain associated with muscle spasm</td>
<td>Clonazepam, Diazepam, Lorazepam</td>
<td>Sedation, additive respiratory depression</td>
</tr>
<tr>
<td>Bone-modifying agents</td>
<td>Osteolytic bone pain; prevention of skeletal-related events</td>
<td>Pamidronate, Zoledronic acid, Denosumab</td>
<td>Pain flare, osteonecrosis of the jaw</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Cerebral edema; spinal cord compression; bone, neuropathic, and visceral pain</td>
<td>Dexamethasone, Methylprednisolone</td>
<td>“Steroid psychosis,” dyspepsia, hyperglycemia, Cushingoid syndrome with long-term use</td>
</tr>
<tr>
<td>Muscle relaxants</td>
<td>Short-term use for musculoskeletal pain</td>
<td>Cyclobenzaprine, Tizanidine, Metaxalone</td>
<td>Sedation, dizziness</td>
</tr>
<tr>
<td>N-methyl-D-aspartate antagonists</td>
<td>Neuropathic pain</td>
<td>Dextromethorphan, Ketamine</td>
<td>Confusion, dysphoria, hallucinations, sedation</td>
</tr>
<tr>
<td>Serotonin norepinephrine reuptake inhibitors</td>
<td>Neuropathic pain; comorbid anxiety or depression</td>
<td>Duloxetine, Venlafaxine</td>
<td>Nausea, electrocardiogram changes, withdrawal symptoms if discontinued too rapidly</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Neuropathic pain, insomnia</td>
<td>Amitriptyline, Desipramine, Nortriptyline</td>
<td>Sedation, anticholinergic effects, cardiotoxicity, orthostatic hypotension, confusion, weight gain</td>
</tr>
</tbody>
</table>

static hypotension, nightmares, weight gain, drowsiness, dry mouth, constipation) (American Pain Society, 2008). Secondary amine tricyclic antidepressants (e.g., nortriptyline, desipramine) are preferred because they are better tolerated than the tertiary amine tricyclic antidepressants (e.g., amitriptyline, imipramine) but have comparable analgesic efficacy. Older adults should not receive amitriptyline because of its toxicity and side effect profile. The initial doses of tricyclic antidepressants can range from 10 to 25 mg/day and can be titrated to 100–150 mg every three days (Saarto & Wiffen, 2010).

The serotonin norepinephrine reuptake inhibitors are another option for neuropathic pain. NCCN recently added duloxetine has to its guidelines for management of chemotherapy-induced peripheral neuropathy (NCCN, 2014). A randomized, double-blind, placebo-controlled trial (N = 231) revealed that almost 60% of patients had a significant reduction in pain with duloxetine after five weeks of treatment (Smith et al., 2013).

Anticonvulsants are frequently used to treat neuropathic pain and are recommended in patients with neuropathic pain (NCCN, 2014). Gabapentin and pregabalin are two anticonvulsants used in the management of neuropathic pain. These two drugs modulate cellular calcium influx into nociceptive neurons by binding to voltage-gated calcium channels and decrease the release of glutamate, norepinephrine, and substance P, thereby decreasing spontaneous firing of sensory neurons that contribute to neuropathic pain and sensitization to pain (Brant, 2010b). Compared to other coanalgesics, gabapentin produces fewer intolerable side effects. The most common side effects are sedation and dizziness. Gabapentin is started at doses of 100–300 mg at bedtime and can be titrated every three days until an effective dose of 1,800–3,600 mg/day is reached (American Pain Society, 2008). Dose titration may take several weeks.

Pregabalin is a newer anticonvulsant that has shown efficacy in a variety of neuropathic pain conditions. The side effects of pregabalin are similar to those of gabapentin. Pregabalin is started at doses of 75–150 mg/day (in either two or three divided doses). The maximum dose ranges from 300 to 600 mg/day (Moulin et al., 2007).

Local anesthetic infusions (e.g., lidocaine), which work by stabilizing the cell membrane, are another effective option for cancer-related neuropathic pain. Specifically, sodium influx into the cell is inhibited, preventing an action potential from occurring along the neuron. A systematic review of 30 trials demonstrated efficacy over placebo (Challapalli, Tremont-Lukats, McNicol, Lau, & Carr, 2005).

Bone-modifying agents such as zoledronic acid or denosumab are important adjuncts in patients with bone metastases (Wong & Wiffen, 2002). Bone turnover is kept in balance through the production of osteoblasts (bone building cells) and osteoclasts (bone destroying cells). Bisphosphonates work by promoting osteoclasts to undergo apoptosis, or programmed cell death. These agents are now routinely used to prevent skeletal-related events and subsequently provide pain relief in the majority of patients (Wong & Wiffen, 2002). Prior to therapy initiation, patients should have a dental examination and have ongoing oral care follow-up, as these agents have been associated with osteonecrosis of the jaw. They can also compromise renal function, and serum creatinine should be monitored throughout treatment (Van Poznak et al., 2011).

Pain blocks can be employed to manage localized cancer pain syndromes. Celiac plexus block to control pain related to pancreatic cancer has shown the best efficacy through several clinical trials, systematic reviews, and meta-analyses. Improvement in pain intensity and reduction in opioid consumption are both noted in the literature (Arcidiacono, Calori, Carrara, McNicol, & Testoni, 2011; Puli, Reddy, Bechtold, Antillon, & Brugge, 2009; Yan & Myers, 2007). Preemptive celiac plexus block at diagnosis was also shown to be more effective than oral opioids at one and three months after intervention (Wyse, Carone, Paquin, Usatii,
Sahai, 2011). Novel methods of locating the celiac plexus nerve via an endoscopic approach have aided the success of this procedure (Wyse et al., 2011).

**Likely to Be Effective**

While the World Health Organization (WHO) analgesic ladder is widely recognized as a stepwise approach to manage pain, some studies suggest that earlier intervention (e.g., moving from Step 1 to Step 3) may provide optimal management with a reduction in pain and higher quality of life (Maltoni et al., 2005; Tessaro et al., 2010). Cannabis oral spray is a pharmacologic option that may be an effective adjunctive treatment for various types of cancer pain (Johnson et al., 2010). The product is approved in Canada but not yet in the United States.

**Effectiveness Not Established**

Studies are lacking that establish effectiveness in several pharmacologic areas. This may not mean that the drug is not effective, only that there are perhaps more trials needed. Trials using dimethyl sulfoxide (Hoang et al., 2011) or ketamine (Jackson et al., 2010) for refractory cancer pain showed some pain improvement, but small sample sizes limit generalizability. For breakthrough pain, two separate studies using intranasal sufentanil (Good, Jackson, Brumley, & Ashby, 2009) or a combination of tramadol and acetaminophen (Ho et al., 2010) reduced pain, but again, sample size was insufficient to recommend these modalities for practice. Evidence is also limited for the routine use of acetaminophen in cancer pain control (Cubero & del Giglio, 2010; Israel, Parker, Charles, & Reymond, 2010).

**Nonpharmacologic Interventions**

In most cases, effective management of chronic cancer pain requires use of analgesic medications. Nonpharmacologic interventions often are used as adjuncts to pharmacologic approaches. Psychoeducational interventions such as patient and family education and other supportive nursing interventions such as education, support groups, supportive nursing interventions, and counseling are recommended for practice in reducing pain intensity and providing a positive coping benefit (Dy et al., 2008). An analysis of 25 studies involving 1,354 patients revealed that music, hypnosis, relaxation, imagery, counseling, and support groups had a positive effect on pain control (Irwin et al., 2012). These recommended interventions underscore the importance of interdisciplinary team member involvement in providing pain management and oversight for optimal care (Flemming, 2010).

Cognitive and behavioral approaches (e.g., distraction, relaxation, cognitive restructuring and reframing, music therapy) are designed to reduce the cognitive and affective components of pain (Lovell et al., 2010; Syrjala et al., 2008; Tulipani et al., 2010). Several multisite randomized controlled trials using educational booklets, videos, and multifaceted education and counseling interventions confirmed the positive effects that psychoeducational interventions have on pain intensity. These interventions give patients assistance and direction with how to interpret painful sensations and associated events. Oncology nurses can teach patients and their family caregivers how to use techniques such as relaxation and breathing exercises or music to reduce the anxiety and distress associated with cancer pain. These techniques may be useful in decreasing muscle tension. In addition, they may serve to distract patients from their pain. Family members can learn these techniques and assist patients in implementing them on an as-needed basis to achieve optimal pain control. These behavioral approaches are recommended for practice or are likely to be effective in reducing pain and promoting quality of life (Irwin et al., 2012). Oncology nurses should readily employ these strategies as part of the overall management plan. Effectiveness has not been established because of
insufficient evidence in nonpharmacologic interventions including transcutaneous electrical nerve stimulation, massage, progressive muscle relaxation, therapeutic touch, exercise, herbal formulations, acupuncture, and emotional disclosure (Irwin et al., 2012) but can be trialed if the patient desires. In addition, physical strategies (e.g., heat, cold, massage) can improve pain for some patients.

Patient Teaching Points

Patient and family caregiver education is the cornerstone of effective cancer pain management (NCCN, 2014). As noted in the American Pain Society and ONS PEP cancer pain guidelines, patients and family caregivers should be given accurate and understandable information about the importance of effective cancer pain management, the use of analgesic medications, other methods of pain relief, and how to communicate effectively with clinicians about disturbing side effects and unrelieved pain.

Side effects can influence adherence to the pain management plan and compromise quality of life. Patients should be instructed to communicate side effects so that effective management approaches can be employed to address concerns. Side effects of opioid analgesics need to be anticipated and treated either prophylactically or as they occur. Constipation and sedation are the most common side effects associated with opioid analgesics. Other side effects include nausea and vomiting, dry mouth, urinary retention, pruritus, myoclonus, altered cognitive function, dysphoria, euphoria, sleep disturbances, respiratory depression, sexual dysfunction, and inappropriate secretion of antidiuretic hormone (American Pain Society, 2008). The transdermal route has been associated with less constipation (Tassinari et al., 2008). Great interindividual variability exists in the side effects that patients experience. Oncology nurses need to perform systematic assessments to determine which side effects patients are experiencing and proceed to develop an appropriate management plan.

Constipation is the most common side effect and is estimated to occur in 40%–70% of patients on oral opioid analgesics (McNicol et al., 2005). Patients do not develop tolerance to opioid-induced constipation. At the time that the opioid prescription is written, patients should be started on a bowel regimen that includes a stool softener and a stimulant laxative to increase bowel motility. A useful laxative regimen includes docusate sodium (100–300 mg/day) with senna (2–6 tablets twice a day), laxative suppositories, or lactulose (Enck, 2009).

Patients will develop tolerance to the side effects of sedation and nausea and vomiting in about five to seven days if the opioid dose is not escalated. Sedation may not require treatment once the dose of the opioid analgesic is stabilized. Central nervous system stimulants (e.g., caffeine, methylphenidate) may be used to reduce opioid-induced sedation. Antiemetics may be required until patients develop tolerance to nausea and vomiting.

Usually, respiratory depression is not a significant clinical problem in patients with cancer who are on chronic opioid therapy. Caution is advised when opioid antagonists (e.g., naloxone) are given to patients who have received opioids for more than one week. In these cases, symptomatic respiratory depression should be treated with a dilute solution of naloxone (0.4 mg in 10 ml of saline) administered in 0.5 ml (0.02 mg) bolus IV push every two minutes as needed for reversal. The dose should be titrated to avoid precipitating profound withdrawal symptoms, seizures, and severe pain (Miaskowski et al., 2005).

In addition, patients and family caregivers may have numerous myths and misconceptions about cancer pain and its management, such as fear of addiction. Patient and family education should clarify these myths and misconceptions. In particular, patients and family care-
givers should be taught the differences between physical dependence, tolerance, and psychological addiction. They should understand that tolerance and physical dependence are expected to occur with long-term opioid treatment. The presence of tolerance and physical dependence does not equate with psychological addiction (American Academy of Pain Medicine, American Pain Society, & American Society of Addiction Medicine, 2001).

A pain management diary may be a useful tool to assist patients and family caregivers in evaluating the effectiveness of their pain management plan. Patients and family caregivers can be taught to use the diary data to adjust and titrate their dose of analgesic medication when changes in pain intensity occur. In addition, they should be taught how to communicate with their clinicians about unrelieved pain. Some patients may benefit from using a script to communicate with their clinician about pain management. Patients and family caregivers should receive a written pain management plan that includes the cause of pain; types of medications prescribed, their purpose, possible side effects, how to manage side effects, storage information, and how to titrate them; names and telephone numbers of people to call if their pain is not relieved or if they experience side effects; and nonpharmacologic options.

**Expected Patient Outcomes**

Chronic cancer pain is a multidimensional experience that affects patients’ physical, psychological, and social well-being (Brant, 2010a). The goals of cancer pain management are to reduce pain and improve patients’ level of function and quality of life. In addition, the achievement of optimal pain control with minimal side effects should improve patients’ mood, as well as their ability to interact with individuals who are important to their psychological and spiritual well-being.

Uncontrolled pain, on the other hand, can interfere with healing, function, and overall quality of life. Patients who are reluctant to report pain and take analgesics for pain should be reminded of the negative consequences of pain. Oncology nurses need to remember that unrelieved pain in patients can also have deleterious effects on family caregivers. For example, family caregivers who care for patients with cancer have been shown to report higher levels of anxiety, depression, fatigue, and caregiver strain, as well as decreased quality of life, compared to family caregivers who cared for pain-free patients with cancer (Black et al., 2011; Fletcher et al., 2008). Nurses need to encourage family caregivers to speak with patients about their pain experience and to work with them to achieve optimal pain control.

**Need for Future Research**

Most of the pharmacotherapeutic management of cancer pain is inferred from studies of other chronic pain conditions (e.g., diabetic neuropathy, postherpetic neuralgia) or is based on clinical experience. Little is known about the factors that predict interindividual differences in responses to specific analgesic medications in patients with cancer. Additional research is also warranted on optimal approaches to manage opioid-induced side effects. Research also is needed to determine the most effective methods for educating patients and family caregivers about cancer pain management.

Opportunity exists for expansion of patient-reported outcomes. Some studies have reported success with patient report of symptoms in the waiting room prior to ambulatory visits (Brant et al., 2011). Studies that examine patient portals with report of symptoms at home are lack-
ing. Technology offers great potential for patient-reported outcomes but is yet to be thoroughly explored.

Measures need to be developed for consistently reporting pain so that studies can be compared to yield best evidence. Breakthrough pain, for example, lacks a consistent approach because of the variability of its definition; therefore, comparison is difficult.

Throughout the body of pain research, clinically significant changes in pain levels should be established so that interventions can be measured that truly make an impact on pain, according to the patient’s perspective. Well-controlled randomized trials should be employed to test differences and yield meaningful results that are applicable in clinical practice.

Conclusion of Case Study

Recall that B.V. was admitted with a pain score of 7 on a 0–10 scale, which is considered a pain emergency. B.V. was admitted to the hospital and placed on the intractable pain protocol using IV morphine. B.V.’s oral morphine dose was 540 mg per day, thus calculated at 180 mg IV morphine over 24 hours. Per the intractable pain protocol, a continuous infusion was initiated at 8 mg/hour with an optional bolus dose of 4 mg every 10 minutes as needed. In this acute care setting, the nursing staff monitored B.V., and the patient received rapid titration of an IV opioid to quickly control the pain crisis. Each hour, the nurse titrated the basal rate and bolus dose when (a) respiratory status was stable, (b) pain intensity was 4 or greater, and (c) bolus doses were more than two per hour. For each titration, the basal rate was increased by one-third and the bolus dose was increased to equal 50% of the basal rate. The nurse performed two titrations within two hours to achieve comfort. B.V.’s pain intensity decreased to 2 on a scale of 0–10 at rest within two hours, and incident pain was rated at 4. Unfortunately, B.V.’s pain quickly escalated within 24 hours, and she developed myoclonus. An interdisciplinary team meeting was convened with the patient and family to discuss an intraspinal option. The patient opted for a tunneled epidural catheter that was connected to a pump delivering a basal rate and optional bolus dose. A trial was conducted prior to epidural placement, and B.V. reported complete disappearance of pain without side effects. She returned home one week following the hospital admission and was able to attend her daughter’s wedding.

Conclusion

Oncology nurses play a central role in helping patients to achieve optimal pain control. The cornerstone of cancer pain management is a comprehensive initial assessment and ongoing reassessment that evaluates the effectiveness of the pain management plan in terms of patients’ pain intensity, ability to function, mood, and quality of life. Patients with cancer and their family caregivers require education on how to use and titrate their analgesics to achieve optimal pain control and how to report or manage side effects of analgesic medications. Finally, oncology nurses need to encourage patients to incorporate nonpharmacologic interventions into their pain management plan and report pain when the desired comfort level is incongruent with their individual goal.

The authors would like to acknowledge Christine Miaskowski, RN, PhD, FAAN, for her contribution to this chapter that remains unchanged from the first edition of this book.
References


Case Study

C.S. is a 55-year-old woman who was diagnosed with multiple myeloma. During first-line therapy with vincristine, doxorubicin, and dexamethasone, she became partially disabled. C.S. was unable to work outside the home, mainly because of significant disease- and treatment-related fatigue. Although she was too fatigued for strenuous work, she was able to continue to help raise her three school-aged grandchildren. In addition to her fatigue, C.S. developed mild numbness and tingling in her feet, indicating the presence of chemotherapy-induced peripheral neuropathy (CIPN). At the time, she considered the peripheral neuropathy to be more of a nuisance than a true side effect of therapy. In fact, she never mentioned the numbness and tingling to her oncologist, and he never asked about it. C.S. also did not tell her oncology nurse about the peripheral neuropathy because it did not seem as important as learning effective strategies to manage the fatigue. C.S. wanted to get the most out of the limited time she had with her oncology nurse.

At C.S.’s next visit, her oncologist recommended a clinical trial using a combination of thalidomide and an investigational drug to treat her cancer. During the consent process, the nurse informed C.S. that CIPN is one of the side effects of thalidomide therapy. C.S. then indicated that she was already experiencing numbness and tingling in her feet. She asked the oncology nurse if the new cancer treatment might worsen her ongoing peripheral neuropathy symptoms. The nurse stated that participating in the clinical trial could indeed worsen her CIPN and may even cause her to develop new neuropathy symptoms. The oncology nurse also explained that the thalidomide dose may need to be reduced or stopped if the peripheral neuropathy becomes too severe. C.S. then realized for the first time what a devastating symptom CIPN could be.

Overview

Peripheral neuropathy is a broad term used to describe changes in sensory, motor, and autonomic nerve function that result from damage to the peripheral nerves of the body (National Institute of Neurological Disorders and Stroke, 2014b). Peripheral neuropathy is a complex phenomenon attributable to a number of distinct etiologies. Patients with cancer are at risk for developing peripheral neuropathy caused by their cancer, their cancer treatment(s),
and other comorbid illness. For example, amyloid deposits on peripheral nerves, a common manifestation of multiple myeloma, may cause people to be more susceptible to developing peripheral neuropathy. Patients with diabetes mellitus often develop peripheral neuropathy, and treatment with neurotoxic chemotherapy can intensify existing diabetes-related peripheral nerve damage. Peripheral neuropathy caused by neurotoxic anticancer drugs, or CIPN, is the main focus of this chapter.

Figure 21-1 lists common CIPN clinical manifestations. Although the most common manifestations are symptoms of numbness and tingling in the toes and fingers that appears in a symmetrical stocking-glove distribution, peripheral neuropathy can affect any body part that is innervated by peripheral nerves. In addition to numbness and tingling, other manifestations of CIPN include sensitivity to cold; burning, shooting, and electric shock–like sensations; neuropathic pain; muscle weakness; impaired balance; orthostatic hypotension; constipation; urinary retention; and erectile dysfunction (Argyriou, Bruna, Marmiroli, & Cavaletti, 2012; Hausheer, Schils, Bain, Berghorn, & Lieberman, 2006; Wickham, 2007; Windebank & Grisold, 2008). Because of the diversity of manifestations, the impact of CIPN can be serious. Impaired sensation in the upper and lower extremities can place patients at increased risk for mechanical or heat- or cold-induced injuries. Impaired ability to know where their limbs are in space (proprioception) can affect patients’ balance and can put them at risk for falls (Tofthagen, Overcash, & Kip, 2012). Altered sensation, pain, and numbness can affect patients’ ability to independently perform personal care needs such as dressing and hygiene. These same CIPN symptoms can threaten patients’ ability to maintain employment by making it difficult to complete tasks requiring normal sensation in the feet, hands, and fingers. In all cases, CIPN symptoms and their associated functional limitations can negatively influence the quality of life (QOL) for many cancer survivors.

General Causes

Peripheral neuropathies can be classified as either inherited or acquired (National Institute of Neurological Disorders and Stroke, 2014b). Inherited peripheral neuropathies are
Peripheral Neuropathy

the result of genetic miscoding or mutations. The most common form of inherited peripheral neuropathy is known as Charcot-Marie-Tooth disease, named after the three physicians who discovered the disease in 1886 (National Institute of Neurological Disorders and Stroke, 2014a). Charcot-Marie-Tooth disease (also known as hereditary motor and sensory neuropathy) develops slowly, causing progressive deterioration of peripheral nerves and eventual loss of muscle and sensory function in the extremities (National Institute of Neurological Disorders and Stroke, 2014a). Patients with the genetic abnormalities associated with inherited peripheral neuropathy are at increased risk for developing CIPN (Baldwin et al., 2012; Kroetz et al., 2010).

In contrast to inherited neuropathies, acquired peripheral neuropathies can be caused by a number of different etiologies, including trauma (e.g., burns, chemical injury, laceration), infection (e.g., bacterial and viral infections, such as the bacterium Borrelia burgdorferi, which causes Lyme disease, and the herpesviruses, which cause herpes zoster and herpes simplex infections), autoimmune disorders such as AIDS, systemic diseases (e.g., diabetes, kidney disease, alcoholism, vitamin deficiencies, vascular damage, cancer), and antineuritis (National Institute of Neurological Disorders and Stroke, 2014b). Sometimes the etiology of peripheral neuropathy is idiopathic in that no cause can be determined. Presentations of peripheral neuropathy can be acute or chronic, transient or persistent, mild to severe in intensity, and hardly noticeable or totally disabling.

Incidence

The incidence of CIPN varies widely based on many factors, such as neurotoxic drug type, dose, treatment frequency, and administration schedule, as well as the presence of comorbid illnesses also associated with peripheral neuropathy (Argyriou et al., 2012; Bergmann et al., 2011; Hausheer et al., 2006; Hertz et al., 2012; Kroetz et al., 2010; Schneider et al., 2011; Sissung et al., 2006; Visovsky, Meyer, Roller, & Poppas, 2008; Windebank & Grisold, 2008). CIPN incidence rates are 10%–100% (Argyriou et al., 2012; Smith, 2013). CIPN is probably more common than once thought because signs and symptoms are frequently overlooked by patients and clinicians. As illustrated in the case study at the beginning of this chapter, patients often hesitate to report CIPN symptoms for fear that doing so will distract their clinicians from more salient problems. Patients also may fail to report CIPN because of concerns that their symptoms will necessitate reduction in the dosage of life-prolonging and lifesaving antineuritis drugs. Clinician assessment practices also contribute to the incomplete knowledge regarding CIPN incidence and outcomes; continued reliance on inaccurate and unreliable CIPN assessment methods and inconsistent assessment in those receiving chemotherapy make it difficult to determine CIPN’s true incidence (Cavaletti et al., 2010; Frigeni et al., 2011; Griffith, Merkies, Hill, & Cornblath, 2010; Smith, 2013). Standardized use of better measurement tools and reporting methods is needed to advance the understanding of CIPN’s incidence and impact on clinical outcomes.

Risk Factors

Risk factors for CIPN include the presence of comorbid conditions such as diabetes, alcohol overuse, metabolic imbalances, vitamin $B_{12}$ deficiency, cachexia, HIV, or paraneoplastic syndrome; cancer type; and older age (Argyriou et al., 2012; Hausheer et al., 2006; Stubblefield et al., 2009; Windebank & Grisold, 2008). Several studies have also suggested
that genetic predisposition for developing CIPN may be an important risk factor for some patients (Baldwin et al., 2012; Beutler et al., 2013; Dennison et al., 2006; Hertz et al., 2013; Kroetz et al., 2010; Renbarger, McCammack, Rouse, & Hall, 2008; Schneider et al., 2011). Specifically, genetic polymorphisms linked with inherited neuropathy, race, and neurotoxic drug metabolism may be associated with increased risk of developing more severe CIPN. Additional studies are needed to validate these findings and determine how to harness insights to improve outcomes for patients determined to be at increased risk for CIPN based on genetic factors.

As noted earlier, some classes of chemotherapy drugs are more likely to cause peripheral neuropathy than others, although the reasons for this are not fully understood. Platinum analogs, taxanes, vinca alkaloids, proteasome inhibitors, and epothilones are well known to clinicians for their tendency to cause CIPN (Argyriou et al., 2012; Hausheer et al., 2006; Stubblefield et al., 2009; Windebank & Grisold, 2008). A summary of chemotherapy drugs known to cause peripheral neuropathy and the frequency of the sensory, motor, and autonomic neuropathy can be found in Table 21-1.

Factors associated with drug administration also may influence the risk of developing peripheral neuropathy (i.e., cumulative doses, individual dosage [usually measured in milligrams per meter of body surface area (mg/m2)], length of infusion, treatment frequency/dose density) (Argyriou et al., 2012; Hausheer et al., 2006; Stubblefield et al., 2009; Windebank & Grisold, 2008).

### TABLE 21-1 Neurotoxic Anticancer Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Sensory</th>
<th>Motor</th>
<th>Autonomic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epothilones</td>
<td>Ixabepilone</td>
<td>+++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Platinum analogs</td>
<td>Cisplatin</td>
<td>++</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Carboplatin</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxaliplatin</td>
<td>+++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Proteasome inhibitors</td>
<td>Bortezomib</td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Sedative hypnotics</td>
<td>Thalidomide</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taxanes</td>
<td>Docetaxel</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nab-paclitaxel</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Vinca alkaloids</td>
<td>Vinblastine</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vincristine</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

* The “+” symbols indicate frequency: + = seen in 5%–20% of patients; ++ = seen in 21%–50% of patients; +++ = seen in > 50% of patients.

Note. Based on information from Argyriou et al., 2011, 2012; Hausheer et al., 2006; Stubblefield et al., 2009; Windebank & Grisold, 2008.
Clinical Manifestations

Clinical manifestations associated with CIPN fall into three basic categories that correspond to the type of nerve being damaged: sensory, motor, and autonomic manifestations (see Figure 21-1). Sensory neuropathy occurs more often than motor or autonomic neuropathy, and its clinical manifestations are quite varied. Sensory symptoms commonly include a diminished ability to feel (hypoesthesia), numbness (anesthesia), increased sensation (hyperesthesia), abnormal sensations like tingling and prickling (paresthesias), and painful symptoms such as burning, shooting, or electrical sensations (dysesthesia) (Baron, Binder, & Wasner, 2010; Baron & Tölle, 2008). In addition, patients often develop allodynia (a painful response to a nonpainful stimulus) and hyperalgesia (a phenomenon where stimuli that would normally be only slightly painful are now very painful) (Baron et al., 2010). For example, patients with CIPN often feel pain simply when the bedsheets rest upon their toes. Although many of these sensations are triggered when the patient touches something, symptoms can occur spontaneously without an external stimulus. Occasionally, people with peripheral neuropathy lose the ability to accurately determine where their limbs are in space (proprioception), which affects balance and coordination. To compensate, patients often rely on visual cues by watching where they are actually placing their feet.

The most common manifestations of motor neuropathy are muscle weakness and loss of deep tendon reflexes (Dougherty, Cata, Cordella, Burton, & Weng, 2004). Weakness often becomes apparent when the patient is unable to turn on or off sink faucets, reports frequent tripping and falls, or has difficulty climbing stairs, walking, or driving. Yet, weakness in these circumstances is not always the direct result of CIPN because generalized weakness can occur from cancer and its treatment, inactivity, and other chronic illnesses. Sometimes, patients will develop a foot drop resulting from motor nerve injury. Autonomic symptoms of constipation, urinary retention, sexual dysfunction, and blood pressure alterations also may be manifestations of CIPN (Argyriou et al., 2012; Hausheer et al., 2006).

Pathophysiology

Having a basic knowledge of the structure and function of the nervous system can help nurses to better understand the clinical manifestations associated with CIPN. The nervous system is divided into central and peripheral portions. The brain and spinal cord make up the central nervous system (CNS), while the peripheral nervous system (PNS) consists of nerves and ganglia that are connected to the brain or spinal cord. These nerves and ganglia include (a) 12 pairs of cranial nerves (olfactory, optic, oculomotor, trochlear, trigeminal, abducens, facial, auditory-vestibular, glossopharyngeal, vagus, spinal accessory, and hypoglossal), (b) 31 pairs of spinal nerves (8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal), and (c) the corresponding dermatomes (Bear, Connors, & Paradiso, 2007). Peripheral nerves can be further divided into three categories: sensory, motor, or autonomic. Outgoing (efferent) nerve impulses leaving the brain and spinal column activate motor functions (skeletal and smooth muscle) and stimulate autonomic functions (which include involuntary and semi-voluntary functions such as heart rate, blood pressure, sweating, urinary retention, pupil size, and bowel function) (Bear et al., 2007). Incoming (afferent) impulses from peripheral nerves send information about temperature, touch, vibration, body position, and different types of pain to the CNS (Bear et al., 2007).

Exactly how chemotherapy damages nerves is not well understood, but several consistent findings may provide important clues. Exposure to chemotherapy often affects sen-
sory nerves before motor nerves; CIPN symptoms typically start in distal ends of the longest axons, proceeding up the feet, legs, hands, and arms in a “stocking and glove” fashion. In most cases, symptoms improve after chemotherapy is stopped. Because symptoms often start in the longest axons first, many researchers have focused on chemotherapy’s ability to disrupt a class of proteins involved in transporting energy and neurotransmitters up and down the length of the nerve (microtubules). In addition to altering microtubule function, chemotherapies that cause CIPN have been shown to cause nerve inflammation, changes to the channels that regulate ion movement, partial or total demyelination of nerves, and damage to the DNA and DNA repair pathways that support healthy nerve function (Argyriou, Koltzenburg, Polychronopoulos, Papapetropoulos, & Kalofonos, 2008; Carlson & Ocean, 2011; Gracias et al., 2011; Swain & Arezzo, 2008; Theiss & Meller, 2000). Taken together, these factors may lead to erratic nerve signaling and hyper-sensitivity. Changes to nerves in the periphery can lead to potentially permanent changes in nerve function at the level of the brain and spinal cord (known as central sensitization). A brief description of the most common neurotoxic drug classes follows. This chapter will not delve deeply into drug-specific pathophysiologic mechanisms because other excellent review papers have been published on this topic (see Argyriou et al., 2012; Hausheer et al., 2006; Windebank & Grisold, 2008).

**Microtubule-Stabilizing Agents**

Taxanes are commonly used to treat many cancer types (e.g., breast, lung, prostate, gynecologic). Taxane-induced peripheral neuropathy occurs in 8%–83% of patients receiving paclitaxel, docetaxel, and nab-paclitaxel (Smith, 2013). Taxanes cause sensory, motor, and autonomic neuropathy. Paclitaxel acute pain syndrome, pain experienced in the trunk, arms, and legs usually within the first week after paclitaxel administration, was once believed to be the result of musculoskeletal pathology. However, recent evidence suggests that this pain syndrome is another manifestation of peripheral nerve injury (Loprinzi et al., 2011).

Ixabepilone, a semisynthetic epothilone B analog, is a microtubule-stabilizing agent that has a safety profile similar to paclitaxel (Argyriou et al., 2012; Argyriou, Marmiroli, Cavaletti, & Kalofonos, 2011). Up to 88% of patients receiving ixabepilone will develop sensory CIPN (Argyriou et al., 2011). Motor neuropathy occurs as well but is less common.

**Platinum Analogs**

Platinum analogs also are used to treat many cancer types, such as lung, testicular, gynecologic, and colorectal cancers. Cisplatin, carboplatin, and oxaliplatin are examples of first-, second-, and third-generation platinum analogs, respectively. Treatment with these drugs is associated mainly with the development of sensory neuropathy. Carboplatin is the least neurotoxic of the three drugs. Unique to platinum-associated CIPN, symptoms often continue to worsen for several months after platinum treatment has stopped, termed coasting (Argyriou et al., 2012). Oxaliplatin causes two distinct types of neuropathy: first is an acute, largely reversible neuropathy, and the second is a more chronic, cumulative neuropathy (Argyriou et al., 2012; Gamelin, Boisdron-Celle, Morel, & Gamelin, 2006; Loprinzi et al., 2013). The acute neuropathy typically occurs within five days after each oxaliplatin dose. Patients report increased sensitivity when touching cold items, discomfort when swallowing cold liquids, muscle cramps, and throat discomfort (Gamelin et al., 2006; Loprinzi et al., 2013). Patients who experience acute oxaliplatin-induced neuropathy may be more likely to develop chronic CIPN (Loprinzi et al., 2011).
**Proteasome Inhibitors**

Bortezomib is a proteasome inhibitor that is commonly used to treat multiple myeloma and mantle cell lymphoma. Given that bortezomib is used most commonly to treat a condition that in itself can cause peripheral neuropathy (i.e., multiple myeloma), CIPN incidence due to the drug alone is difficult to ascertain based on data from multiple myeloma clinical trials. In a large phase III study (N = 672) of bortezomib, melphalan, and prednisone conducted with newly diagnosed patients with multiple myeloma, CIPN occurred in 47% (all grades) and 13% (grade 3 or higher) of participants (Dimopoulos et al., 2011). The presence of preexisting peripheral neuropathy and bortezomib cumulative dose are the main risk factors associated with the development of CIPN in this patient population (Argyriou, Iconomou, & Kalofonos, 2008; Dimopoulos et al., 2011). Common CIPN signs and symptoms include diminished reflexes as well as numbness, tingling, and neuropathic pain in the lower and upper extremities (Argyriou, Iconomou, et al., 2008; Chaudhry, Cornblath, Polydefkis, Ferguson, & Borrello, 2008).

**Hypnotic Sedatives**

Hypnotic sedatives such as thalidomide are another type of anticancer drug associated with the development of peripheral neuropathy. Thalidomide became infamous in the late 1950s and 1960s for its propensity to cause serious birth defects in pregnant women (Apfel & Zochodne, 2004; Fullerton & O’Sullivan, 1968; Ghobrial & Rajkumar, 2003). From 1956 to 1962, women who took thalidomide as a sleep aid and to prevent morning sickness gave birth to children with a unique physical deformity known as phocomelia. In these children, thalidomide crossed the uterine barrier and disrupted the formation of blood vessels (angiogenesis) to their newly developing arms and legs. The result was that children were born with shortened or absent long bones of the arms, and some had flipper-like hands or feet. Many years later, researchers explored whether this same ability of thalidomide to disrupt blood vessel formation could be harnessed to fight cancer cells. Subsequently, it was discovered that thalidomide did in fact inhibit angiogenesis in and around malignant tumors, leading to inhibition of cancer cell growth (Amato, 2002). Mild thalidomide-induced neuropathy occurs in 20%–85% of those receiving the drug for six months or more (Argyriou et al., 2012; Chaudhry et al., 2002, 2008). The peripheral neuropathy associated with thalidomide is similar to what is seen with other neurotoxic anticancer drugs. Studies of thalidomide-induced peripheral neuropathy suggest that symptoms may be reversible if treatment is stopped when numbness in the toes or feet is first experienced. However, if treatment continues, peripheral neuropathy may become permanent (Apfel & Zochodne, 2004).

**Vinca Alkaloids**

Vinca alkaloids are extracted from the periwinkle plant and include vinblastine, vincristine, and vinorelbine tartrate (a semisynthetic derivative of vinblastine) (Argyriou et al., 2012; Hausheer et al., 2006; Windebank & Grisold, 2008). These drugs are used to treat a wide variety of cancers, including childhood leukemia. Unlike other types of CIPN in which the symptoms are primarily sensory in nature, vinca alkaloid–induced peripheral neuropathy is characterized by sensory, motor, and autonomic signs and symptoms. Cranial nerves can be affected, resulting in double vision (diplopia), jaw pain, metallic taste, and vocal cord paralysis. In addition to progressive numbness and tingling, patients experience the loss of deep tendon reflexes, muscle weakness, and constipation (Argyriou, Kyritsis, Makatsoris, & Kalofonos, 2014).
Assessment

Comprehensive CIPN measurement should include the evaluation of three components: symptoms, objective signs of nerve function based on physical examination, and patient-reported effects on QOL and functional ability (Cavaletti et al., 2010; Griffith et al., 2010). Obtaining a thorough health history is also important. When obtaining a health history, nurses should inquire about the following.

- Diabetes, alcohol use, vitamin B₁₂ deficiency, paraneoplastic syndrome, HIV infections, atherosclerosis, and vascular insufficiency
- Hereditary neuropathy
- Nutritional status
- Change in vision or hearing
- Gait stability, falls, and tripping
- Dropping things, trouble dressing, or difficulty picking up coins
- Painful numbness and tingling (neuropathic pain)
- Nonpainful numbness, tingling, and abnormal sensations in extremities
- Bowel and bladder habits
- Medications, including prescription and over-the-counter medications, herbs, vitamins, and alternative therapies
- Previous cancer therapies, radiation, and/or surgery for cancer
- Ability to perform daily activities and performance status
- Employment characteristics, such as current status, type of work, and occupational exposures to hazards

Baseline (prechemotherapy) and ongoing assessments will help patients and clinicians to keep apprised of changes over time. Prospective screening for signs of CIPN during chemotherapy and ongoing monitoring once symptoms start can inform the need to dose-reduce neurotoxic chemotherapy, help tailor nursing interventions, and raise awareness of advancing toxicity before severe and protracted symptoms develop (Argyriou et al., 2012; Cavaletti et al., 2010; Griffith et al., 2010; Smith, 2013). Comprehensive CIPN assessment should include assessment of large- and small-fiber peripheral nerve function. A simple evaluation for adequate large-fiber peripheral nerve function can be accomplished by assessing vibration sensibility by placing a vibrating 128 Hz tuning fork over a bony prominence on an extremity, such as a knuckle, and also by evaluating for a sense of touch by assessing the patient’s ability to feel a cotton swab lightly brushed against the fingers or toes when the patient’s eyes are closed. Small-fiber peripheral nerve function can be quantified by assessing the patient’s ability to sense the coldness of a metal tuning fork when placed on the skin. Table 21-2 contains more details on the components of a neurologic examination. While conducting a physical assessment, nurses should pay particular attention to the following.

- Vital signs—orthostatic changes in heart rate and blood pressure
- Gait evaluation—instability and hugging the wall while walking
- Decreased muscle strength
- Coordination—speed and accuracy of rapidly alternating hands and touching the nose with s finger
- Movement—tremors and spasms
- Deep tendon reflexes—diminished or absent; Achilles reflex may be first deep tendon reflex lost
- Sensations—abnormal responses to sharp and dull pain, vibration, position, temperature, and touch
Although most physical examination approaches are not difficult to learn how to perform and interpret, it is important that clinicians undergo training in how to conduct CIPN assessments in a standardized fashion so that results are reproducible, accurate, and interpretable.

**Neurologic Tests**

Neurophysiologic testing, such as nerve conduction tests, electromyography, skin and nerve biopsies, quantitative sudomotor axon reflex testing (known as QSART), and tilt table tests, is available but not widely used in oncology clinical practice settings (see Table 21-3) (Bril et al., 2011; England et al., 2009). These tests, usually conducted by a neurologist, are mainly used when CIPN signs and symptoms are atypical. Because CIPN is an expected side effect, and the cost, inconvenience, and discomfort associated with these tests are significant, most patients with CIPN are not evaluated by a neurologist.

**Measurement Tools**

Several grading scales are available for quantifying CIPN. These include the Eastern Cooperative Oncology Group system and the National Cancer Institute Cancer Therapy Evaluation Program’s Common Terminology Criteria for Adverse Events (see Table 21-4). Grading

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**Table 21-2: Objective Measures of Neuropathy**

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Nerve Fibers Tested</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semmes-Weinstein monofilaments</td>
<td>Small</td>
<td>With the patient’s eyes closed, apply the finest filament perpendicularly to specified locations on each hand and foot in a three-second sequence. Instruct the patient to note when the filament is felt. If the filament is not felt at a specific location after two attempts, the next-largest monofilament is used for testing.</td>
</tr>
<tr>
<td>Temperature sensation</td>
<td>Small</td>
<td>Place a cold metal tuning fork on the skin, beginning at the toes, and assess additional locations distally to proximally. Ask the patient whether the tuning fork feels cold.</td>
</tr>
<tr>
<td>Vibration sensation</td>
<td>Large</td>
<td>Strike a 128 Hz tuning fork with the heel of the hand and hold stem to a bony surface of the index finger or great toe, moving from distal to proximal areas if no vibration is felt.</td>
</tr>
<tr>
<td>Sharp-versus-dull sensation</td>
<td>Large</td>
<td>Two objects are used, one sharp and the other dull or soft. As each object is randomly applied to different areas on the extremities, the patient states whether the sensation felt is sharp or dull.</td>
</tr>
<tr>
<td>Deep tendon reflexes</td>
<td>Large</td>
<td>A reflex hammer is used to strike the Achilles and patellar tendons. After the strike of the hammer, a quick reflex resulting in plantar flexion of the foot and extension of the leg results. Reflexes are graded from 0 (absent) to 4 (enhanced).</td>
</tr>
<tr>
<td>Proprioception</td>
<td>Large</td>
<td>Testing of proprioception can include several tests that relate to balance and coordination. Such tests include the Romberg test, up/down test, finger-to-nose test, and thumb-to-finger test.</td>
</tr>
</tbody>
</table>

### TABLE 21-3 Neurologic Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Evaluates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve conduction studies</td>
<td>Nerve transmission of electric stimuli</td>
</tr>
<tr>
<td>Electromyography</td>
<td>Electric activity within muscle</td>
</tr>
<tr>
<td>Skin biopsy</td>
<td>Loss of epidermal nerve fibers (small-fiber neuropathy)</td>
</tr>
<tr>
<td>Quantitative sudomotor axon reflex test</td>
<td>Autonomic nerve fibers that stimulate sweating</td>
</tr>
<tr>
<td>Tilt table test</td>
<td>Autonomic nerve involvement; changes in blood pressure and pulse</td>
</tr>
<tr>
<td>Nerve biopsy</td>
<td>Vasculitis; inflammation; demyelination; amyloid deposits</td>
</tr>
</tbody>
</table>

### TABLE 21-4 Chemotherapy-Induced Peripheral Neuropathy Grading Scales

<table>
<thead>
<tr>
<th>Tool</th>
<th>Type of Neuropathy</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Eastern Cooperative Oncology Group Common</td>
<td>Motor</td>
<td>Subjective weakness; no objective findings</td>
</tr>
<tr>
<td>Toxicity Criteria</td>
<td>Sensory</td>
<td>Mild paresthesias; loss of deep tendon reflexes</td>
</tr>
<tr>
<td>National Cancer Institute Common Terminol</td>
<td>Motor</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
</tr>
<tr>
<td>ogy Criteria for Adverse Events (version 4.03)</td>
<td>Sensory</td>
<td>Asymptomatic; loss of deep tendon reflexes or paresthesia</td>
</tr>
</tbody>
</table>

ADL—activities of daily living

*Note.* Based on information from Eastern Cooperative Oncology Group, 2007; National Cancer Institute Cancer Therapy Evaluation Program, 2010.
scales are not all the same, and because the grading categories are not clearly defined, different clinicians may assign different grades to the same patient, illustrating poor reliability. For example, a small study of two neurologists who assessed 37 patients using different grading scales demonstrated poor interobserver agreement (Postma et al., 1998). Although easy to use, the grading scales are insensitive and unreliable. Consequently, they do not consistently and accurately capture CIPN presence and severity (Cavaletti et al., 2010; Griffith et al., 2010; Smith, Cohen, Pett, & Beck, 2011).

The Total Neuropathy Score (TNS) is a composite measure that can be used to quantify CIPN signs and symptoms, as well as nerve conduction study findings. However, the original TNS has been critiqued for not including an assessment of pain severity and for being too burdensome, and this has led to the development and testing of more abbreviated versions (Smith, Beck, & Cohen, 2008). The TNS’s psychometric properties have been extensively evaluated (Cavaletti et al., 2010; Griffith et al., 2010; Smith et al., 2008). Based on findings from 12 studies evaluating the TNS, mounting evidence supports that the TNS and its short-form versions are sensitive, reliable, valid, and responsive when used in adult and pediatric populations (Cavaletti et al., 2003, 2007; Chaudhry et al., 2002; Chaudhry, Rowinsky, Sartorius, Donehower, & Cornblath, 1994; Cornblath et al., 1999; Gilchrist & Tanner, 2013; Gilchrist, Tanner, & Hooke, 2009; Smith et al., 2011; Smith, Li, et al., 2013; Smith, Cohen, Pett, & Beck, 2010; Wampler et al., 2006). The shorter versions have the advantage of being easier to use in busy clinical settings.

Experts suggest that having patients complete a patient-reported outcome (PRO) measure enhances the evaluation by providing information regarding CIPN-related effects on function and QOL from the patient’s perspective (Cavaletti et al., 2010; Griffith et al., 2010). However, a major concern is that PRO measures are burdensome for patients. Because of this concern, PRO measures are currently used mainly as research tools. Implementation in busy oncology practice settings will require new approaches to automate instrument administration, scoring, and interpretation so that patients can become more engaged in the CIPN assessment process without placing additional burden on clinicians to administer and score a PRO measure.

Two PRO measures have been tested in oncology settings and could be used in clinical practice. The Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-Ntx) questionnaire is a 38-item survey that measures QOL and includes an 11-item neurotoxicity subscale that measures the domains of sensory, hearing, and motor function and dysfunction. It was designed to measure platinum- and taxane-induced neurologic symptoms in women with breast cancer on clinical trials. Huang, Brady, Cella, and Fleming (2007) were able to condense the evaluation to a four-item scale that is as reliable as and more efficient than the 11-item scale (see Figure 21-2), making the tool more user-friendly (Huang et al., 2007). The 20-item European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy Scale (QLQ-CIPN20) is another CIPN PRO measure that should be considered for future use (Postma et al., 2005). The QLQ-CIPN20 contains nine items assessing sensory function, eight items assessing motor function, and three items assessing autonomic function; two studies support its reliability and validity (Postma et al., 2005; Smith, Barton, et al., 2013).

Earlier detection of and routine monitoring for CIPN are likely to lead to more

<table>
<thead>
<tr>
<th>FIGURE 21-2</th>
<th>Four Sensory-Focused Items of the FACT/GOG-Ntx Subscale</th>
</tr>
</thead>
<tbody>
<tr>
<td>• I have numbness or tingling in my hands.</td>
<td></td>
</tr>
<tr>
<td>• I have numbness or tingling in my feet.</td>
<td></td>
</tr>
<tr>
<td>• I feel discomfort in my hands.</td>
<td></td>
</tr>
<tr>
<td>• I feel discomfort in my feet.</td>
<td></td>
</tr>
</tbody>
</table>

FACT/GOG-Ntx—Functional Assessment of Cancer Therapy/ Gynecologic Oncology Group–Neurotoxicity

Note. Based on information from Huang et al., 2007.
timely chemotherapy dose modifications and subsequently could prevent severe disability, injury due to falls, chronic pain, and diminished QOL. Yet, despite having adequate knowledge regarding the importance of CIPN monitoring, clinicians do not routinely assess CIPN for several reasons (Binner, Ross, & Browner, 2011). Comprehensive assessment takes too much time to complete, and clinicians lack knowledge and confidence regarding how to conduct the assessment (Binner et al., 2011; Smith, 2013; Smith et al., 2009). In addition to clinician-related barriers, CIPN is frequently undetected because patients are often reluctant to report their symptoms (Binner et al., 2011; Smith et al., 2009). Patients may be aware that cancer therapies may be reduced, delayed, or completely stopped as a result of peripheral neuropathy. This may cause them to be reluctant to disclose symptoms that are not readily apparent. Moreover, CIPN is quite different from many of the side effects of cancer treatments. Many of the other side effects have visual confirmations that the patient is experiencing toxicity, whereas peripheral neuropathy is more subtle. Markman (2006) suggested that the sharp contrast between the abrupt treatment-induced emesis and bone marrow suppression and the subtle onset of peripheral neuropathy contributes to peripheral neuropathy being underappreciated and underreported.

**Evidence-Based Interventions**

The Oncology Nursing Society (ONS) Putting Evidence Into Practice (PEP) Chemotherapy-Induced Peripheral Neuropathy Team conducted an extensive literature review of interventions to prevent or reduce the effects of peripheral neuropathy for people with cancer. The project team then provided a critical analysis of the data based on their scientific merit as being evidence-based. Evidence-based analyses enhance real-time application of scientifically sound research, when available, and guide oncology nursing care with expert opinion when research evidence is not available.

The ONS PEP Chemotherapy-Induced Peripheral Neuropathy Team was not able to recommend any intervention to prevent or reduce peripheral neuropathy, nor was it able to provide recommendations that are likely to be effective for nursing practice (Visovsky, Collins, Abbott, Aschenbrenner, & Hart, 2007). These conclusions were based on the lack of strong evidence to support prophylactic or therapeutic interventions. However, the team provided expert opinion on five low-risk nursing interventions (see Figure 21-3).

The American Society of Clinical Oncology published clinical guidelines for CIPN prevention and treatment based on a systematic review of 48 randomized controlled trials (Hershman et al., 2014). Based on the results of a rigorous process for evaluating the level of the current scientific evidence, no interventions currently can be recommended for preventing CIPN or for the treatment of nonpainful CIPN symptoms (e.g., numbness, tingling). Most concerning is that CIPN in some studies actually worsened as a result of the experimental intervention. This illustrates the importance of teaching patients that untested drugs, herbal remedies, and other over-the-counter agents should not be used until their efficacy and safety have been established.

For established CIPN symptoms, two recently completed phase III trials have provided moderately strong evidence of efficacy. Smith and colleagues tested the efficacy of duloxetine 60 mg daily for the treatment of painful CIPN caused by paclitaxel or oxaliplatin (N = 231) (Smith, Pang, et al., 2013). Duloxetine-treated patients reported a significant decrease in average pain compared to those receiving placebo (p = 0.003). QOL also improved to a greater degree in the duloxetine group versus placebo-treated patients (p = 0.03). Another phase III study (N = 208) demonstrated that topical treatment with baclofen, amitriptyline, and ketamine (BAK) applied directly to the feet and hands decreases motor neuropathy symptoms (p = 0.021) (Barton et al., 2011). Sensory neuropathy symptoms also improved, but the
findings did not meet the *a priori* standards for statistical significance (*p* = 0.053). Duloxetine and BAK side effects in both studies were minimal and no different from placebo. Both the Smith, Pang, et al. (2013) and the Barton et al. (2011) studies should be replicated via a second phase III trial to verify that the results are true.

### Quality of Life and Functional Outcomes

CIPN has a negative influence on functional capacity and QOL. Peripheral neuropathy is a daily nuisance that interferes with a person’s full enjoyment of life. Oncology nurses, through their knowledge of CIPN etiology, symptoms, and treatment options, have the opportunity to improve patients’ QOL.

Bakitas’ (2007) qualitative research study (*N* = 28) on the experience of CIPN highlighted how peripheral neuropathy symptoms negatively influence functional, social, familial, and occupational dimensions of patients’ lives. Participants described CIPN symptoms as “painful,” “annoying,” and “unpleasant” and remarked on how symptoms made exercise, grocery shopping, housework, hobbies, and work more difficult (Bakitas, 2007). Importantly, half of the research participants did not recall being told to expect peripheral neuropathy as a side effect of their cancer treatment. This is particularly important in light of the findings from another qualitative study (*N* = 20) suggesting that when patients expected CIPN symptoms, they managed them more effectively (Boehmke & Dickerson, 2005).

Several studies have suggested that people with peripheral neuropathy are at an increased risk for falling (Stubblefield, McNeely, Alfano, & Mayer, 2012; Thurman, Stevens, & Rao, 2008; Tofthagen et al., 2012). Physical therapy may be helpful to decrease fall risk. For example, physical therapy may include neurostimulation, muscle strengthening, low-impact exercise, massage, whirlpool therapy, foot-drop prevention, hand exercises, and acupuncture (Armstrong, Almadrones, & Gilbert, 2005; Wickham, 2007). An occupational therapist may offer helpful strategies to maintain or improve functional disabilities. For example, an occupational therapist may provide instructions on the proper use of orthopedic devices to facilitate self-care hygiene.

### Patient Teaching Points

Although no strong evidence is available to support nursing interventions for CIPN, the ONS PEP resource indicates that education and support to preserve patient safety may prevent or reduce the effects of peripheral neuropathy for people with cancer (Visovsky et al., 2007).
2007). In addition, nurturing a trusting, therapeutic relationship will promote self-disclosure of symptoms and optimize oncology nursing care.

Several commonsense, low-risk CIPN interventions seem reasonable, despite lack of scientific evidence supporting their efficacy. Experts recommend that when teaching patients about CIPN, nurses should encourage patients to use several strategies for minimizing CIPN-related negative outcomes (Visovsky et al., 2007). These strategies focus on encouraging patients to report their symptoms, as well as several safety-enhancing approaches (see Figure 21-3).

Need for Future Research

Given the current lack of strong evidence supporting the use of CIPN interventions, additional research is needed to uncover effective treatments and nursing care approaches. Data outcomes from randomized controlled clinical trials will provide the strongest evidence to support evidence-based practice. Scientists continue to conduct studies exploring pathophysiologic mechanisms, risk factors, patterns, assessment approaches, and potential interventions. The anticipated outcomes of this work are decreased symptom severity, improved function and QOL, and optimized cancer treatment efficacy when using neurotoxic anticancer drugs.

Conclusion of Case Study

Prior to the third cycle of C.S.’ therapy, her oncology nurse notes a change in the patient’s neuropathy symptoms. C.S. previously had denied having trouble picking up coins, buttoning her clothes, and tying her shoes, but now she hesitates with her responses and gazes down at her untied shoe. C.S. was reluctant to disclose the changes because she did not want anything to interfere with the proposed treatment plan. C.S. recalled her oncology nurse previously advising her that sometimes the medication needs to be reduced or stopped completely when peripheral neuropathy worsens. The oncology nurse senses the patient’s anxiety and notes a change in her physical appearance. In addition to the untied shoe, a button on her blouse was not fastened. The oncology nurse provides reassurance that disclosing the signs and symptoms of peripheral neuropathy is very important for C.S.’ overall treatment plan and may prevent severe and permanent complications. A thorough health history, a comprehensive physical examination, and information obtained using a PRO measure would inform the treating physician and nurse regarding the need for chemotherapy dose modifications to prevent further worsening of C.S.’ symptoms.

The oncology nurse is aware that education and support to preserve the patient’s safety are recommended nursing practice interventions (Visovsky et al., 2007). In addition to stressing the importance of promptly sharing signs and symptoms of peripheral neuropathy, she teaches C.S. what she can do to ensure her safety. This includes strategies to prevent falls and protect her extremities. Because C.S. may not be able to sense the position of her feet, she should watch her feet as she walks. The oncology nurse stresses that C.S. should practice this skill in a level area that is free of hazards. She advises that it may take some time for C.S. to become accustomed to looking down at her feet as she also gazes forward. Other safety tips to prevent falls include keeping walkways well lighted, removing scatter rugs, installing handrails as needed, using assistive mobility devices, and consulting with a physical therapist.
C.S. can adapt strategies used by people with diabetes who have peripheral neuropathy to care for her extremities. She should avoid wearing restrictive shoes and clothing. She should inspect her feet and hands for injuries that may result from pressure, penetrating objects, irritants, and temperature changes. These injuries may occur even without C.S. being aware of them.

Recalling that peripheral neuropathy can cause autonomic dysfunction in addition to sensory and motor dysfunction, the oncology nurse teaches C.S. how to manage postural hypotension, constipation, and urinary retention. She should dangle her feet before standing; change positions slowly, especially when moving from lying to standing; maintain a high-fiber diet; and drink adequate amounts of fluids. C.S. should report vertigo and imbalance, which could be symptoms of postural hypotension, as well as changes in her bowel and bladder habits, which could be symptoms of constipation and urinary retention. Lastly, the nurse teaches C.S. to report painful CIPN if it develops. She informs C.S. that treatments exist for painful symptoms that might be effective and well tolerated (Hershman et al., 2014; Smith, Pang, et al., 2013; Visovsky et al., 2007).

C.S. understands that the treatment dose reduction is necessary to prevent worsening and permanent peripheral neuropathy. She realizes the importance of reporting the signs and symptoms of peripheral neuropathy. C.S. feels empowered through the education provided to help with the assessment and management of CIPN.

**Conclusion**

Patients may underreport symptoms and minimize the severity of disability associated with peripheral neuropathy. CIPN-causing anticancer drugs may be delayed, dose-reduced, or stopped completely as a result of reporting CIPN. Therefore, patients may stretch their comfort zone and safety limits beyond normal capacities in order to continue with therapy as originally scheduled. Oncology nurses have an essential role to educate patients about the clinical manifestations of peripheral neuropathy and the value of reporting symptoms. Peripheral neuropathy can be distressing, causing pain and limiting function. CIPN symptoms may diminish with chemotherapy modifications or resolve completely after chemotherapy has stopped. Scientists have discovered effective interventions for painful CIPN, but no preventive treatments are known.

As indicated by the lack of scientific evidence supporting interventions to prevent or reduce the effects of peripheral neuropathy for people with cancer, additional research is needed to provide strong evidence for practice. Oncology nurses can help to provide evidence for practice by becoming more involved with scientifically sound clinical research and encouraging patients to participate.

*The authors would like to acknowledge Barbara A. Biedrzycki, MSN, CRNP, AOCNP®, for her contribution to this chapter that remains unchanged from the first edition of this book.*

**References**


CHAPTER 22

Sexuality and Reproductive Issues

Patricia W. Nishimoto, RN, DNS, FT, FAAN, and Debra D. Mark, PhD, RN

Case Study

M.K, a 76-year-old Caucasian man, has been diagnosed with stage II prostate cancer. He and his wife enjoy traveling, dancing, and maintaining an active lifestyle. Before making a treatment decision, they attended a local prostate cancer support group, searched the Internet, and spoke with M.K’s surgeon. Today M.K. is being discharged from the hospital, and the nurse is providing discharge instructions. He looks at his wife and says, “After 52 years of marriage, I guess the most important thing is that I’m still healthy enough to take out the garbage, right dear?” M.K’s wife, with tears in her eyes, squeezes his hand and whispers, “I love you.”

Although two more patients are awaiting discharge, the nurse takes a seat, establishes eye contact, and says, “It sounds like you have concerns about what life is going to be like now that you’ve had surgery.” He answers, “That’s all right, nurse. I know you’re busy. We’ll be fine. We’ve had 52 years of a great marriage, and that’s more than most.”

Overview

Thirty years ago, cancer commonly came with a terminal diagnosis. Today, survivorship is at the forefront of oncology care, with an emphasis on quality of life (QOL) (Brotto et al., 2008; Ramirez et al., 2010). Unbeknownst to many healthcare professionals, three of seven essential components identified for successful survivorship care relate to aspects of sexuality: (a) assessment of medical and psychosocial late effects, (b) intervention for consequences of cancer and its treatment, such as sexual dysfunction, and (c) intervention for psychological distress experienced by cancer survivors and their caregivers (Hewitt, Greenfield, & Stovall, 2006).

It is often assumed that cancer survivors report higher levels of sexual dysfunction. Yet, 10%–65% of the general adult U.S. population report sexual dysfunction. The incidence of sexual dysfunction in cancer survivors is consistent with the general population—41% of cancer survivors experience sexual dysfunction, and 52% have alterations in body image (Tierney, 2008; Zebrack, Foley, Wittmann, & Leonard, 2010). These changes affect not only the
patient but also the partner (Altschuler et al., 2009; Antoine, Vanlemmens, Fourmier, Trocmé, & Christophe, 2013; Gilbert, Ussher, & Hawkins, 2009; Kadmon, Ganz, Rom, & Woloski-Wruble, 2008; Tierney, 2008).

Although sexual dysfunction during cancer treatment may occur and can have a negative effect on QOL, not all who are diagnosed with cancer are so affected (Hautamäki-Lamminen, Lipiäinen, Beaver, Lehto, & Kellokumpu-Lehtinen, 2013; Kingsberg, 2010). Many have noted that a diagnosis of cancer can actually result in improved QOL and intimacy (Lindau, Surawska, Paice, & Baron, 2011; Neuman, Park, Fuzesi, & Temple, 2012; Ohlsson-Nevo, Andershed, Nilsson, & Anderzén-Carlsson, 2012; Ussher, Perz, & Gilbert, 2012). Because cancer and its treatment can alter sexual function in both positive and negative ways, this chapter focuses on altered sexuality patterns and not sexual dysfunction.

Being cognizant of the physical care of cancer survivors is no longer sufficient. Care must be expanded to focus on QOL, which is influenced by healthy sexual function (Kingsberg, 2010). By bringing up the topic of sexuality as a routine part of nursing care, nurses acknowledge its importance, legitimacy, and impact on QOL for survivors. Rather than implying that sexual changes are the inevitable “cost” of treatment, it is the role and responsibility of nurses caring for cancer survivors to create new avenues of sexual functioning for survivors and their partners (Bolte & Zebrack, 2008; Kingsberg, 2010).

Why is it the nurse’s responsibility to bring up the topic of sexuality? Discussing sexual issues may be an unknown territory to the patient (Klaeson, Sandell, & Berterö, 2011; Sekse, Raaheim, Blaaka, & Gjengedal, 2010). That can become a barrier when patients are uncertain as to which words to use to discuss sexuality and worry about sounding unsophisticated, crass, or superficial (Krebs, 2008).

Too often it is assumed that if a patient has a problem, he or she will bring it up at appointments. However, when questions at appointments are focused on physiologic recovery, the healthcare team gives the message that sexuality may not be important or a “legitimate” topic (Behrend, 2013). Barriers to engaging in a conversation about sexuality include resource-limited systems that do not allow time to explore the psychological, relational, and social components of survival; a nurse’s discomfort level; lack of time, knowledge, evidence, privacy, or education; the misbelief that it is not part of nursing care; perceived risk of potential legal liability; and societal or personal values related to the discussion of sexuality with someone who is not married, has a same-sex partner, is elderly, or is critically ill (Behrend, 2013; Flynn, Kew, & Kiselny, 2009; Hordern et al., 2009; Julien, Thom, & Kline, 2010; Krebs, 2008; White, Faithfull, & Allan, 2013). Even among the few nurses who do discuss sexual concerns with their clients, to be effective, the discussion cannot be a onetime event but rather must be an ongoing conversation (Galbraith, Hays, & Tanner, 2012). After diagnosis, survivors often discover aspects of changed function that may not be realized at the earlier phase of their recovery. This is borne out by the survivors of childhood malignancies, who require age-appropriate education throughout the trajectory (Zebrack et al., 2010).

Patients may feel a sense of loneliness, shame, or even embarrassment when they do not have the opportunity to talk with their providers. Lack of communication can underscore the fear that cancer is a stigma, especially if it is a malignancy of a sexual organ or if it is a human papillomavirus (HPV)-related malignancy (e.g., anal, cervical, vulvar, vaginal, and head and neck cancers). Concern can be intensified if there is a fear that HPV-related malignancies might be sexually transmitted to a partner (Goodwin, 2013).

Through the lens of evidence-based literature, this chapter discusses alterations in sexual function. The phrase was chosen by the authors to reinforce that changes are not always negative. Cancer can be, and often is, life changing. Survivors have the opportunity to reflect on their experiences and can use those reflections to build their new identity (Klaeson et
al., 2011). Symbolic Interaction (Blumer, 1969) is the theory that helps explain that ability of self-reflection, gaining a sense of the “new me,” and explains how intertwined in that recreation of self are society’s messages about sexuality, how nurses react to patients’ questions about sexuality, and how partners may react. Survivors have the opportunity to have a more authentic life when they reflect and create their “new” selves (Sekse et al., 2010).

Nurses are in a key position to assess and intervene to facilitate that growth (Galbraith et al., 2012). Overlaying a Symbolic Interaction framework can facilitate nurses to “de-medicalize” sexuality and be aware of biomedical aspects while also addressing the broader psychosexual issues (White et al., 2013). This framework potentiates an increased focus on the psychosocial variables, which have been found to be more powerful than biologic variables (Kingsberg, 2010).

To meet the evidence-based challenge of this chapter, the first thought was to include only the two sexuality-related concerns that have strong (levels I and II) evidence-based interventions: erectile dysfunction (ED) and infertility. This approach would have left out three commonly identified concerns of patients—dyspareunia, body image, and changes in libido—as these concerns do not yet have solid research findings surrounding treatment. Typically, patients ask their nurses about all five concerns; hence, they have been included in this chapter. To avoid repetition, expected outcomes and teaching points common to all five are discussed at the end of the chapter.

Erectile Dysfunction

Overview

Busy oncology nurses may be tempted to focus on helping men understand their new diagnosis of cancer and ignore issues of ED. Yet, it is at the moment of deciding whether or not to have a physical examination that many men begin to question how screening, diagnosis, and treatment may affect their sexual function. If sexuality is not directly discussed, nurses may later learn that patients selected less-than-optimal treatment because of unspoken fears or misunderstandings. When men are hesitant to discuss sexual issues with their healthcare team, they may try home remedies to regain erectile function, and those “remedies” can ultimately endanger their health. Selection of less-than-optimal treatment for cancer and possible risks of home remedies are two reasons why oncology nurses need to address ED with their patients.

Definition

Erectile dysfunction is the inability to achieve or maintain an erection for satisfactory sexual performance and is not unique to men diagnosed with cancer (Albaugh, 2010; Heidelbaugh, 2010). This definition is purposefully selected so that it applies to both heterosexual and homosexual men. ED is estimated to happen in up to 1 in 3 men in the United States (Heidelbaugh, 2010). Because ED can be caused by cancer or its treatment, oncology nurses need to have information about ED to address patient concerns and prevent it from becoming an invisible concern (Dowswell et al., 2011).

Risk Factors

When a patient complains of ED, nurses should not automatically assume it is due to cancer. Noncancer-related risk factors affect ED as well. These include age, obesity, and medica-
tions (see Figure 22-1); diseases such as diabetes, hypertension, hypogonadism, heart disease, neurologic conditions, atherosclerosis, and hypercholesterolemia; use of alcohol, tobacco, or recreational drugs; depression; pain; anxiety; fatigue; and nerve damage. Cultural or religious beliefs, such as the belief that the cancer was caused by past sexual misbehavior, may contribute to the belief that as a consequence, ED is a punishment (Heidelbaugh, 2010; Marberger, Wilson, & Rittmaster, 2011). Commonly overlooked risk factors for ED may be related to the health of the partner and the partner’s interest in sexual activity.

Often, it is not the specific cancer diagnosis that directly affects ED but rather the symptoms surrounding cancer, such as fatigue. Treatment modalities such as radiation therapy, hormone therapy, chemotherapy, and surgery can affect the risk of ED. For example, some surgeries (e.g., retroperitoneal lymph node dissection; rectal, bladder, penile, or prostate surgery) increase the risk of ED. Predictors of erectile function following prostatectomy include the patient’s age; the grade, stage, and localization of disease; degree of nerve preservation; preoperative erectile function; and if or when penile rehabilitation is started (Gonzalgo & Eastham, 2007).

Pathophysiology

Why It Happens

To understand ED, it helps to understand erection physiology. The penis is innervated by autonomic nerves. When there is a stimulus, smooth muscle relaxation takes place and blood begins to fill the penis. Erection occurs as blood accumulates in the penis.

ED can occur as a result of physical or psychological reasons. Physiologic reasons include changes due to aging, damage to nerve or venous blood flow, and response to diagnosis or treatment side effects. The pathophysiology of ED caused by aging is morphologic deterioration of the corpus cavernosa, which is the penile tissue that fills with blood during erection. ED may be a consequence of autonomic nerve damage causing less vasocongestion. Nerve-sparing surgery can help preserve the hypogastric and cavernous nerves (Gervaz et al., 2008). The cause of immediate postsurgery ED is neurapraxia, or surgical trauma to the neurovascular system (Peltier, van Velthoven, & Roumeguère, 2009). Surgery also can alter nitric oxide synthesis, which affects smooth muscle relaxation and vasodilation (Albaugh, 2010).

<table>
<thead>
<tr>
<th>FIGURE 22-1</th>
<th>Risk Factors for Erectile Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age</td>
<td>Kidney disease</td>
</tr>
<tr>
<td>• Alcohol use</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>• Anxiety</td>
<td>Nerve damage (injury or surgery)</td>
</tr>
<tr>
<td>• Atherosclerosis</td>
<td>Neurologic conditions (stroke, Alzheimer disease, multiple sclerosis, Parkinson disease)</td>
</tr>
<tr>
<td>• Belief that erectile dysfunction is a “punishment”</td>
<td>Obesity</td>
</tr>
<tr>
<td>• Blood vessel disease</td>
<td>Pain</td>
</tr>
<tr>
<td>• Cultural beliefs</td>
<td>Partner issues: Lack of interest in sexual activity, conflict, poor health of partner</td>
</tr>
<tr>
<td>• Depression</td>
<td>Prescribed medications</td>
</tr>
<tr>
<td>• Diabetes</td>
<td>Prolonged bicycling</td>
</tr>
<tr>
<td>• Fatigue</td>
<td>Recreational drugs</td>
</tr>
<tr>
<td>• Heart disease</td>
<td>Tobacco use</td>
</tr>
<tr>
<td>• Hormonal changes</td>
<td>Venous leak</td>
</tr>
<tr>
<td>• Hypercholesterolemia</td>
<td></td>
</tr>
<tr>
<td>• Hypertension</td>
<td></td>
</tr>
<tr>
<td>• Hypogonadism</td>
<td></td>
</tr>
</tbody>
</table>

Note. Based on information from Heidelbaugh, 2010; Marberger et al., 2011.
Unlike surgical ED, which can be immediate, ED caused by external radiation therapy (XRT) tends to have a delayed onset because of progressive damage to the cavernosal tissue of the penis (Peltier et al., 2009). The risk of developing ED following XRT is correlated to technique and the dosage received by the bulb of the penis. Brachytherapy can reduce risk of ED (Snyder, Stock, Buckstein, & Stone, 2012), but permanently implanted seeds can cause changes in the volume, color, and consistency of ejaculate (Huyghe et al., 2013).

Psychological factors such as anxiety, pain, stress, relationship problems with a partner, decreased sexual self-confidence, or concerns of masculinity can have a dramatic impact on ED. There seems to be a stigma for some men if they think ED is caused by psychological factors. It often is helpful to remind patients that the brain is the most important sexual organ. For example, using the analogy of how anxiety can increase pain sensation may decouple the man’s perceived link between the psychology of ED and its physiologic effects.

**What Causes It**

Prostate surgery technique can affect erection. Open versus closed surgical techniques for prostate cancer have different postsurgical recovery consequences on erectile function (e.g., venous leakage following prostatectomy or nerve damage). Recent research indicates that ED occurring after prostate surgery may not be due to just damage to nerves or blood flow (Albaugh, 2010). Investigators have performed penile biopsies and found physiologic changes in the muscle fibers and collagen content that contribute to deterioration of the penile tissue (Albaugh, 2010). In addition to prostatectomy-induced ED arising from nerve damage or venous leakage, penile biopsies indicate changes in the trabecular elastic, smooth muscle fibers, and collagen content, which may be contributing factors in the process of cavernosal fibrosis (deterioration) (National Cancer Institute [NCI], 2013). Radical prostatectomy surgery is perceived by survivors to cause more risk of ED and penile shortening (Carlsson et al., 2012).

In the case of surgical treatment of rectal cancer and the risk of ED, a total mesorectal excision improves the cure rate, but the pelvic autonomic nerves are at risk (Sartori, Sartori, Vigna, Occhipinti, & Baiocchi, 2011). The risk of ED after treatment for colorectal cancer tends to be less consistently discussed with patients than the risk after prostate surgery (Dowswell et al., 2011).

Surgical treatment, such as a radical cystectomy, removes the bladder, prostate, seminal vesicles, and proximal urethra, which causes subsequent nerve damage and ED. Besides surgical causes, hormone and androgen deprivation therapy can cause ED (Mearini, Zucchi, Costantini, Bini, & Porena, 2011). Psychological factors of anxiety, sleep deprivation, or changes in body image can affect libido and result in lack of blood engorgement of the penis. Psychological and physiologic factors can cause ED; therefore, multifocused assessment is vital to determine appropriate treatment options.

**Assessment**

**Medical Assessment**

A history, including medical, sexual, and psychosocial history, is recommended (Heidelbaugh, 2010). The medical history should address the possible causes discussed in the previous section.

**Subjective Assessment**

The most important aspect of nursing assessment of ED is the subjective assessment of the patient himself and the meaning of the ED to him. The meaning of ED to the patient
and the partner is what will affect how they choose to cope with this. Figure 22-2 lists questions that the provider can ask the patient when assessing for ED. Using the PLISSIT (Permission, Limited Information, Specific Suggestions, and Intensive Therapy) model as part of the assessment can begin to set the basis for intervention (Ayaz & Kubilay, 2009). The assessment needs to include questions for and about the partner, including the partner’s perception of ED and level of support for treatment of ED. Viewing ED as a couple’s issue reinforces the value of including the partner in assessment and treatment planning (Pel-tier et al., 2009).

### Laboratory Tests

Testosterone level is often the first factor considered by providers. Although testosterone level affects libido and sleep-related erections, no direct correlation has been shown between testosterone level and erection (Marberger et al., 2011). Controversy exists as to whether testosterone should be tested and if so, which of the three forms of testosterone to measure. Contributing to the controversy of the importance of testosterone level is the finding that intermittent androgen suppression therapy in men with prostate cancer results in improved QOL, erectile function, and sexual function when patients were “off” androgen suppression therapy and their testosterone levels increased (Mearini et al., 2011).

Other tests that may be performed include lipid panel, thyroid-stimulating hormone test, and fasting blood sugar (Heidelbaugh, 2010). Optional laboratory tests include complete blood count, luteinizing hormone (LH), prolactin levels, sex hormone-binding globulin test, and urinalysis. These tests are done to determine whether other medical conditions may be contributing to the symptom of ED. Penile ultrasound is not recommended (Heidelbaugh, 2010). Possible tests that may be done but are not routine include nocturnal penile tumescence, cavernosometry to check penile vascular pressure, or cavernosography where dye is injected to assess blood flow to the penis. The nurse’s role, as with all parts of oncology care, is to help explain the tests, what the test results may or may not mean or indicate, and ensure that patients do not have misunderstandings about them.

### Physical Examination

Providers should conduct the following as part of the physical examination with men who have ED: (a) blood pressure and pulse readings, (b) assessment of femoral and pop-

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**FIGURE 22-2** Questions the Provider Can Ask When Assessing for Erectile Dysfunction (ED)

- Clarify what the patient’s concerns are. Sometimes the patient or his partner will “self-diagnose” symptoms as ED when actually the patient is not having a desire for sexual activity.
- Assess duration: When did it begin? Was it a gradual onset or a sudden change?
- When does it occur? Is it situational (such as after going out to dinner and drinking)? Does it occur with all partners? Men need physical stimulation to obtain an erection when older, so ask whether the concern is that he does not get an erection with visual stimuli only.
- Ask detailed questions of what happens: Is it shortly after orgasm or ejaculation? Does he have erections when he wakes or engages in self-pleasuring?
- Ask about partner: Desire level, if he has a new partner, if the partner is healthy, and if there is couple conflict. How does the partner react to ED?
- What has he used for ED?
- What was his score on the International Index of Erectile Function Survey, or whichever instrument is being used for assessment?

*Note. Based on information from Sexual Medicine Society of North America, n.d.*
lateral pulses to ascertain atherosclerotic disease, (c) abdominal examination, (d) examination of genitals for testicular size and consistency, penile shaft fibrosis, and foreskin retractability, evaluation of obesity, and digital rectal examination (Heidelbaugh, 2010; Peltier et al., 2009). A neurologic examination will be indicated for some patients, depending on their medical history.

Evidence-based interventions available for men with ED are listed in Figure 22-3, and Figure 22-4 depicts the number of studies synthesized from the literature.

**FIGURE 22-3 Evidence-Based Practice Interventions for Erectile Dysfunction**

**Recommended for Practice**
- Tailoring patient treatment and counseling for postoperative erectile dysfunction (ED) can be based on or predicted by patient and surgical variables (Alemozaffar et al., 2011; Briganti et al., 2009; Huyghe et al., 2013; Katz et al., 2010; Kimura et al., 2011; Sommers et al., 2008; Steinsvik et al., 2012).
- Oral phosphodiesterase type 5 inhibitor drugs (sildenafil, tadalafil) effectively treat ED (Bruner et al., 2011; Candy et al., 2008; Hatzimouratidis et al., 2010; Nishizawa et al., 2011; Padma-Nathan et al., 2008; Ricardi et al., 2010).
- Vacuum devices have established safety and effectiveness for the treatment of ED (Lehrfeld & Lee, 2009; Montorsi et al., 2010).
- Penile prostheses are recommended when medical therapy is contraindicated or ineffective (Hatzimouratidis et al., 2010; Montorsi et al., 2010).
- Intracavernous injections are vasodilators injected into the base of the penis (Hatzimouratidis et al., 2010).
- Alprostadil (Medicated Urethral System for Erections [MUSE®]) relaxes the penile muscles, allowing increased blood flow (Hatzimouratidis et al., 2010).
- Penile rehabilitation is the use of medications or a combination of medications and devices and has demonstrated potential benefits to patients and their partners; the ideal combination of therapies is unknown (Montorsi et al., 2010; Raina et al., 2010).
- Interactive educational systems enhance the decision making of patients with prostate cancer regarding treatment choices and erectile function (Diefenbach et al., 2012; Schover et al., 2012).
- Pelvic floor biofeedback training improved erectile function in patients who had a radical prostatectomy for prostate cancer (Prota et al., 2012).

**Likely to Be Effective**
- Minimally invasive radical prostatectomy may affect incidence of ED (Ahallal et al., 2011; Asterling & Greene, 2009; Ayyathurai et al., 2008; Heer et al., 2011; Koehler et al., 2012; Prasad et al., 2011)—radical prostatectomy may result in penile shortening (Carlsson et al., 2012).
- ED is common when patients with prostate cancer receive combined endocrine and radiation therapy, but long-term survival benefits of the therapy are significant (Daly et al., 2012; Fransson et al., 2009).

**Benefits Balanced With Harms**
- Healthcare providers cannot assume that only men diagnosed with certain types of cancer or of certain ages receive or want information about ED. Instead, all patients should be informed about the possibility of ED secondary to their cancer or cancer treatment, when relevant, and provided with information and treatment as requested (Dowswell et al., 2011; Ellis et al., 2010; Eton et al., 2010; Flynn et al., 2011; Letts et al., 2010; Milne et al., 2008; Mulhall et al., 2010; Walker & Robinson, 2012; Wittmann et al., 2009).
- Patients and their partners have different interpretations of the outcomes of prostate cancer surgery and may both benefit from counseling to improve adjustment after surgery (Tsivian et al., 2009).
- For patients with prostate cancer, the benefits of a radical prostatectomy need to be weighed against watchful waiting. Younger men without comorbidities experienced fewer complications with radical prostatectomy and better long-term functional outcomes than older men (Hugosson et al., 2011; Johansson et al., 2011; Loeb et al., 2008; Roberts et al., 2011).
- Prostate cancer treatments may result in penile shortening (Carlsson et al., 2012; Parekh et al., 2013).

(Continued on next page)


**Expected Outcomes Specific to Erectile Dysfunction**

Patients will be provided with enough information to make an informed decision about their optimal treatment options. When open communication exists between patients and nurses, patients will be less likely to choose potentially unsafe strategies to increase erectile function. The overall goal and anticipated outcome is respectful, open discussion and opportunities to include the partner in that discussion (Ohlsson-Nevo et al., 2012).
Patient Teaching Points Specific to Erectile Dysfunction

Patient and partner education should include a discussion about the fact that the lack of erection does not mean loss of desire for the partner. It is helpful when both the patient and partner are interested in exploring various options. Because several options are available, nurses need to discuss the pros and cons of each so that the couple can make decisions that best fit their values and lifestyle. Of greater importance is the necessity to assess patients for ED and encourage early intervention to prevent complications, such as scarring and fibrosis of erectile tissue.

Patient and partner education should include emphasis of the following certain points as applicable to the individual situation.

- All men following radical prostate surgery and 50% of men following abdominoperineal resection will have ED (Gervaz et al., 2008). Nerve-sparing prostate surgery reduces the incidence of ED to less than 30% (Albaugh, 2010).
- Urinary continence occurs before erectile function returns (Smilow Comprehensive Prostate Cancer Center, n.d.).
- Return of erectile function following surgery takes an average of 18 months to two years (Smilow Comprehensive Prostate Cancer Center, n.d.).
- Combination therapy may be an effective treatment approach.
- Brachytherapy has less risk for ED (approximately 20%) (NCI, 2013).
- Brachytherapy may cause burning with ejaculation; semen may be bloody and if ejaculatory ducts are blocked, ejaculatory fluid may be decreased (Huyghe et al., 2013).
- Condoms should be used for four months after palladium brachytherapy and 12 months after iodine brachytherapy to prevent radiation seeds from being expelled with ejaculation. Medications and devices are intended to help with erections, not orgasms, as orgasms are possible without an erection (Smilow Comprehensive Prostate Cancer Center, n.d.).
- Open communication about the effectiveness of therapy is key, with nurses being prepared to offer other options (Lombrana, Izquierdo, Gomez, & Alcaraz, 2012). Nurses should discuss the possibility of better response if combination rather than monotherapy is used (Costa & Potempa, 2012).
- Nurses need to ensure that patients are aware of the possible side effects of ED treatment when they are deciding on options. Phosphodiesterase type 5 (PDE-5) inhibitors can cause headache, flushing, backache, muscle aches, dyspepsia, rhinitis, or abnormal vision (Heidelbaugh, 2010; Li, 2009). Vacuum pumps can be cumbersome, and the constrictional band at the penis base may cause pain. Intravaginal suppositories are not as invasive but can be costly for some men, and the burning sensation and hypotension may be barriers. Injection therapy also may cause burning, in addition to scarring or priapism. Inflatable penile implants are expensive, require manual dexterity, and may malfunction (Albaugh, 2010).
- Patients should be reminded that erections do not occur immediately after taking oral ED medications and that taking the medication close to consumption of food can slow the onset of effectiveness (Li, 2009).
- When nurses are open and nonjudgmental, patients may be forthcoming about possible complementary and alternative medicine options they are considering. This provides the opportunity for the nurses to evaluate safety. For example, Regenerect, Spontane-ES, Virility Max, Via Xtreme Ultimate Sexual Enhancer, and X-Rock are all considered unsafe by the National Center for Complementary and Alternative Medicine (2013). Some herbal treatments such as Tribulus terrestris may interact with medications and increase the effect of diuretics, antihypertensive drugs, or diabetic medications. Deaths have been reported from the use of yohimbine (Anderson, Anderson, Harre, & Wade, 2013).
• Nurses should discuss safety concerns associated with purchasing medications over the Internet (e.g., PDE-5 inhibitors), borrowing a pill from a friend, and cutting pills in half, which may result in unequal distribution of the active ingredient.

• Nurses should offer suggestions for how to deal with the loss of spontaneity that occurs when sexual activity is interrupted by the use of an external device (i.e., a vacuum device or an erection ring to trap blood in the penis).

• For patients with diabetes or those with circulatory and sensory compromise, nurses should describe the safety issues that accompany the use of herbal treatments, vacuum devices, “splints,” or erection rings that keep blood in the penis to maintain erection.

• Men using a vacuum device should be informed that the penis might become discolored or bruised, that there may be discomfort of the glans, and that the erection ring may interfere with ejaculation (Li, 2009). Vacuum devices are not to be used by men with sickle-cell disease or blood dyscrasias and those using anticoagulants (Heidelbaugh, 2010).

• Nurses should explain that vasoactive drugs injected into the cavernous bodies may create a burning urethral sensation or throbbing penile sensation (Li, 2009).

• Nurses should provide written information or websites that may be shared with partners and help to ensure consistency of treatment expectations, as well as where and how to obtain treatments.

• Patients can be referred to individualized or group psychosocial support or intervention resources (Elliott et al., 2010; Melnik, Soares, & Nasello, 2007).

• Education about possible changes in sexual function can reduce the misperception that one’s sexuality should be minimized (Le et al., 2010).

• Erectile dysfunction does not always correlate with level of sexual satisfaction (Flynn et al., 2011).

Need for Future Research Specific to Erectile Dysfunction

Future studies are needed with respect to physical issues, such as investigations about the changes that couples make in sexual activity when using an erection aid and the success of such changes, as well as psychosocial and QOL issues. Of interest are how men weigh possible sexual outcomes and what factors they consider when making decisions about treatment options (Rosen, Fisher, Beneke, Homering, & Evers, 2007). Studies are needed on both the incidence of partners feeling pressured to engage in penetrative sex when ED is treated and the identification of effective strategies for clinicians to use when assessing partners for the occurrence of feeling pressured.

Dyspareunia

Definition

For women, dyspareunia is the pain experienced during vaginal entry or intercourse. For men, dyspareunia is penile pain that persists for three months or longer with vaginal or anal intercourse (Oommen & Hellstrom, 2013).

Risk Factors

The risk of experiencing dyspareunia increases with the types of surgical procedures, such as neovagina creation (surgery to construct a vaginal canal), hysterectomy, vulvectomy, cystec-
tomy, or penile or rectal surgery; with aging or menopausal symptoms that result in a decrease of vaginal lubrication; with the use of certain medications; with vaginal ulcers resulting from treatment; or with radiation therapy or laser treatment for penile carcinoma (see Figure 22-5). Men who have pretreatment pain with ejaculation have a greater risk of painful ejaculation after brachytherapy (Huyghe et al., 2013). Dyspareunia is one of the two most common sexual concerns after gynecologic surgery (Stilos, Doyle, & Daines, 2008), and unlike other menopausal symptoms that may decrease over time, dyspareunia may increase without treatment (Portman, Bachmann, Simon, & Ospemifene Study Group, 2013). Those with depression often report a greater incidence of dyspareunia (Can et al., 2008).

Pathophysiology

Why It Happens

The causes of dyspareunia are numerous. Radiation can cause fibrosis from the blood vessel changes (Katz, 2009). Surgery can damage pelvic nerves (e.g., with hysterectomy) and may lead to less vasocongestion, less lubrication, enlargement of the vagina, and less feeling of heat or vibration in the vagina. Blood flow to the vulva, clitoris, and vagina is mediated by nerve roots S2 and S3 and the hypogastric plexus autonomic fibers. Because of surgical risk, nervesparing surgery is becoming more common even for cancer-related surgeries (Li et al., 2012).

What Causes It

One physiologic reason for female dyspareunia is vaginal atrophy occurring when the vaginal epithelium thins from decreased estrogen levels. This creates decreased elasticity and increased friability (Tan, Bradshaw, & Carr, 2012). Surgery, radiation therapy, aging, and medications may contribute to female gonadal failure, causing vaginal dryness (Bradford, 2013; Katz, 2009; Li, 2009). In the case of aging, approximately 17%–30% of menopausal women have decreased vaginal lubrication. Cancer-related drugs that increase dyspareunia are aromatase inhibitors, chemotherapy, and hormonal manipulation. Aromatase inhibitors have been found to affect vaginal lubrication and libido more than tamoxifen (Baumgart, Nilsson, Evers, Kallak, & Poromaa, 2013; Bradford, 2013; Mok, Juraskova, & Friedlander, 2008). Aromatase inhibitors can decrease not only lubrication but also vaginal elasticity and pliability.
(DiGiulio, 2013). Dyspareunia is a complex issue, and although a specific physiologic cause of its occurrence might be identified, psychosocial factors also have an impact (Bradford, 2013; Oommen & Hellstrom, 2013). Dyspareunia may be associated with certain types of cancer. Women with advanced, recurrent, or persistent cervical cancer have a greater incidence of decreased vaginal lubrication and are more likely to suffer dyspareunia. In addition to cervical cancer, treatment for other gynecologic malignancies (i.e., vulvar, uterine, ovarian) can cause dyspareunia (Brotto et al., 2008; Jefferies & Clifford, 2011; Katz, 2009; Zeng, Ching, & Loke, 2011). Men with penile carcinoma are at risk for dyspareunia resulting from the cancer or the side effects of treatment (Oommen & Hellstrom, 2013).

Physical causes of dyspareunia include surgery that affects innervation to the vagina or vaginal lubrication, scar tissue (contractures), increased sensitivity to vaginal barrel distention, muscle tension, genital infections or ulcers, or treatments that cause thinning of the skin of the penis or vagina. Women who receive pelvic or intracavitary vaginal brachytherapy may experience dyspareunia as a result of a shortened vagina, radiation-induced urethral irritation or stenosis, or a decrease in vaginal lubrication (Quick, Seamon, Abdel-Rasoul, Salani, & Martin, 2012). Because of weight loss as a consequence of the cancer treatments or the cancer itself, women may suffer pain from the loss of the fat pad around the mons pubis.

Although male dyspareunia is relatively uncommon, 90% of men who experience it consider the condition serious. The four broad categories of male dyspareunia are pain during or after ejaculation; chronic prostatitis or pelvic pain syndrome; medical diagnoses such as phimosis, pudendal nerve entrapment, infections, or cystitis; and other causes such as medications, anodypareunia (if they engage in anal sex), or psychological (Oommen & Hellstrom, 2013).

**Assessment**

**Medical Assessment**

Taking a history is vital to determine when and where the pain occurs. Assessment questions include whether the pain occurs during penetration, with depth of thrusting, with position changes, with ejaculation or orgasm, during postcoital urination, or some time after coitus (Russell et al., 2010). An additional question is whether sexual arousal occurred before penetration was attempted.

**Laboratory Tests**

Laboratory tests that may help to identify possible causes of dyspareunia include vaginal alkalinity (pH greater than 5); predominance of basal cells in the vaginal wall; fasting blood sugar (diabetes can cause dyspareunia, and treatments that include steroids will affect glucose control); follicle-stimulating hormone (FSH) and LH to ascertain menopausal status; prolactin, which affects testosterone production; and thyroid function, which can affect energy level (Tan et al., 2012). A urinalysis may help to identify whether the pain is due to cystitis or renal calculi rather than dyspareunia (Oommen & Hellstrom, 2013). Vaginal blood flow may be measured by vaginal photoplethysmography, oxygenation temperature method, or laser Doppler perfusion imaging (Woodard & Diamond, 2009).

**Physical Examination**

For women, the gynecologic examination should focus on the loss of vaginal rugae; presence of pale, dry vaginal tissue; vaginal ulcers or lesions; petechiae or microfissures; loss of vaginal elasticity; labial fusion; clitoral shrinkage; and shortening and narrowing of the vaginal barrel (Bond & Horton, 2010; Katz, 2007; Kingsberg, Kellogg, & Krychman, 2009; Tan et al., 2012). Examination of the external genitalia includes labia majora, labia minora, and
mons pubis. A rectal examination should be performed because hemorrhoids, anal fissures, or stool impaction may cause dyspareunia.

For men, the physical examination should include evaluation of the scrotum for masses, assessment of the anal sphincter tone, and identification of any lesions or thinning of the penile skin. Checking the bulbocavernosus reflex can diagnose pudendal nerve entrapment (Oommen & Hellstrom, 2013).

Male or female patients receiving steroids or antibiotics are at increased risk for vaginal or penile fungal infections, and immunosuppressive therapy increases the risk of recurrent genital herpes and thinning of vaginal or penile tissue.

Evidence-based interventions available for dyspareunia are listed in Figure 22-6, and Figure 22-7 depicts the number of studies synthesized from the literature.

Expected Outcomes Specific to Dyspareunia

Patients will be provided with information on possible causes of dyspareunia and the physiologic as well as the psychosexual effects (Bradford, 2013). The goal is that patients will feel

<table>
<thead>
<tr>
<th>FIGURE 22-6</th>
<th>Evidence-Based Practice Interventions for Dyspareunia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended for Practice</strong></td>
<td>Of all pharmaceutical interventions, hormone therapy is considered the most effective (safe only for non-hormone-related cancer survivors) (Tan et al., 2012).</td>
</tr>
<tr>
<td><strong>Likely to Be Effective</strong></td>
<td>Consistent use of moisturizers and lubricants on an as-needed basis (Tan et al., 2012)</td>
</tr>
<tr>
<td></td>
<td>Psychosocial/educational interventions (Abbott-Anderson &amp; Kwekkeboom, 2012; Ayaz &amp; Kubilay, 2009; Classen et al., 2013; Decker et al., 2012; Reese, 2011; Reese et al., 2012; van Lankveld et al., 2010)</td>
</tr>
<tr>
<td></td>
<td>Pelvic floor rehabilitation (Massa, 2011; van Lankveld et al., 2010)</td>
</tr>
<tr>
<td><strong>Benefits Balanced With Harms</strong></td>
<td>When compared to open surgery, minimally invasive (laparoscopic) surgery for rectal cancer may reduce complaints of dyspareunia (McGlone et al., 2012).</td>
</tr>
<tr>
<td></td>
<td>Types of cancer treatments can result in dyspareunia (Bruheim et al., 2010; Cesnik &amp; dos Santos, 2012; Corte et al., 2011; Doeksken et al., 2011; El-Bahnsawy et al., 2011; Lammerink et al., 2012; Perera et al., 2008; Song et al., 2012; Tekkis et al., 2009), but physiologic changes do not fully explain sexual dysfunction (Gilbert et al., 2010, 2011; Li, 2009; van Lankveld et al., 2010).</td>
</tr>
<tr>
<td></td>
<td>The use of an evidence-based clinical pathway in women receiving cervical cancer treatment improved understanding of vaginal stenosis and increased the use of vaginal dilators (Tanner et al., 2011).</td>
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<tr>
<td></td>
<td>Vaginal estrogen therapy is considered effective; however, there is controversy regarding endometrial stimulation (Tan et al., 2012).</td>
</tr>
<tr>
<td></td>
<td>Painful intercourse is often cited after various types of cancers. The use of vaginal lubricants may mediate this symptom (Carter, Goldfrank, et al., 2011; Damast et al., 2012; Lalos et al., 2009; Melisko et al., 2010).</td>
</tr>
<tr>
<td><strong>Effectiveness Not Established</strong></td>
<td>Selective estrogen receptor modulators and tissue-selective estrogen complexes (Tan et al., 2012)</td>
</tr>
<tr>
<td></td>
<td>Dehydroepiandrosterone (Tan et al., 2012)</td>
</tr>
<tr>
<td></td>
<td>Vitamin D (Tan et al., 2012)</td>
</tr>
<tr>
<td><strong>Effectiveness Unlikely</strong></td>
<td>Alternative therapies (i.e., acupuncture, plant estrogens, herbal supplements) (Tan et al., 2012)</td>
</tr>
<tr>
<td><strong>Not Recommended for Practice</strong></td>
<td>No interventions at the time of publication</td>
</tr>
</tbody>
</table>
comfortable in discussing sexual functioning with their nurses so that culturally sensitive and patient-focused interventions can be suggested.

The goals of the interventions are that patients will have either no dyspareunia or reduced dyspareunia. This is intended to increase patients’ perception of QOL. Decreasing or eliminating dyspareunia will decrease the risk of negative changes in body image, sexual satisfaction, and libido.

**Patient Teaching Points Specific to Dyspareunia**

Creation of a trusting, safe environment will enable open, full discussion to learn if the woman or man desires coitus as part of his or her life. Assuming coitus to be the goal is culture-bound and may create additional stress for the patient (Ramirez et al., 2010).

Patient and partner education should include a discussion that dyspareunia is treatable and may not be permanent (Kingsberg et al., 2009). Communication is important not only between partners but also between patients and providers so that interventions can be evaluated and changes can be made.

Patients with dyspareunia should be educated about its causes and treatments, encouraged to consider the interventions, and taught behavioral skills about using vaginal lubricants, performing Kegel exercises, accessing reliable websites, and using vaginal dilators (Cleary, Hegarty, & McCarthy, 2013; Massa, 2011).

For example, provide the following specific instructions on the use of a vaginal dilator (International Clinical Guideline Group, 2012; Katz, 2009).

- Start using dilators gently within two to eight weeks post-therapy after acute inflammatory tissue changes have subsided.
- Begin with narrow diameter according to the woman’s anatomy and increase to maximum of 1.5 inches.
- Use the dilator daily if possible. If not, use it a minimum of three times a week for a period of 10–15 minutes.
- Use dilators until weekly coitus or no pain with physical examination occurs, usually one to two years after therapy.
Education should include ensuring that patients understand the difference between using vaginal lubricants versus vaginal moisturizers. Lubricants help reduce the friction; they are temporary and used at the time of sexual activity. Moisturizers also help reduce friction, but they are absorbed into the vaginal tissue and are used regularly, not just at the time of sexual activity. Scented or dyed lubricants should be avoided because they can further irritate the tissue (Katz, 2009). Glycerin-based lubricants may increase the risk of fungal infections (Katz, 2009).

Men with penile dyspareunia who are having same-sex activity should consider using a thicker lubricant, such as silicone, to protect the tissue.

**Need for Future Research Specific to Dyspareunia**

Two areas that require future research include ascertaining how local estrogen therapy affects women after six months of use (Katz, 2007) and identifying the typical coping strategies used by women with dyspareunia. Little is known about the risk of cancer caused by continued local estrogen therapy, how it affects the vaginal mucosa, or if it increases the risk of infection. Preliminary work currently is looking at women on aromatase inhibitors and the risk of using low-dose topical hormones, but further work needs to be conducted with survivors being diagnosed at earlier ages and having longer prognoses (Bond & Horton, 2010). Questions about how men or women cope with dyspareunia would include Do they avoid sexual situations that affect their relationships? Do they change positions? Do they have decreased libido? How does dyspareunia coping style affect their body image or sexual function?

**Altered Body Image**

**Definition**

Body image is individually subjective and is based on self-observation, reaction of others, and the importance the person places on his or her appearance (Dahl, Reinertsen, Nesvold, Fosså, & Dahl, 2010). Body image affects psychosocial adjustment and functioning, influences rehabilitation, is an important component of QOL (Snöbohm, Friedrichsen, & Heiwe, 2010), and can affect treatment choices based on cosmesis (Collins et al., 2009).

**Risk Factors**

People who have poor self-esteem or who are unsatisfied with their body image prior to diagnosis are at risk for experiencing further alterations in body image following a diagnosis of cancer. Assessing for and providing patient support for changes in body image are part of the nursing role because such changes affect self-perception, identity, sense of body integrity, and social functioning (Adamsen et al., 2009). Body image assessment is not usually performed at the time of diagnosis when the focus is on diagnosis and treatment.

Treatments such as surgery, chemotherapy, and hormonal therapy can affect body image (Bloom, Stewart, Oakley-Girvan, Banks, & Shema, 2012; Salonen et al., 2011). After treatment, a resulting poor body image may be attributed solely to cancer treatment, but it may have been present prior to diagnosis (Dahl et al., 2010). In fact, pretreatment body image scores, fatigue, mental stress, and perceived QOL are strong factors in the body image of breast cancer survivors (Dahl et al., 2010). Krouse et al. (2007) found that those having stoma surgery reported body image versus having gas or traveling challenges as having the great-
rest impact on their QOL. Surgery for nonmalignant reasons resulted in greater reduction in body image satisfaction than surgery for malignant reasons. Neuman et al. (2012) examined the question of whether the stoma was temporary or permanent had an effect on body image, and they reported that having a temporary stoma does not significantly affect QOL, but the length of time living with a stoma does affect QOL.

Factors that might influence body image are the reaction of partners and others (Ohlsson-Nevo et al., 2012), as well as receiving appropriately timed postoperative counseling (Dahl et al., 2010). Age, an additional factor, has an impact on body image (Adamsen et al., 2009; Bloom et al., 2012; Fan & Eiser, 2009; Salonen et al., 2011; Williamson, Harcourt, Halliwell, Frith, & Wallace, 2010), but what remains to be teased out is how age affects coping styles. The physiologic changes of aging include loss of muscle mass, changes in skin elasticity (wrinkles, sagging breasts), and sparse pubic hair. Age, maturity, gender, and developmental stage of patients will affect how they perceive changes. Men often express greater concern about body function changes than body image changes (Campbell-Enns & Woodgate, 2013).

**Pathophysiology**

**Why It Happens**

Multiple factors can cause changes in body image, which is a multidimensional, complex concept. They include the type of cancer diagnosis, precocious puberty (the onset of puberty before age 8 in girls and age 9 in boys), delayed development of secondary sex characteristics, weight changes, alopecia, surgical changes, lymphedema, and scars (Boehmer, Linde, & Freund, 2007; Fan & Eiser, 2009). The site of the cancer, when associated with an individual’s identity as a woman or a man, can significantly affect body image (Sacerdoti, Laganà, & Koopman, 2010). It is not necessarily the changes themselves alter the body image, but rather how the patient perceives the changes or how the patient perceives his or her partner’s views of the changes. For example, fear of alopecia can cause some patients to decline treatment because of body image concerns, but others experience no changes in body image related to it (Lemieux, Maunsell, & Provencher, 2008). Alopecia can result in patients having to deal more publicly with their diagnosis and treatment. Men more than women may express concerns about overall body alopecia and resulting feelings of being “feminized” (Campbell-Enns & Woodgate, 2013).

**What Causes It**

The type of cancer and the corresponding treatments may significantly affect body image despite lack of objective visible changes (Fan & Eiser, 2009). Visible changes that have been correlated with changes in body image include breast reconstruction where preoperative breast size, use of XRT, and axillary dissection can affect esthetic results (Tomita, Yano, Matsuda, Takada, & Hosokawa, 2008).

Chemotherapy, radiation therapy, and hormone therapy may cause delayed development of secondary sex characteristics, delay in menarche, or alopecia. Weight changes, either a decrease or increase, that affect body image can occur because of anorexia from malignancy, side effects of treatment, and the use of steroids or hormones. Hormone therapy can cause loss of muscle bulk or gynecomastia, changes in penis size, and fatigue, which can interfere with the image of oneself as a strong, self-sufficient individual (Harrington, Jones, & Badger, 2009; Reese, 2011). Gynecomastia (male breast enlargement) is common in men being treated with androgen deprivation therapy for a diagnosis of prostate cancer. Incidence ranges from 15% for those treated with a combination of gonadotropin-releasing hormone and an antiandrogen to 75% for those treated with an antiandrogen monotherapy (Braunstein, 2014).
Side effects of chemotherapy affect body image. The change in cognitive function can affect how a person views himself or herself, and the change in body smell while receiving chemotherapy can affect body image in ways that the healthcare team often forgets to assess. Alopecia (see Chapter 2) can affect body image more than surgical removal of a breast for some (Sun et al., 2013). Bone marrow transplantation can result in body image changes seen in those treated with chemotherapy but may be intensified if graft-versus-host disease occurs (Russell, Harcourt, Henderson, & Marks, 2011).

While the loss of a body part or change in the shape of a body part can affect body image, the impact is magnified depending on the meaning of the body part to the patient or how easily it can be concealed. Head and neck cancer survivors often identify body image changes as their primary concern (Howren, Christensen, Karmell, & Funk, 2013). Surgical changes influence the fitting of clothes and appearance when dressed and consequently may affect body image (Hill & White, 2008). Indeed, women may choose reconstructive breast surgery for the practical reasons of being able to wear their usual clothes rather than for concern of how they appear to a partner (Lee et al., 2010). Patients with a stoma may have to wear larger-size clothes to conceal the appliance or wear non-belted clothes because of stoma placement (Sun et al., 2013).

Cultural factors may affect the meaning and significance of the loss or change of the body part (Alicikus et al., 2009; Can et al., 2008). Penis size can decrease after surgery for penile cancer or after radical prostatectomy (Parekh et al., 2013). A penile graft may be done to help with body image, but graft overgrowth or poor graft take of penile-preserving surgery can occur and further damage body image.

Body image alterations from XRT include concerns about permanent tattoos, skin color and texture changes, and thinning or loss of hair in the irradiated field. Daily XRT to breasts or sexual organs that have to be exposed during treatment can lead patients to see that body part as “diseased” and not pleasurable, causing almost a dissociative effect.

Precocious puberty that alters body image can be caused by high-dose cranial radiation therapy (greater than 50 gray [Gy]), causing gonadotropin deficiency. Doses of 18–47 Gy increase the risk of precocious puberty (Alvarez et al., 2007).

The incidence of lymphedema (see Chapter 17) following breast cancer treatment has decreased because of earlier detection, sentinel lymph node dissection, and changes in XRT technique (Stamatakos, Stefanaki, & Kontzoglou, 2011). Although lymphedema in patients with breast cancer is declining, awareness is still needed because it can occur many years after therapy (Ridner, Bonner, Deng, & Sinclair, 2012; Stamatakos et al., 2011).

Research about sexual function and body image often focuses on patients with curable disease, although the body image of terminally ill patients with lower-limb lymphedema or cancer-related anorexia-cachexia syndrome can be greatly affected (Rhondali et al., 2013). Thus, a patient’s prognosis should not stop the nurse from assessing body image.

**Assessment**

Assessment is much more than the traditional laboratory tests and physical examinations. Baseline body image assessment includes performance status, partner availability, health status, depression, anxiety, and the meaning of the cause of cancer. Assessment includes asking if the alterations in body image cause concern or distress.

**Laboratory Tests**

No traditional laboratory tests are done to diagnose body image alterations. Multiple body image surveys are available for clinical use and assessment. Examples of these surveys include
Body Shape Questionnaire, Objectified Body Consciousness Scale, Body Esteem Scale, Drive for Muscularity Scale, and Male Body Dissatisfaction Scale (Parent, 2013).

**Physical Examination**

Multiple physical factors, such as a stoma, change in muscle mass, loss of a body part, change in hair distribution on the body (usually involves loss of hair, but sometimes treatment can cause hair growth, which also affects hair distribution), surgical scars, delayed development of secondary sex characteristics, precocious puberty, lymphedema, and acne can affect body image. As stated previously, though, it is not the physical factors that cause the changed body image but rather how the person perceives the changes. For example, nurses cannot automatically assume that a stoma has affected the person’s body image. Instead of assuming, nurses should ask if having a stoma has affected how that person sees himself or herself. Because it is the perception that affects body image, there can be “invisible” changes or diagnosis not evident to others that still affect body image (Shell, Carolan, Zhang, & Meneses, 2008).

Evidence-based interventions available for altered body image are listed in Figure 22-8, and Figure 22-9 depicts the number of studies synthesized from the literature.

**Expected Outcomes Specific to Altered Body Image**

Because body image changes are common for patients of both sexes and of all ages, nurses should address this aspect of care with all patients. Expected outcomes include staff members feeling comfortable to discuss body image changes and sexuality with patients. When body image changes or sexuality issues are present, they will be addressed in a culturally sensitive manner. Consultations for body image change and sexual counseling will be made available to patients if they so desire. Body image changes and sexuality will be discussed with patients despite their age (Greenberg et al., 2008), sex, ethnicity, sexual orientation, marital status, socioeconomic status (Chen et al., 2009), or prognosis (Vitrano, Catania, & Mercadante, 2011).

**Patient Teaching Points Specific to Altered Body Image**

Cultural background, response of others, age, developmental stage, sex, and belief systems can all affect how individuals will respond to changes in body image. Nurses should not assume that a particular type of surgery or treatment will automatically create an altered body image (Fallbjörk, Salander, & Rasmussen, 2012). Instead, they should be aware of possible changes that might occur with specific treatments.

Nurses should educate patients that reconstructive surgery may not consistently improve body image (Lee, Sunu, & Pignone, 2009). The difference may be due to preoperative body image score or type of plastic surgery (Macadam, Ho, Lennox, & Pusic, 2013; Zhong et al., 2012). Furthermore, the need for rapid treatment initiation may prevent pretreatment discussion about options to help decrease negative body image. For example, testicular cancer can require rapid treatment initiation without time for discussion about the option of a testicular prosthesis or possible complications (Seymour-Smith, 2013). When possible, nurses should make time for patients to reflect on their values before they make a treatment decision. When this is elicited, the patient’s choice of treatment will be fully informed and not based on cosmesis alone (Collins et al., 2009).

Nurses should be able to provide in-depth teaching points for patients commonly seen by each nurse. For example, nurses who often work with people who have stomal sur-
FIGURE 22-8  Evidence-Based Practice Interventions for Altered Body Image

Recommended for Practice

- Social support interventions moderate negative perceptions of body image related to anxiety, depression, and behavioral problems in children and adolescents (Fan & Eiser, 2009; Salonen et al., 2011; Williamson et al., 2010).
- Body image is not significantly different in women with or without breast reconstruction who have had a mastectomy for breast cancer (Alicikus et al., 2009; Lee et al., 2009; Parker et al., 2007).
- Decision aids and physician-patient discussions enhance knowledge of surgical therapy and surgical choices among women with early-stage breast cancer (Alderman et al., 2008; Chen et al., 2009; Cohen et al., 2012; Collins et al., 2009; Greenberg et al., 2008; Heller et al., 2008; Lardi et al., 2012; Lee et al., 2011; Opatt et al., 2007; Waljee et al., 2007).

Likely to Be Effective

- Exercise interventions are likely to enhance body image (Adamsen et al., 2009; Parent, 2013; Snöbohm et al., 2010).
- Psychoeducational interventions improved the body image of women with gynecologic cancer (Brotto et al., 2008; Decker et al., 2012; Jun et al., 2011).
- Partner training and support were likely to be effective in improving body image (Altschuler et al., 2009; Lewis et al., 2008).
- Reconstructive surgery helps some but not all (Guyomard et al., 2007; Hill & White, 2008; Macadam et al., 2013; Zhong et al., 2012).

Benefits Balanced With Harms

- Young women with breast cancer need support, information, child care, counseling, and spiritual support (Adams et al., 2011).
- Discussing body image and sexuality with women diagnosed with breast cancer prior to surgical treatment may facilitate self-efficacy and improve mood after therapy (Adachi et al., 2007; Ayaz & Kubilay, 2009).
- Education may reduce negative body image post-surgery (Atkinson et al., 2013).
- Persons with Type D personalities and melanoma report higher impact of cancer on body image and may require special screening and attention (Mols et al., 2010, 2012). (Type D personalities tend to have more social inhibition, more distress, and negative affectivity.)
- Well-timed educational interventions may assist female colorectal cancer survivors with ostomies who express a desire to continue to have intercourse (Ramirez et al., 2010).
- Androgen deprivation therapy worsens body image perceptions (along with other negative psychological effects), requiring education about the risks and benefits of its use (Saini et al., 2013).
- Types of treatment impact body image (Chen et al., 2012; Dahl et al., 2010; Rossen et al., 2012).
- Body image is affected by prophylactic surgery (Sayakhot et al., 2011; Unukovych et al., 2012).
- Anticipatory preparation for alopecia can increase anxiety for some but provides a sense of control for others (Frith et al., 2007).

Effectiveness Not Established

- Interventions effective for enhancing body image for women are not necessarily effective for men (Donovan & Flynn, 2007).
- Couple-based psychosocial interventions (Scott & Kayser, 2009)
- Dream analysis and discussion (Giordano et al., 2012)
- Relaxation protocol (Sacerdoti et al., 2010)

Effectiveness Unlikely

- No interventions at the time of publication

Not Recommended for Practice

- No interventions at the time of publication
gery can offer suggestions to patients prior to the first experience of engaging in sex. These include

- Using a belt, cummerbund, or picture-frame taping to keep the appliance from dislocating during sexual activity
- Emptying the appliance to reduce weight and decrease the risk of the appliance slipping during sex
- Wearing crotchless underwear, an attractive teddy or T-shirt, or a pouch cover
- Using pouch deodorants and avoiding gassy food or drinks to avoid embarrassing odors
- Using a smaller stoma appliance to reduce bulk or changing positioning to avoid lying directly on the stoma
- Referral to a stoma therapist (Gervaz et al., 2008), clinical nurse specialist, or a sex therapist with expertise in oncology, which may help patients develop a “response shift” in coping with these changes.

Nurses should encourage social and peer support (Williamson et al., 2010). These act as a facilitator of adjustment to changes (Fan & Eiser, 2009). Online cancer forums allow patients to gather information relatively quickly, and even if they do not post messages, reading the discussions can be helpful (Seymour-Smith, 2013).

Nurses need to provide accurate information regarding potential side effects that could affect body image (Fan & Eiser, 2009; Williamson et al., 2010). Having a clear understanding of exactly what results plastic surgery may or may not provide and interactive digital education have helped women with breast cancer to better anticipate realistic postoperative results (Heller, Parker, Youssef, & Miller, 2008). Patients report that what they want from their healthcare team when discussing body image concerns is honest, direct communication (Cohen et al., 2012).

Patient education should also include

- Couple-based intervention (Jun et al., 2011; Lewis et al., 2008; Reese, Porter, Somers, & Keefe, 2012; Scott & Kayser, 2009).
- Timely referral to a lymphedema specialist to prevent long-term complications (Stamatakos et al., 2011)
• Practical tips on how to conceal or minimize changes (Frith, Harcourt, & Fussell, 2007; Williamson et al., 2010)
• Information about resources for changes in body image, such as the “Look Good Feel Better” program by the American Cancer Society (ACS, 2014), Internet support groups (Sheppard & Ely, 2008) and resources, and a bibliography of suggested readings.

Additionally, for young adults who have experienced changes in weight or muscle mass, exercise has a significant positive impact on body image (Adamsen et al., 2009).

**Need for Future Research Specific to Altered Body Image**

Studies need to be conducted on patients’ reactions to body image changes due to cancer or treatment (Collins et al., 2009) and to examine how ethnicity, age, and sex affect their reactions. Intervention studies are needed to investigate how to facilitate a healthy body image during and after treatment for cancer. Qualitative studies could contribute to a deeper understanding of subtle changes that may not be detected through use of questionnaires (Fan & Eiser, 2009). Longitudinal studies to explore the development of resiliency and its impact on body image perception would help with determining a baseline and designing interventions. Studies examining changes in body image need research designs that include pre-treatment body image evaluation (Lee et al., 2009). For adolescents, investigations could be done online to increase the depth of openness and participation (Williamson et al., 2010).

**Changes in Libido**

**Overview**

Decreased libido is the most common sexual dysfunction in women 18–59 years of age (Sandhu, Melman, & Mikhail, 2011). Approximately 15% of men report hyposexual desire disorder (HSDD) (Cunningham & Seftel, 2014), although this may be higher due to the frequency of ED being misdiagnosed as HSDD (Montgomery, 2008). Changes in libido can be one of the more discouraging and distressing symptoms resulting from the diagnosis or treatment of cancer. Loss of libido is the sexual side effect that often is most disturbing to patients and can remain upsetting to them for long periods of time, yet it is a hidden problem often shrouded in shame or embarrassment. Patients often ask, “How does a person whose life has been ‘saved’ due to medical technology complain about the loss of libido without feeling ungrateful?” and “Is the loss of libido not a small price to pay?” So, the symptom often remains unspoken in the clinic office.

Changes in libido can herald the onset of certain malignancies (e.g., a primary brain tumor, testicular cancer). The *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2013) lists changes in libido as the most common sexual problem for women (33%) and less common for men (5%–15%).

**Definition**

Although *libido* is a term often used interchangeably with sexual appetite, sexual desire, or “life force,” there is a difference, although a close relationship exists between *arousal* and *libido*. *Arousal* is the physiologic response (i.e., erection, vaginal lubrication), whereas *libido* is the desire. A person can be aroused and be able to have an erection or vaginal lubrication but have a loss of libido and have no desire to engage in sexual activity.
Risk Factors

Risk factors for changes in libido include aging or medical conditions such as a diagnosis of cancer, medications and their side effects, and other treatments such as surgery. It is the second most common issue for women treated with gynecologic cancer (Stilos et al., 2008). Psychological risk factors include anxiety, partner interaction, and depression.

Pathophysiology

Why It Happens

Changes in libido are multifactorial and include psychological and physiologic reasons. When working with patients who have changes in libido, nurses need to ask if the changes cause them concern. Decreased libido may not be perceived as a problem by everyone who experiences it.

What Causes It

Psychological factors include depression (Shell et al., 2008), invasive surgery that provokes a post-traumatic stress disorder of past sexual abuse, concern that sex may cause recurrence or metastasis of disease, partner relationship, and stress that decreases androgen, thus resulting in decreased desire. The two greatest psychological predictors for lowered libido following surgical menopause for benign reasons include preoperative depression and preoperative sexual problems (Shifren & Avis, 2007).

Physiologic factors include surgery, drugs, treatment side effects, type of cancer diagnosis, and noncancer-related causes. Surgery may cause a decrease in libido. For example, patients experience decrease in libido after rectal surgery (Sartori et al., 2011; Stamopoulos et al., 2009). Men who have an orchietectomy indicate a loss of libido, but it is undetermined whether the cause is physical or psychological because testosterone levels remained stable after removal of one testicle (Eberhard et al., 2009; Kim, McGlynn, et al., 2012). Libido can be affected by side effects from the surgical procedure, such as urine leakage after prostate surgery or creation of a neobladder. Loss of libido also can occur because of an intentional reduction of sexual hormones via chemicals or gonadal ablation.

Multiple drugs (antidepressants, antihistamines, antihypertensives, narcotics, oral contraceptives, and long-term use of sedatives), alcohol, and chronic use of cocaine and marijuana can affect libido. Many people being treated for cancer use other drugs, and therefore a complete medication history is needed. There is not always a clear cause and effect between libido and medications taken to treat cancer. For example, a selective estrogen receptor modulator such as tamoxifen can affect libido, but it is not due just to taking the drug; it is multifactorial (e.g., grief about a cancer diagnosis; fatigue from chemotherapy or radiation therapy that was done prior to the start of tamoxifen; reaction of a partner, such as the partner being so upset about the patient having a diagnosis of cancer that the partner leaves the relationship). Furthermore, a decrease or loss of libido in patients undergoing chemotherapy has been observed. Hormone ablation therapy can also cause loss of libido.

Treatment side effects can affect sexual desire, which may contribute to a loss of libido. For example, nausea, either from treatment or from abdominal pressure caused by a sexual position; vaginal or oral stomatitis; fatigue (i.e., if the person is very tired and therefore may not have desire and vaginal lubrication, thus causing dyspareunia); or dyspareunia secondary to treatment can cause a decrease in libido due to pain with intercourse (Tan et al., 2012). The type of cancer affects libido, for example, women with advanced, recurrent, or persistent cervical cancer have a greater incidence of decreased libido. Also, frontal lobe brain
tumors can result in disinhibition, or a lack of socially appropriate sexual restraint, and can influence how a person responds to increased libido. Noncancer-related reasons for loss of libido include age and medical conditions (Cunningham & Seftel, 2014). Serum total and free testosterone concentrations decrease with age (Shah, Montoya, & Persons, 2007), but no absolute correlation exists between testosterone level and libido. Known medical conditions that affect libido are diabetes, hypertension, myxedema, hyperthyroidism, Addison disease, acromegaly, chronic renal failure, multiple sclerosis, chronic respiratory conditions, and cardiac disease (Russell et al., 2010).

Many times patients who are reticent to ask about decreased libido will use the Internet to try to find answers. When providers are not aware of the questions, patients may turn to products that have not been rigorously clinically evaluated and therefore may be potentially unsafe, such as “Libido Magic” (U.S. Food and Drug Administration, n.d.).

Assessment

Taking a history is imperative and should include (a) past history of libido, (b) the patient’s current partner status, and if there is a partner, what is the partner’s health status, (c) past sexual abuse, (d) past sexual experiences, (e) whether the change in libido is a concern to the patient or partner, and (f) cultural or religious values or beliefs that may affect the change in libido (Russell et al., 2010). The use of the ACS Desire Diary can help in evaluating patient concerns (ACS, 2013). Based on the history and patient assessment, nurses may want to consider recommending that patients

• Use a Desire Diary for one week.
• Evaluate their Desire Diary to see if there are any patterns, such as settings, people, or times of the day that resulted in an increased sense of desire. Once they have noted some patterns, they can begin putting themselves in the situations that spark a sexual mood such as exercising, planning a relaxed evening out with their partner, making a special effort to look and feel sexy, reading a steamy story involving sex, watching a movie with a romantic or sexual plot, or fantasizing about a sexual encounter.
• Get their partner’s input. Discuss any fears either of them has about their sexual relationship. Patients or partners should discuss questions about medical risks with their doctor (ACS, 2013).

Laboratory Tests

A low serum testosterone level, less than 300 ng/dl, can be helpful in identifying a possible cause for a decreased libido (Rosen, 2007). The testosterone level alone is not an absolute cause of low libido; however, an association exists between the two even in patients without cancer. This helps to explain why testosterone replacement is not 100% effective and may diminish over treatment time.

A second laboratory test that can be done is prolactin level. Hyperprolactinemia, which inhibits gonadotropin-releasing hormone, is relatively common after stem cell transplantation and can decrease libido in men (Katz, 2007).

History and Physical Examination

No specific physical examination is done for evaluation of decreased libido. A “well-person” examination would identify physical conditions such as pulmonary or cardiac disorders that could affect libido. What is more important for a patient with cancer and who has decreased libido is that a detailed history is taken that includes consideration of the patient’s libido history. Clinicians should inquire about nausea, pain, fatigue, or a patient’s concern about scars
or body changes that would affect libido. The physical examination serves as a time to focus on the history and the patient’s perception and meaning of any changes.

Evidence-based interventions available for decreased libido are listed in Figure 22-10, and Figure 22-11 depicts the number of studies synthesized from the literature.

**Expected Outcomes Specific to Changes in Libido**

Providing patients an opportunity to discuss concerns about changes in libido is the overall outcome and part of treatment. Patients should feel that their concerns are being taken seriously and that options will be discussed with them. Refer to the common expected outcomes presented at the end of this chapter.

**Patient Teaching Points Specific to Changes in Libido**

Teaching points include addressing how depression, medications, fatigue, constipation, nausea, vomiting, body image changes, and partner availability can affect libido. Nurses should

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**FIGURE 22-10 Evidence-Based Practice Interventions for Libido**

<table>
<thead>
<tr>
<th>Recommended for Practice</th>
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<tr>
<td>• Healthcare providers should attend to physical as well as psychological and social sexual concerns of patients (Abbott-Anderson &amp; Kwekkeboom, 2012; Ratner et al., 2010; Rutledge et al., 2010; Singer et al., 2008; Tang et al., 2010).</td>
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<tr>
<td>• Intermittent androgen deprivation therapy (as opposed to continuous therapy) provides potential benefits for libido (Crook et al., 2012; Mearini et al., 2011).</td>
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<tr>
<td>• Patients with localized prostate cancer face persistent sexual, bowel, and/or bladder problems, depending on the chosen treatment options. Survival benefits are becoming more predictable but require that healthcare providers inform patients about treatment options and risks to maximize prognosis (King et al., 2012; Sartori et al., 2011).</td>
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<th>Likely to Be Effective</th>
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<tr>
<td>• Nerve-sparing surgical techniques preserve erectile function and overall sexual satisfaction in patients undergoing radical cystectomy and urinary diversion as compared to non–nerve-sparing techniques (Hekal et al., 2009; Le et al., 2010).</td>
</tr>
<tr>
<td>• Patients with localized prostate cancer were more sexually active if they were placed in an active surveillance program as opposed to undergoing a radical prostatectomy and/or radiation therapy (van den Bergh et al., 2012).</td>
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<tr>
<td>• Psychosocial/educational interventions are helpful for some patients (Decker et al., 2012; Reese et al., 2012).</td>
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<tr>
<th>Benefits Balanced With Harms</th>
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<tr>
<td>• Types of cancer treatments can result in altered libido (Cesnik &amp; dos Santos, 2012; El-Bahnasawy et al., 2011; Singer et al., 2008; Song et al., 2012).</td>
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<tr>
<td>• The quality of relationships with partners often predicts sexual desire in patients with cancer. Interventions to support couples are recommended (Alder et al., 2008; Badr &amp; Taylor, 2009; Elliott et al., 2010; Letts et al., 2010; Sayakhot et al., 2011; Tang et al., 2010; Tsivian et al., 2009; Walker &amp; Robinson, 2012).</td>
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<th>Effectiveness Not Established</th>
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be aware of cultural values or beliefs (e.g., self-stimulation is evil, sex is a duty and not meant to be enjoyed, sex is for procreation, sexual activity may have caused the cancer or has the ability to cause recurrence) (Khoo, 2009). Nurses should be sensitive to counseling patients on the partner’s possible reaction to the diagnosis and body image changes, as patients may worry that their partner will be repulsed by these changes. Suggestions may include the use of the ACS Desire Diary, which is useful for finding patterns and planning interventions (ACS, 2013), or suggesting care at a sexuality clinic (Barbera et al., 2011).

Need for Future Research Specific to Changes in Libido

Continued research is needed regarding changes in libido for patients with cancer. Examples include (a) How might studies of libido be incorporated into clinical trials of new therapies being tested? (b) What are the cultural questions regarding the importance of libido to different cultural belief groups (age, sex, sexual orientation, ethnicity, marital status, socioeconomic status, acceptability of discussing sexual issues [Stilos et al., 2008], and educational level)? (c) Does the potential impact on libido affect decisions about cancer treatment options? (d) Is libido included in treatment discussions? and (e) How does the reaction of a partner to a cancer diagnosis or treatment affect the patient’s libido? Qualitative studies that capture the full scope of libido changes are needed (Shell et al., 2008).

Infertility

Overview

Although cancer often is seen as a disease of older adults, more than 72,000 adolescents and young adults ages 15–39 are diagnosed yearly (Quinn et al., 2011). For those treated in this age cohort, risk of infertility is 50%–95% (Quinn et al., 2011). Of women

FIGURE 22-11 Libido Literature Synthesis

Note. See Melnyk, 2004, for a description of the levels of evidence. Literature search completed August 2013.
younger than age 40, 1 in 47 are diagnosed with cancer (Chuai, Xu, & Wang, 2012). Fertility preservation strategies have been shown to improve emotional coping, whereas infertility increases the risk of emotional distress, which can be as stressful as the diagnosis of malignancy. Many people do not pursue the available options of surrogacy, gamete donation, or adoption because of religious beliefs, personal beliefs, adoption agency criteria, or the lack of information. Reproductive concerns affect sexual functioning (Canada & Schover, 2012), which is why infertility is included in the chapter on altered sexuality patterns.

**Definition**

In the general population, *infertility* is defined as the inability to conceive after one year of unprotected intercourse (Chuai et al., 2012). For many newly diagnosed patients of childbearing/conceiving age, this definition poses an obstacle to obtaining insurance coverage for fertility preservation options (Campo-Engelstein, 2010; Carlson, 2009).

**Risk Factors**

Risk factors for infertility in patients with cancer include decreased fertility present before diagnosis, age, type of malignancy, stage of disease, type of surgery performed, and other treatments used, such as radiation therapy, chemotherapy, or hormonal manipulation (Chuai et al., 2012). The length of therapy may lead to delays in pregnancy attempts, leading to a forgotten risk of infertility (Penrose, Beatty, Mattiske, & Koczwara, 2013).

Many patients undergoing cancer treatment have a lack of information about how to preserve fertility (Penrose et al., 2013). In fact, it has resulted in a new specialty area—oncofertility, which focuses on fertility preservation for cancer survivors (Lange, Hurst, Matthews, & Tait, 2013). One role of healthcare providers is to inform patients and partners about options to preserve fertility (Penrose, Beatty, Mattiske, & Koczwara, 2012). Healthcare providers may not discuss fertility preservation with patients for numerous reasons (see Figure 22-12). For some women, the importance of preserving fertility may outweigh the importance of preventing recurrence (Lee et al., 2010). A 2009 American Society of Clinical Oncology (ASCO) survey found that less than 25% of healthcare providers regularly referred or even provided educational pamphlets about fertility preservation to patients (Carlson, 2009). In 2013, ASCO released updated guidelines on fer-

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**FIGURE 22-12** Reasons Providers May Not Discuss Fertility Preservation With Patients

- Lack of knowledge of fertility preservation techniques
- Concerns that the patient is not able to afford fertility preservation
- Personal judgment that the patient would not want to engage in exploring the option because of age, religious beliefs, or cultural beliefs
- Concern that aggressiveness of the disease requires immediate treatment
- Belief that the type of disease is associated with risk of infertility at time of diagnosis
- Discomfort in discussing the topic
- Concern that discussion will result in additional stress or burden for the patient
- Belief that the patient’s prognosis is poor
- Lack of availability of preservation options in the community
- Workload or environment barriers (e.g., heavy workload or lack of support)

*Note. Based on information from Carlson, 2009; Flemming, 2012; Lange et al., 2013.*
tility preservation to facilitate increased discussions between survivors and providers (Loren et al., 2013).

The risk of infertility can be due to reasons unrelated to cancer, such as age and environmental factors. Ten percent to 12% of healthy couples have difficulty conceiving a child (National Infertility Association, 2014). Today, women often focus on establishing their career and thus delay childbearing. Other contributory environmental factors include smoking, radiation, and chemotherapy decreasing ovarian follicles (atresia).

In men, spermatogenesis is the process by which male spermatogonia develop into mature spermatozoa; the entire process takes approximately 64 days. Similar to infertility in women, environmental factors and age negatively affect sperm development in terms of quantity and/or quality of sperm. Spermatogenesis begins at puberty and usually continues uninterrupted until death.

The type of malignancy may affect male fertility. The three most common diagnoses that affect male fertility at time of diagnosis are Hodgkin disease, testicular cancer, and non-Hodgkin lymphoma. For men diagnosed with Hodgkin disease, 70% have abnormal semen analyses at the time of diagnosis (Lambert & Fisch, 2007). Of patients with testicular cancer, 60%–75% have low sperm counts, poor motility, or low semen volume at diagnosis (Kaufman & Chang, 2007). Elevated FSH level and/or advanced stage of disease increases the risk of infertility (Lambert & Fisch, 2007). However, the stage of testicular cancer does not affect sperm quality.

Surgical interventions that can affect male fertility include bilateral orchiectomy and retroperitoneal lymph node dissection, which can cause retrograde ejaculation (Lambert & Fisch, 2007). Surgeries that can affect female fertility include hysterectomy, bilateral salpingooophorectomy, and radical cystectomy.

The dose, treatment field, and schedule of radiation therapy affect male fertility in a dose-dependent manner; the greater the dose, the longer the time for spermatogenesis to return. If the male has a radiation dose less than 1 Gy, return to fertile levels will take 9–18 months (Girasole et al., 2007); with doses greater than 4 Gy, spermatogenesis can take five years or longer. Doses greater than 6 Gy and total body irradiation usually result in complete sterility (Bashore, 2007).

For women older than age 30, doses of 5 Gy to the ovary or 30 Gy to the hypothalamic or pituitary gland can result in infertility (NCI, 2013). Previously, it was reported that radiation would not be a great risk to prepubertal females. However, preliminary data indicate the same numbers of oocytes are damaged, but the effect on the patient’s fertility may be delayed because young females have a large number of oocytes (Leonard, 2006). Of all the radiation treatments, total body irradiation carries the highest risk of infertility to both sexes. Even when the field of therapy is not near the genitals, such as with cranial radiation therapy, fertility can be affected.

If a female is treated with radiation therapy and is able to conceive, she is at risk of not carrying the fetus to full term. Abdominal radiation of preadolescent and adolescent females can affect growth and development of the uterus, preventing full uterine growth and affecting blood flow to the uterus. Even if the female is postpubertal, radiation to the pelvis will affect the uterus so that it may be unable to enlarge enough for the growing fetus, thus increasing the risk of miscarriage or premature birth. Cranial-spinal radiation can increase the risk of miscarriage by 3.6 times (Alvarez et al., 2007).

Chemotherapy can be a significant threat to fertility depending on the age of the person being treated, type of chemotherapy given, dose of treatment, and length of treatment (NCI, 2013). Androgen deprivation therapy, whether done medically or surgically, will affect fertility in men by preventing spermatogenesis.
Pathophysiology

Why It Happens

The pathophysiology of infertility in patients diagnosed with cancer is not clearly understood. It may be caused by the tumor itself, cytokine response, or disruption of the hypothalamic-pituitary axis (Lambert & Fisch, 2007). Cancer treatment in women can cause premature ovarian failure and decrease ovarian reserve, increasing the risk of infertility (Chuai et al., 2012).

What Causes It

Surgically induced infertility depends on the type of surgical procedure. Removal of reproductive organs in both men and women has an obvious impact on infertility, as well as consequences of surgery, such as retrograde ejaculation or failure of emission in men. Cancer therapies have indirect and direct effects on fertility in men and women. Indirect effects of treatment such as fear of recurrence or chemotherapy impact on cardiac function can result in safety concerns about pregnancy (Canada & Schover, 2012). The pathophysiology of chemotherapy-induced infertility for women is due to ovarian reserve reduction on the number and quality of oocytes in the ovaries (Schover, 2008). Older women (older than age 40) have a low primordial follicle pool and therefore tend to be at greater risk for permanent infertility (Chuai et al., 2012). Chemotherapy-induced male infertility is due to damage to the germinal epithelium. Alkylating agents (busulfan, cyclophosphamide, nitrogen mustard, dacarbazine, chlorambucil, ifosfamide, and melphalan), nitrosoureas (carmustine and lomustine), plant alkaloids (etoposide, vinblastine, and vincristine), platinum agents, antitumor antibiotics (dactinomycin, daunorubicin, doxorubicin, mitomycin, and mitomycin), antimetabolites (cytarabine arabinoside, 5-fluorouracil, and methotrexate), and others (procarbazine, temozolomide, thiopeta, and cisplatin) affect the gonads: follicles are affected, and ovaries decrease in size and fibrose; somatic and germ cell function is disrupted, affecting spermatogenesis (Bashore, 2007).

Chemotherapy can affect both Sertoli cell and Leydig cell functions, which serve to nurture the cell through spermatogenesis and secrete androgens, respectively (Lambert & Fisch, 2007). The amount of DNA damage depends on the patient’s age, dose, and chemotherapy regimen (Tierney, 2008). Men diagnosed with malignancies tend to have sperm with a higher rate of DNA damage, which is associated with lower fertility; however, this does not result in higher rates of birth defects of children born to these men following treatment. It is unknown if the newer treatments (e.g., monoclonal antibodies) will affect fertility.

Radiation therapy can affect fertility. Radiation to the pituitary gland affects production of FSH, LH, and testosterone. XRT to the brain impairs the hypothalamus and reduces the production of gonadotropin-releasing hormone. Radiation to the brain or spinal cord interferes with functioning of the hypothalamic-pituitary axis, which also affects levels of gonadotropin-releasing hormone. Infertility from cranial-spinal irradiation received prior to the advancements in radiation equipment probably is due to scattering of radiation to the ovaries. Total body irradiation creates the highest risk to fertility of all radiation treatments (Lange et al., 2013) with patients at highest risk being young females within two years of menarche (before or after menarche). Combination chemotherapy and XRT can cause spermatogonia destruction or spermatogenesis arrest.

Assessment

When cancer is first diagnosed, the pressing issue often is how quickly treatment can be started (Peddie et al., 2012). Although fertility is not automatically the first concern when
one is confronted with a new potentially life-threatening diagnosis, it must be considered when treatment decisions are being made.

A timely assessment of the meaning of fertility and understanding for the individual, couple, and/or family needs to occur, often before treatment options are chosen. This is a time of great stress, however, responsible professionals will consider fertility for all patients who are newly diagnosed with cancer, regardless of the patient’s age. The assessment of fertility should query the values and belief systems of the patient and/or partner and include a discussion of prediagnosis expectations of parenting. Sensitivity to social, cultural, religious, financial, and legal considerations also should be included in the assessment.

**Laboratory Tests**

Multiple tests can be used to assess fertility (Lambert & Fisch, 2007). Nurses can help to explain the purpose of the tests and provide additional information when requested. For men, semen analysis examines the volume, sperm concentration, motility, and morphology. For women, decreased levels of inhibin B, a reproductive hormone, may be a marker for atresia, the decrease of ovarian follicles. Hormonal analysis of elevated serum FSH, estradiol level, low estrogen level, LH, anti-Müllerian hormone concentration, testosterone, and prolactin can be performed (Kuohung & Hornstein, 2014).

Radiologic studies can include scrotal ultrasound and transrectal ultrasound. If scrotal varicoceles are present, color flow duplex ultrasonography can be performed. Pelvic ultrasounds of women may show decreased ovarian volume and a decreased number of antral follicles (Schover, 2008).

**Physical Examination**

For males, examination of the penis, scrotum, and testicular volume or examination for prostate abnormalities can be performed (Lambert & Fisch, 2007). The scrotal sac should be evaluated for varicoceles. These are found in about 40% of men without a history of cancer who are undergoing evaluation for infertility (Gurevich, 2014).

If a woman has had abdominal XRT as a child, an examination of uterine size can be performed. As with all fertility evaluations, a complete gynecologic examination, including size, shape, and position of the female reproductive organs, should be done.

Evidence-based interventions available for decreased libido are listed in Figure 22-13, and Figure 22-14 depicts the number of studies synthesized from the literature.

**Expected Outcomes Specific to Infertility**

- Nurses will develop a level of comfort and an ability to discuss fertility issues with patients.
- Patients will feel comfortable discussing fertility concerns with staff.
- Fertility issues will be addressed in a culturally sensitive manner.
- Patients will be given options for fertility preservation if it is safe and can be done in a timely manner.
- When aggressiveness of tumor does not allow the initiation of treatment to be safely delayed, patients will be informed why fertility preservation cannot be done. When making this decision, keep in mind that it no longer necessary to wait 36 hours between semen collections.
- Staff support is readily available and receptive for patients to ask questions about the cost of fertility preservation so that they can make informed decisions.
- Nurses will discuss the option of sperm banking with all socioeconomic groups and will not assume patients will not sperm bank because of poor finances.
• If the patient is a minor, issues of fertility are addressed with guardians and the minor if he or she is mature enough to understand. Keep in mind that sexual maturation is an adolescent developmental task.
• Gonadal function is screened as a part of follow-up care.
• Fertility will be discussed with patients regardless of age, sex, ethnicity, sexual orientation, or marital status.

**Patient Teaching Points Specific to Infertility**

• Explain to patients that a multidisciplinary and longitudinal approach, if possible, will best serve their fertility preservation decisions. This may reduce their concerns about multiple staff members discussing fertility issues with them.

<table>
<thead>
<tr>
<th>FIGURE 22-13</th>
<th>Evidence-Based Practice Interventions for Infertility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended for Practice</strong></td>
<td></td>
</tr>
<tr>
<td>• Sperm cryopreservation for males is recommended (Loren et al., 2013).</td>
<td></td>
</tr>
<tr>
<td>• Embryo cryopreservation is an option if treatment delay does not cause risk to patient (Loren et al., 2013).</td>
<td></td>
</tr>
</tbody>
</table>

| Likely to Be Effective | | |
| • Ovarian transposition or oophoropexy can be offered, but risk exists for radiation scatter or remigration of ovaries (Loren et al., 2013; O’Neill et al., 2011). | |
| • Gonadotropin suppression during chemotherapy may reduce the risk of premature ovarian failure for some women (Moore et al., 2014). | |

| Benefits Balanced With Harms | | |
| • Addressing concerns about infertility is important before and after (long-term) cancer treatment (Cana-da & Schover, 2012; Karaöz et al., 2010; O’Neill et al., 2011; Peddie et al., 2012; Penrose et al., 2012). | |
| • The type of treatment can alter fertility (Choi et al., 2013; Loren et al., 2013). | |
| • Hormonal stimulation with nontraditional aromatase inhibitor regimens may be considered in women with hormone-sensitive malignancies (Loren et al., 2013). | |
| • Cryopreservation of unfertilized oocytes may be offered for women who do not have the option of embryo cryopreservation (Loren et al., 2013). | |

| Effectiveness Not Established | | |
| • Photodynamic therapy was effective as a conservative fertility-sparing treatment in young women with early-stage endometrial cancer (Choi et al., 2013). | |
| • The feminine identity of women with cervical cancer was repaired by fertility preservation using radical trachelectomy (Komatsu et al., 2014). | |
| • Ovarian tissue cryopreservation can be offered when embryo or oocyte preservation is not possible (O’Neill et al., 2011). | |
| • Testicular tissue cryopreservation, reimplantation or grafting of testicular tissue, remains experimental (Loren et al., 2013). | |
| • Fertility preservation for children is considered experimental (Loren et al., 2013). | |

| Effectiveness Unlikely | | |
| • No interventions at the time of publication | |

| Not Recommended for Practice | | |
| • Hormonal gonadoprotection for men is unsuccessful (Loren et al., 2013). | |
| • Sperm cryopreservation after initiation of chemotherapy poses risk of genetic damage (Loren et al., 2013). | |
Because discussion about fertility preservation occurs at a time of great stress, which interferes with retention of information, patients will benefit from written handouts that can help to reinforce complex information about options and be used as a reference when a more reflective time may be available.

Patients’ unique social, cultural, or religious characteristics may have an impact on which interventions might be acceptable to them and merit discussion.

Female patients without partners have limited options, but available options are use of donor sperm, ovarian transposition, or cryopreservation of oocyte, embryo, or ovarian tissue.

Awareness of developmental stage is critical. Young adults’ developmental task is parenthood in addition to career and relationship establishments and identity stabilization (Adams et al., 2011). Adolescents are known to desire information about how their diagnosis and treatment might affect sexuality and fertility options (Bashore, 2007).

Older adults may grieve the loss of fertility even when they are beyond their reproductive years. Incorporate fertility preservation information into routine treatment checklists or protocols so that it is not overlooked.

Discussion of fertility should include a section on the legal and cost implications of banking sperm, oocytes, or embryos. For example, if the patient should die, who “owns” the stored tissue, and if pregnancy occurs from use of the stored tissue after the death of the patient, what rights will the child have to insurance or other benefits?

Resumption of regular menstruation is not an indicator of fertility.

**Need for Future Research Specific to Infertility**

Future studies regarding fertility should include the possible effects of biologic agents such as interferons, interleukins, and monoclonal antibodies on fertility and should identify strategies to preserve fertility (e.g., protection of gonadal tissue) (Tierney, 2008). Psychosocial and QOL issues also need to be investigated, such as how do fertility interventions affect...
fertility-related distress and what are the QOL outcomes in patients who become infertile because of cancer treatments (Penrose et al., 2013).

**Expected Outcomes**

**Expected Outcomes of Providers**

It is an expectation that providers will discuss sexual functioning, when possible, prior to treatment initiation. This potentiates patients’ ability to give a fully informed consent (Cavallo, 2013). In the initial patient conversation, the nurse’s focus is on reassuring patients that even though their sexuality may change following diagnosis and treatment, sexuality can continue to be an enjoyable part of life. While nurses need to be proactive in providing this information and not waiting for patients to ask (Shell et al., 2008), they also need to assess if possible changes in sexuality are of concern to the patient before recommending interventions (DiGiulio, 2014).

The expected outcome is that with experience, each staff member will feel more comfortable in discussing, in a culturally sensitive manner, topics of sexuality or fertility with patients of all ages, sexes, ethnicities, sexual orientation, partner status, or prognosis. Even those with a terminal prognosis expect providers to address sexual concerns (Carter, Bryant-Lukosius, DiCenso, Blythe, & Neville, 2011). Using a nonjudgmental approach to build rapport will create a safe environment for open discussion (Davis, Meneses, & Messias, 2010). It is important that providers not assume a heterosexual orientation, but rather ask patients about their sexual orientation (Boehmer et al., 2007) and include the partner when appropriate (Decker, Pais, Miller, Goulet, & Fife, 2012).

For staff members who are not yet comfortable discussing sexuality, each staff member, at a minimum, must be able to raise the topic and then direct the patient to a team member who is more comfortable in discussing the topic and providing detailed information. This is not yet the standard practice as evidenced in studies that have reported approximately 25% of oncologists and 19% of oncology nurses do not discuss possible changes in sexual function from treatment (Sacerdoti et al., 2010).

When addressing altered sexual functioning issues, nursing care includes assessing the effectiveness of interventions. When the intervention is determined not to be helpful, the provider will consult with another professional for further options. It is expected that the provider will reinforce that the discussion and assessment will continue through the cancer trajectory and even years after treatment with tailored information provided as their experiences and circumstances change. Resources will be offered (Bober & Varela, 2012) both verbally and written, as a combination is more effective (Cleary, McCarthy, & Hegarty, 2012).

**Expected Patient Outcomes**

Patients will recognize that sexual health is part of the survivorship care plan (Cavallo, 2013). They will develop a comfort level enabling them to ask nurses and physicians questions about sexuality and/or fertility. With knowledge, patients’ awareness will increase and they will potentially avoid unsafe experimentation with folk remedies for sexual dysfunction because open discussion of the pros and cons of these strategies may limit their use. Patients will have access to and knowledge of resources at their discretion, such as books, journals, websites, and support groups. The patient and partner will be able to dis-
cuss changes in sexual functioning related to the disease and treatment, with the hope of creating a satisfying sex life.

**Patient Teaching Points**

Patients can suffer from information overload during diagnosis and treatment. Therefore, written information with resources can be invaluable (Cleary et al., 2012). An information-rich source of written information is available on the ACS website at www.cancer.org using a search for *sexuality and cancer*. Other helpful websites are available from Macmillan Cancer Support (2011) and NCI (2013; see also www.cancer.gov). Development of a list of self-help books and of a network of colleagues to whom clients can be referred will contribute to patient education and care (Bolte & Zebrack, 2008; Park, Norris, & Bober, 2009).

Following the crisis created by a diagnosis and treatment of cancer, a key role of nurses is to reassure patients and their partners that counseling about marital/couple functioning during diagnosis and treatment has the potential to strengthen the patient and partner’s relationship rather than counseling being seen as a sign of weakness or marital discord (Kadmon et al., 2008). Patients should be informed that the oncology team is available to discuss sexual concerns throughout the cancer care trajectory because sexual functioning can change long after completion of therapy (Cleary et al., 2012). Providing the opportunity for discussions about sexual functioning and including partners in the discussion are two key patient teaching points (McGrath, 2012). Because changes in sexuality affect both the patient and partner, the patient should be encouraged to invite and include the partner in the conversations about possible side effects of diagnosis and treatments (McCorkle, Siefert, Dowd, Robinson, & Pickett, 2007). Given that a partner may have different concerns than the patient, specific information may need to be provided to the partner (Sandham & Harcourt, 2007). If the survivor has or will have a new partner, the nurse can help him or her rehearse and even role-play how to disclose the diagnosis and changes in sexual function (Bolte & Zebrack, 2008). Routine use of clinically pragmatic self-assessment scales for survivors to report sexual and body image concerns will help identify those who would benefit from intervention (Ferguson et al., 2012). Including sexuality as a factor in survivorship care plans will facilitate increased attention to this aspect of life (Cavallo, 2013).

**Need for Future Research**

Future studies need to focus on multiple areas related to sexuality, despite the increased number of studies conducted in the last few years. Because patients are living longer, future research on the longitudinal and prospective sexual effects of cancer treatment and diagnosis continues to be a need to better examine the trajectory to include the strengths that are developed and the positive outcomes (Salonen et al., 2011; Zeng et al., 2011). QOL instruments need to be designed that include contextual factors, not just the physiologic changes. This would allow identification of contributing factors (i.e., social life disruptions, comorbidities, partner support, effect on partners and families) to sexual challenges faced by survivors (Sawin, 2012; Ussher et al., 2012; White & Boehmer, 2012; Zebrack et al., 2010; Zeng et al., 2011). In fact, investigators are challenged to delete the coital imperative and instead examine the total relationship (Abbott-Anderson & Kwekkeboom, 2012; Cleary et al., 2013; Ussher et al., 2012).

Future research could include examination of the development of a collective language and epistemology, cultural aspects that may be barriers to accurate assessment, the role of sex-
ual identity of same-sex partners, and the impact of religion on sexuality (Boehmer, Potter, & Bowen, 2009; Cleary et al., 2013; Jabson, Donatelle, & Bowen, 2011; Klaeson et al., 2011; Yoon et al., 2008). More specific instrument designs to measure the sexual function of young adult survivors are critical with the increase in the number of young adult survivors (Zebrack et al., 2010). Studies could address the lack of treatment options for female sexual disorders, such as studies on sex steroid hormones (Sandhu et al., 2011). The majority of studies discuss the need to address the sexual impact of a cancer diagnosis and treatment with patients and their partners, but there is a paucity of research on what to discuss, when to discuss it, and with whom (Anderson et al., 2011; Jefferies & Clifford, 2011).

Conclusion of Case Study

The nurse responds, “It sounds to me as if you have questions about your married life and how surgery might affect you as a husband. I’ve been a nurse for seven years now, and the most common questions men have after prostate surgery are about urinary incontinence and sexual function. We have an oncology clinical nurse specialist here at the hospital. She works with survivors, and you’ll be meeting her at your postoperative visit. She is a great resource. Until you meet with her, let me give you her business card and this handout we have about sexuality after surgery.”

The oncology nurse was able to do multiple things with that less-than-two-minute intervention. She normalized and validated the concerns in a respectful manner. With awareness that the time of discharge is not an opportune time to begin this conversation and that she had two other patients awaiting discharge and her responsibility to them, she used the PLISSIT model to intervene: She gave permission that it was common to have postoperative concerns about sexual functioning. She gave them limited information via the handout, and then she referred them to the oncology clinical nurse specialist.

Conclusion

The goal of this chapter was to stimulate nurses’ awareness that changes in sexual functioning and perceived risks to fertility can have both an immediate and a future impact on patients. Although some evidence-based interventions are known, much still needs to be investigated that can lead to improvements in patient care. Survivors are entitled to healthy sexual functioning (Kingsberg, 2010), and nurses have the responsibility to be their advocates. Nevertheless, nurses are in a perfect position to complete a comprehensive and thorough assessment and to share knowledge of effective interventions to improve the sexual health of their patients.

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CHAPTER 23

Skin and Nail Alterations

Megan Dunne, RN, MA, ANP-BC, AOCNP®, Chhiu-Mei Liu, NP, and Mario Lacouture, MD

Case Study

M.C. is a 62-year-old woman newly diagnosed with metastatic stage IV non-small cell lung cancer (NSCLC). She is a never-smoker and her pathology revealed an epidermal growth factor receptor (EGFR) mutation. Her oncologist prescribed first-line systemic therapy with the oral epidermal growth factor receptor inhibitor (EGFRI) erlotinib 150 mg daily in accordance with National Comprehensive Cancer Network® (2014) guidelines. The nurse meets with the patient prior to starting erlotinib to review topical and oral therapies to prevent the acneform rash associated with this therapy. Seven days after initiating erlotinib, the patient presents to the clinic with a grade 1 rash on her face, chest, and back. Papules and pustules are noted. One week later, after 14 days of erlotinib, the patient returns, stating the rash is now tender, itchy, and more widespread on her face, chest, and now her scalp. She comments, “I don’t even want to see my friends because my face looks awful.”

Overview

Skin and nail changes related to treatment with systemic anticancer agents have been reported since the inception of chemotherapy. These alterations are now occurring with increasing frequency, as novel agents that target specific pathways critical to tumor growth, such as erlotinib, cetuximab, panitumumab, sunitinib, and sorafenib, gain wider use. Over the past 15 years, the approach to cancer has changed because of an improved understanding of how tumors develop and grow. Targeted anticancer strategies, such as EGFRIs, now exist that inhibit proteins and pathways involved in cancer cell growth. These drugs have gained notoriety because many of the more common treatment toxicities (e.g., neutropenia, nausea) are avoided with these new agents. However, they present their own adverse events (AEs), including dermatologic toxicities. Although most patients receiving EGFRIs develop dermatologic toxicities, few large, randomized controlled studies have been performed to determine best practices. Recently, a multinational interdisciplinary panel of experts in supportive care in cancer reviewed pertinent studies using established criteria to develop first-generation recommendations for EGFR-associated dermatologic toxicities and infection (Lacouture et al., 2011). Many of these recommendations are included here along with assessment strategies and interventions based on expert opinion and randomized trials. With proper education and management, patients often can tolerate these agents quite well.
In addition, BRAF inhibitors, such as vemurafenib and dabrafenib approved for the treatment of melanoma, paradoxically activate adenosine triphosphate–dependent wild-type RAF and the mitogen-activated protein kinase (known as MAPK) pathway (Holderfield et al., 2013). Various cutaneous AEs include but are not limited to cutaneous squamous cell carcinoma, hyperkeratotic lesions, maculopapular rashes, keratosis pilaris–like reactions, and photosensitivity (Anforth, Fernandez-Peñas, & Long, 2013), which warrant close dermatologic monitoring. Some studies have shown that using a BRAF inhibitor, such as dabrafenib, in conjunction with an MEK inhibitor, such as trametinib, greatly reduced the incidence rate of cutaneous neoplasms (Anforth et al., 2013). Dermatologic toxicities can range from localized nonbothersome changes to serious generalized alterations that are so severe they lead to dose reductions or even discontinuation of therapy, which could potentially diminish response rates or disease management. Skin and nail alterations often are reversible within a few weeks to months of withdrawal of the causative agent (Dasanu, Vaillant, & Alexandrescu, 2006). Anticipation of and comprehensive symptom management for these changes may lead to prolonged therapy and improved tolerance of treatment regimens. This, in turn, may lead to a better chance for control of patients’ respective cancers.

A summary of targeted therapies and their common side effects are listed in Table 23-1.

**Quality-of-Life Issues**

Although anticancer therapies can lead to improvement of cancer symptoms and prolonged survival, dermatologic toxicities can significantly affect patients’ quality of life (Hackbarth, Haas, Fotopoulou, Lichtenegger, & Sehouli, 2007). The cosmetic changes can interfere with body image and can be painful enough to limit one’s ability to perform usual activities. A study of 91 patients receiving chemotherapy agents including taxanes, polyethylene glycol (PEG) doxorubicin, other anthracyclines (epirubicin and doxorubicin), topotecan, and other agents found that the overall incidence of dermatologic AEs (including skin, nail, and hair side effects) was 87% (Hackbarth et al., 2007). This study used the health-related quality-of-life score, and skin changes were the most frequently reported bothersome side effect (34%).

Among dermatologic toxicities, rash and pruritus are reported to have the greatest negative effect on quality of life, even more so than alopecia, mucositis, and painful nail changes (Rosen, Case, et al., 2013). Therefore, preparing patients to both prevent and treat these AEs is of great importance.

**Assessment**

Nurses must accurately describe skin and nail alterations. A familiarity with common dermatologic descriptive terms is imperative to accomplish this. Many terms will be defined further in this chapter, but the following are some commonly used descriptions and terms for rash or skin changes (definitions from Merriam-Webster, 2014).

- **Skin lesion**—localized, pathologic change in skin
- **Macule**—flat lesion
- **Papule**—raised lesion measuring less than 5 mm
- **Pustule**—lesion with inflamed base; lesion that contains pus
- **Plaque**—a localized abnormal patch on a body part or surface and especially on the skin (i.e., psoriasis plaque)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Targets</th>
<th>Indications</th>
<th>Dermatologic Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib</td>
<td>EGFR, ErbB2</td>
<td>Melanoma</td>
<td>Nail changes (40%), rash/acne (14.6%)</td>
</tr>
<tr>
<td>Axitinib</td>
<td>VEGFR1, VEGFR2, VEGFR3, PDGFRB, c-KIT</td>
<td>RCC, advanced</td>
<td>Palmar-plantar erythrodysesthesia syndrome (27%; grade 3–4: 5%), rash (13%; grades 3–4: &lt; 1%)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>VEGF</td>
<td>CRC, glioblastoma, NSCLC, RCC, breast cancer, ovarian cancer, STS, angiosarcoma</td>
<td>Alopecia (6%–32%), dry skin (7%–20%), exfoliative dermatitis (3%–19%)</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>Bcr-Abl, Src</td>
<td>Ph1-positive CML, refractory</td>
<td>Rash (35%)</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>c-Met and VEGFR2</td>
<td>Medullary thyroid cancer, metastatic</td>
<td>Rash (19%), dry skin (19%), alopecia (16%), erythema (11%), hyperkeratosis (7%)</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>ErbB1</td>
<td>Metastatic CRC, KRAS mutation-negative (wild-type), head and neck SCC, advanced NSCLC</td>
<td>Rash/desquamation (95%; grades 3–4: 16%), acneform rash (all studies: 76%–88%; grades 3–4: 1%–17%; onset: &lt; 14 days), dry skin (57%), pruritus (47%), nail changes (31%)</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>ALK, Met</td>
<td>Advanced ALK-positive NSCLC</td>
<td>Rash (16%)</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Multiple targets</td>
<td>ALL, CML</td>
<td>Rash (11%–21%; includes drug eruption, erythema, erythema multiforme, erythematous rash, erythrosis, exfoliative rash, follicular rash, heat rash, macular rash, maculopapular rash, milia, papular rash, pruritic rash, pustular rash, skin exfoliation, skin irritation, urticaria vesiculosa, vesicular rash)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>ErbB1</td>
<td>Recurrent or metastatic NSCLC, pancreatic cancer</td>
<td>Rash (49%–75%; grade 3: 5%–13%; grade 4: &lt; 1%; median onset: 8 days), dry skin (4%–17%), paronychia (4%–16%), alopecia (14%–15%), pruritus (7%–13%), acne (6%–12%)</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>EGFR</td>
<td>Metastatic NSCLC</td>
<td>Rash (43%–54%), acne (25%–33%), dry skin (13%–26%), paronychia (14%)</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Bcr-Abl</td>
<td>CML, GIST</td>
<td>Rash (9%–50%; grades 3–4: 1%–9%), dermatitis (GIST &lt; 39%), pruritus (8%–26%), alopecia (GIST 10%–15%)</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>ErbB1, ErbB2</td>
<td>HER2-positive advanced breast cancer</td>
<td>Palmar-plantar erythrodysesthesia (hand-foot syndrome) (with capecitabine: 53%; grade 3: 12%), rash (28%–44%), dry skin (10%–13%), alopecia (&lt; 13%), pruritus (&lt; 12%), nail disorder (&lt; 11%)</td>
</tr>
</tbody>
</table>

(Continued on next page)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Targets</th>
<th>Indication</th>
<th>Dermatologic Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nilotinib</td>
<td>Bcr-Abl</td>
<td>CML, GIST</td>
<td>Rash (29%–38%), pruritus (20%–32%), alopecia (11%–13%)</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>EGFR</td>
<td>CRC, metastatic, KRAS mutation negative</td>
<td>Skin toxicity (90%; grades 3–4: 14%–16%), erythema (65%; grades 3–4: 5%), acneform rash (57%; grades 3–4: 7%), pruritus (57%; grades 3–4: 2%), nail toxicity (29%; grades 3–4: 2%), exfoliation (25%; grades 3–4: 2%), paronychia (25%), rash (22%; grades 3–4: 1%), fissures (20%; grades 3–4: 1%), acne (13%; grades 3–4: 1%), dry skin (10%)</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>VEGFR2, PDGFR, c-KIT</td>
<td>STS, thyroid cancer, RCC</td>
<td>Hair color change (38%–39%), rash (8%–18%), alopecia (8%–12%), palmar-plantar erythrodysesthesia (6%–11%), skin depigmentation (3%–11%), dry skin (6%), nail disorder (5%)</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>Bcr-Abl</td>
<td>ALL, CML</td>
<td>Rash (34%–54%), dry skin (24%–39%), cellulitis (&lt; 11%)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Chimeric monoclonal antibody</td>
<td>CLL, HL, NHL</td>
<td>Rash (10%–17%; grades 3–4: 1%), pruritus (5%–17%), angioedema (11%; grades 3–4: 1%)</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Multiple targets</td>
<td>Advanced RCC, hepatocellular cancer, angiosarcoma, GIST, thyroid cancer</td>
<td>Rash/desquamation (19%–40%; grade 3: &lt; 1%), hand-foot syndrome (21%–30%; grade 3: 6%–8%), alopecia (14%–27%), pruritus (14%–19%), dry skin (10%–11%)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Multiple targets</td>
<td>GIST, PNET, RCC (advanced), STS, thyroid cancer (refractory)</td>
<td>Skin discoloration (25%–30%), rash (14%–29%), hand-foot syndrome (14%–29%; grades 3–4: 4%–8%), hair color changes (7%–29%), dry skin (&lt; 23%), alopecia (5%–14%), erythema (12%), pruritus (12%)</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>ErbB2</td>
<td>Breast cancer, adjuvant treatment, HER2 positive; gastric cancer, metastatic, HER2 positive</td>
<td>Rash (4%–18%), acne (2%), nail disorder (2%), pruritus (2%)</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>RET, VEGFR, EGFR</td>
<td>Medullary thyroid cancer</td>
<td>Rash (53%; grades 3–4: 5%), dermatitis acneform/acne (35%; grades 3–4: 1%), dry skin (15%), photosensitivity (19%), pruritus (11%)</td>
</tr>
</tbody>
</table>

(Continued on next page)
Chapter 23  Skin and Nail Alterations  603

**Keratoacanthoma**—a dome-shaped epithelial nodule with a central keratin-filled crater; is a variant of squamous cell carcinoma

**Milia**—also known as a whitehead; a small, white to yellow, pearly, firm, keratin-containing epidermal cyst, located on the eyelids, cheeks, and forehead in pilosebaceous follicles

**Discrete**—refers to a single lesion with well-defined borders

**Confluent**—refers to multiple lesions with ill-defined borders that are conjoined

**Erythema**—redness, inflammation (often painful)

**Follicular**—lesion of or surrounding a hair follicle in skin

**Blister**—a fluid-filled elevation of the epidermis, may be large

**Vesicle**—a small abnormal elevation of the outer layer of skin enclosing a watery liquid

Skin alterations should be described as either localized to one small area or generalized over a broader area of skin. Body surface measurement can be done using the rule of nines (see EMTResource.com, 2014).

Although other grading systems for skin toxicities exist, nurses should be familiar with the Common Terminology Criteria for Adverse Events (CTCAE) (National Cancer Institute Cancer Therapy Evaluation Program [NCI CTEP], 2010), a grading system used by clinicians to describe AEs of cancer therapies (see Table 23-2).

### Nail Changes

A number of anticancer agents are known to produce pigmentary changes affecting the skin or nails. Nail changes are reported in up to 40% of patients receiving docetaxel therapy (Robert et al., 2005). Nail bed changes also commonly occur with the chemotherapy agents 5-fluorouracil (5-FU), doxorubicin, methotrexate, paclitaxel, and bleomycin. These changes in appearance range from cosmetic changes, such as Beau lines (transverse white lines or grooves), which signal a cessation of nail growth, or hyperpigmentation appearing as linear dark bands, to severe deformities in the appearance of the nails (onychodystrophy). Nails

### TABLE 23-1  Dermatologic Side Effects of Targeted Therapies (Continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Targets</th>
<th>Indication</th>
<th>Dermatologic Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vemurafenib</td>
<td>BRAF</td>
<td>Melanoma</td>
<td>Rash (37%-52%; grade 3: 7%-8%), photosensitivity (33%-49%; grade 3: 3%), alopecia (36%-45%), pruritus (23%-30%); skin papilloma (21%-30%), hyperkeratosis (24%-28%), cutaneous SCC (24%; grade 3: 22%-24%), maculopapular rash (9%-21%), dry skin (16%-19%), actinic keratosis (8%-17%), seborrheic keratosis (10%-14%), sunburn (10%-14%), erythema (8%-14%), papular rash (5%-13%)</td>
</tr>
</tbody>
</table>

ALK—anaplastic lymphoma kinase; ALL—acute lymphocytic leukemia; CLL—chronic lymphocytic leukemia; CML—chronic myeloid leukemia; CRC—colorectal cancer; EGFR—epidermal growth factor receptor; GIST—gastrointestinal stromal tumor; HL—Hodgkin lymphoma; NHL—non-Hodgkin lymphoma; NSCLC—non-small cell lung cancer; PDGFR—platelet-derived growth factor receptor; PDGFRB—beta-type platelet-derived growth factor receptor; Ph—Philadelphia chromosome; PNET—pancreatic neuroendocrine tumor; RCC—renal cell cancer; SCC—squamous cell cancer; STS—soft tissue sarcoma; VEGF—vascular endothelial growth factor; VEGFR—vascular endothelial growth factor receptor

**Note.** Based on information from Wilkes & Barton-Burke, 2012; Wolters Kluwer Health, n.d.
### TABLE 23-2 Common Terminology Criteria for Adverse Events for Skin Changes

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papulopustular rash</td>
<td>Papules and/or pustules covering &lt; 10% BSA with or without symptoms (e.g., pruritus, tenderness)</td>
<td>Papules and/or pustules covering 10%–30% BSA with or without symptoms (e.g., pruritus, tenderness); associated with psychosocial impact; limiting instrumental ADL</td>
<td>Papules and/or pustules covering &gt; 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated</td>
<td>Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences</td>
<td>Death</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesi syndrome</td>
<td>Minimal skin changes or dermatitis (e.g., erythema, edema, hyperkeratosis) without pain</td>
<td>Skin changes (e.g., peeling, blisters, bleeding, edema, hyperkeratosis) with pain; limiting instrumental ADL</td>
<td>Severe skin changes with pain; limiting self-care ADL</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Dry skin</td>
<td>Covering &lt; 10% BSA and no associated erythema or pruritus</td>
<td>Covering 10%–30% BSA and associated with erythema or pruritus; limiting instrumental ADL</td>
<td>Covering &gt; 30% BSA and associated with pruritus; limiting self-care ADL</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Skin hyperpigmentation</td>
<td>Hyperpigmentation covering &lt; 10% BSA; no psychosocial impact</td>
<td>Hyperpigmentation covering &gt; 10% BSA; associated psychosocial impact</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Paronychia</td>
<td>Nail fold edema or erythema; disruption of the cuticle</td>
<td>Localized or oral intervention indicated; edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL</td>
<td>Surgical intervention or IV antibiotics indicated; limiting self-care ADL</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

(Continued on next page)
can appear ridged, and cuticles and periungual areas (areas surrounding fingernails or toenails) can become erythematous, edematous, and painful, resulting in paronychia characterized by inflammation of the tissues adjacent to the nail, usually accompanied by tenderness, infection, and pus formation (Robert et al., 2005).

**Paronychia and Onycholysis**

Paronychia presents as inflammation of the periungual folds of nails (see Figure 23-1). It usually occurs after two or more months of treatment with EGFRIs and can cause patients significant pain and become dose limiting (Ocvirk & Cencelj, 2010). Management consists of topical antibiotics, chemical cauterization, and nail avulsions. It can affect any finger or toe but most often is seen in the thumb or great toe (Lacouture, 2006b). It is not known

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**TABLE 23-2** Common Terminology Criteria for Adverse Events for Skin Changes *(Continued)*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>Mild or localize; topical intervention indicated</td>
<td>Intense or widespread; intermittent; skin changes from scratching; oral intervention indicated; limiting instrumental ADL</td>
<td>Intense or widespread; constant; limiting self-care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

ADL—activities of daily living; BSA—body surface area

why some nails are affected and others are not. Paronychial inflammation can be painful and prevent patients from performing certain activities or wearing shoes other than sandals. If not treated, paronychia may take months to resolve, and secondary infections are common (see Figure 23-2). The pathogenesis of paronychia is unknown, but when the appearance suggests the presence of infection with pus or erythema, a culture should be obtained. Paronychia does not seem to have an infectious origin, although superinfection with *Staphylococcus aureus* and gram-negative organisms is common (Robert et al.,

---

**FIGURE 23-2  Paronychia Treatment Algorithm**

<table>
<thead>
<tr>
<th>Severity Grading (CTCAE)</th>
<th>Description</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>–</td>
<td>Institute prophylactic therapy with applying moisturizing creams to periungual areas; avoid wearing tight-fitting shoes; keep nails short; avoid hot water when bathing or dish washing. Take biotin oral supplement to strengthen nails.</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Nail fold edema or erythema; disruption of the cuticle</td>
<td>Continue anticancer agent at current dose and monitor for change in severity. Treat with topical antibiotics or antiseptics (e.g., iodine). Reassess after 2 weeks (either by healthcare professional or patient self-report); if reactions worsen or do not improve, proceed to the next step.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL</td>
<td>Continue anticancer agent at current dose and monitor for change in severity. Treat with topical antibiotics and vinegar soaks* daily and silver nitrate applications weekly. Reassess after 2 weeks (either by healthcare professional or patient self-report); if reactions worsen or do not improve, proceed to the next step.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Surgical intervention or IV antibiotics indicated; limiting self-care ADL</td>
<td>Modify dose per package insert; obtain bacterial/viral cultures if infection is suspected. Continue with treatment with systemic antibiotics and silver nitrate applications; consider nail avulsion. Reassess after 2 weeks; if reactions worsen or do not improve, dose interruption or discontinuation may be necessary.</td>
</tr>
</tbody>
</table>

ADL—activities of daily living; CTCAE—Common Terminology Criteria for Adverse Events, version 4.0

*Vinegar soaks: Soak the affected fingers or toes in a 1:1 solution of white vinegar and water for 15 minutes daily.

*Note. From "Dermatologic Toxicities" (p. 377), by E. Balagula and M.E. Lacouture in I.N. Olver (Ed.), The MASCC Textbook of Cancer Supportive Care and Survivorship, 2011, New York, NY: Springer. Copyright 2011 by the Multinational Association of Supportive Care in Cancer. Adapted with permission.*
For infectious cases, treatment with antibiotics may prove helpful. Patients should be advised to avoid paronychial trauma (e.g., nail or cuticle biting, restrictive shoes, use of nonsterile nail care equipment at nail salons during manicures or pedicures) (Robert et al., 2005). In the presence of infection, oral antibiotics driven by sensitivities are indicated. Topical agents that may be effective include mupirocin, bacitracin zinc/poly-myxin B sulfate, iodine solutions or gels, and silver nitrate. The potential for infection requires close monitoring. The use of vinegar soaks for 15 minutes every day is helpful to keep areas devoid of bacteria (Lacouture et al., 2011). Surgical nail removal or excision (nail avulsion) followed by phenol appears to be the most effective treatment but should only be performed by experienced practitioners (Lacouture et al., 2011). Minor surgical excisions of ingrown nails also can prevent recurrences of paronychia (Robert, Sibaud, Mateus, & Cherpalis, 2012).

Onycholysis refers to a condition in which nails are separated partially or completely from the nail bed (see Figure 23-3). A variety of antineoplastic agents, including the anthracyclines, bleomycin, dactinomycin, mitomycin, and mitoxantrone, but more commonly paclitaxel and docetaxel, have been reported to cause this alteration (Daniel & Scher, 1984; Flory et al., 1999).

Subungual hemorrhage (see Figure 23-4) forms within the epidermis of the nail bed and consists of a mass of blood in a layer of squamous cells that adhere to the underlying surface of the nail (Robert et al., 2005). This is seen commonly with taxanes, but linear splinter hemorrhages are seen with vascular endothelial growth factor receptor (VEGFR) inhibitors, such as sorafenib and sunitinib (Wood, 2006). However, hemorrhagic onycholysis and subungual abscesses can lead to substantial discomfort with negative impact on patients’ quality of life. Morbidity associated with these alterations can lead to dose reductions or even discontinuation of treatment with the causative agent because of patients’ intolerance of these effects.

Taxanes include paclitaxel and docetaxel, which were both introduced in the late 1980s. Both drugs have proven efficacy in solid tumors such as lung, breast, prostate, ovarian, and bladder cancers. Unfortunately, both drugs also cause nail changes, including changes in nail pigmentation, splinter hemorrhage, subungual hematoma, Beau lines, acute paronychia, and onycholysis. Paclitaxel has been documented to lead to toxicities of nail discoloration or ridging in approximately 17% of patients treated (Minisini et al., 2003). Grade 2 (NCI CTEP, 2010) onycholysis (separation or loosening of a nail from its bed) or paronychia occurs in 3% of those treated with paclitaxel. The incidence of onycholysis and dyschromia related to docetaxel may be as high as 44%. Possible explanations for these occurrences include taxane-induced thrombocytopenia (low platelet level), distal nerve damage, and vascular abnormalities (Minisini et al., 2003).
Hyperpigmentation

Hyperpigmentation refers to asymptomatic darkening of the skin and is most common in the nails or over the joints of fingers (interphalangeal) or hands (metacarpophalangeal). It can occur within two weeks of treatment with a causative agent and last for several months after the agent has been discontinued (Lacouture, Boerner, & LoRusso, 2006). Hyperpigmentation is strictly cosmetic, without discomfort, and often reversible once treatment is completed but may last for many years. It is more common in patients with olive or dark skin and may be the result of melanocyte stimulation by chemotherapy agents such as bleomycin, busulfan, capecitabine, cetuximab, cyclophosphamide, docetaxel, doxorubicin, erlotinib, 5-FU, gefitinib, paclitaxel, panitumumab, and vandetanib. The underlying mechanism is not known, but inhibitor-induced functional alterations of melanocytes may increase pigment transfer to basal keratinocytes or dermal macrophages (Chang et al., 2004). No treatment is currently known, but sun exposure may worsen the condition; therefore, patients should use broad-spectrum sunscreen (Segaert & Van Cutsem, 2005).

Adverse Events of the Palms and Soles

Over the years, many terms have been used to describe the conditions particularly involving palms and soles: hand-foot syndrome (HFS), hand-foot skin reaction (HFSR), palmar-plantar erythrodysesthesia syndrome (PPES), and acral erythema. These terms have been used interchangeably; however, because of their characteristic histopathologic and clinical differences, the corresponding term should be used for appropriate distinction (Balagula & Lacouture, 2011).

HFS describes a palmar-plantar AE primarily resulting from conventional cytotoxic chemotherapy such as 5-FU, capecitabine, and doxorubicin (see Figure 23-5). HFSR has been increasingly used as a differential description of a reaction unique to the newer targeted agents (not cytotoxic). HFSR from multitargeted kinase inhibitors, such as sorafenib, axitinib, pazopanib, sunitinib, and regorafenib (Belum, Wu, & Lacouture, 2013), is different than HFS from conventional cytotoxic agents (e.g., capecitabine, doxorubicin, 5-FU) in clinical presentation and
FIGURE 23-5 | Hand-Foot Skin Reaction Syndrome (HFS or HFSR) Treatment Algorithm

**Definition:** A disorder characterized by redness, marked discomfort, swelling, tingling in the palms of the hands or the soles of the feet

**Causative agents:** Axitinib, capecitabine, cytarabine, doxorubicin, 5-fluorouracil, pazopanib, sorafenib, sunitinib, vemurafenib

<table>
<thead>
<tr>
<th>Severity Grading (CTCAE)</th>
<th>Description</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>No symptoms</td>
<td>Prophylaxis with an exfoliant moisturizer cream (ammonium lactate 12%, urea 10%–40%, salicylic acid 3%–6%) BID. <strong>Preventive intervention for capecitabine-induced HFS:</strong> Celecoxib 200 mg/m² BID</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Minimal skin changes or dermatitis (e.g., erythema, edema, hyperkeratosis) without pain</td>
<td>Continue drug at current dose and monitor for change in severity. <strong>Apply exfoliant moisturizer cream (ammonium lactate 12%, urea 10%–40%, or salicylic acid 3%–6%) BID.</strong> <strong>Capecitabine-induced HFS:</strong> Celecoxib 200 mg/m² BID</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Skin changes (e.g., peeling, blisters, bleeding, edema, hyperkeratosis) with pain; limiting instrumental ADL</td>
<td>Continue drug at current dose and monitor for change in severity. <strong>Apply potent topical steroid (clobetasol 0.05%, betamethasone) cream BID to painful areas, apply lidocaine (cream, patch) as needed up to QID to painful areas, and control pain with NSAIDs/GABA agonists/narcotics.</strong> <strong>Capecitabine-induced HFS:</strong> Celecoxib 200 mg/m² BID <strong>Doxorubicin or pegylated doxorubicin-induced HFS:</strong> Oral dexamethasone (8 mg BID for 5 days beginning the day before the infusion followed by 4 mg BID for 1 day, then 4 mg once daily for 1 day)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Severe skin changes (e.g., peeling, blisters, bleeding, edema, hyperkeratosis) with pain; limiting self-care ADL</td>
<td>Interrupt treatment until severity decreases to grade 0–1; continue treatment of the reaction with the following. <strong>Apply potent topical steroid (clobetasol 0.05%, betamethasone) cream BID to painful areas, apply lidocaine (cream, patch) as needed up to QID to painful areas, and control pain with NSAIDs/GABA agonists/narcotics.</strong> <strong>Capecitabine-induced HFS:</strong> Celecoxib 200 mg/m² BID <strong>Doxorubicin or pegylated doxorubicin-induced HFS:</strong> Oral dexamethasone (8 mg BID for 5 days beginning the day before the infusion followed by 4 mg BID for 1 day, then 4 mg once daily for 1 day)</td>
</tr>
</tbody>
</table>

ADL—activities of daily living; CTCAE—Common Terminology Criteria for Adverse Events, version 4.0; GABA—gamma-aminobutyric acid; NSAID—nonsteroidal anti-inflammatory drug

*Note.* From “Dermatologic Toxicities” (p. 366), by E. Balagula and M.E. Lacouture in I.N. Olver (Ed.), The MASCC Textbook of Cancer Supportive Care and Survivorship, 2011, New York, NY: Springer. Copyright 2011 by the Multinational Association of Supportive Care in Cancer. Adapted with permission.
histopathology. HFS presents as diffuse and symmetric erythema and edema of the palms and soles, affecting areas of nonpressure or nonfriction, whereas HFSR is a skin reaction of localized blisters and hyperkeratotic lesions to areas of subclinical friction or trauma. They are similar in their palmar-plantar distribution, and severity and pain are dose dependent (Balagula & Lacouture, 2011). Dysesthesia (uncomfortable sensation) and paresthesia (numbness) often precede the full manifestation of HFSR and include erythema, edema, hyperkeratosis, fissures, and callus-like, non-fluid-filled blisters (Rosen, Balagula, Goldfarb, & Lacouture, 2013; Stone, Sood, & Coleman, 2010). The antiangiogenesis of the VEGFR inhibitors (e.g., axitinib, pazopanib, sorafenib, sunitinib) hinders the blood supply to the tumor yet simultaneously causes HFSR in skin because of their vasoconstrictive effect. Asians tend to have a greater propensity for HFSR as a result of genetic polymorphisms, as do patients with prior exposure to VEGFR inhibitors and other comorbidities (Fischer, Wu, Ho, & Lacouture, 2013). There is also an association with particular cancers and their treatments manifesting cutaneous adverse reaction in the hands and feet. These agents are frequently used to treat renal cell carcinoma, hepatocellular carcinoma, and gastrointestinal stromal tumor. Patients with renal cell carcinoma seem to have higher incidence of developing HFSR than patients with other cancers; this is probably due to the baseline compromised renal function (Fischer et al., 2013).

Measures to protect and treat affected areas are critical in improving quality of life for patients experiencing HFSR. Patients should be instructed to avoid friction or pressure on their feet by wearing comfortable footwear, especially during the first two months of therapy. They should also moisturize and exfoliate their feet by applying topical urea 40% cream with salicylic acid at least twice daily. In addition, it is necessary to treat the areas affected with blisters or calluses with potent topical steroids (such as clobetasol 0.05% or betamethasone, to decrease the inflammation) and apply topical anesthetics (such as lidocaine or prilocaine) for the pain so that patients’ functional level is not compromised (Rosen, Gómez-Fernández, Mark, Zic, & Lacouture, 2013) (see Figure 23-5).

PPES is the only term used in the latest CTCAE toxicity grading (NCI CTEP, 2010) and denotes both HFS and HFSR. It refers to skin changes on the hands and feet. Incidence of PPES depends on the agent, dose, and route of drug delivery. PPES was first reported in 1982 and occurred in 34% of patients receiving 5-FU continuous-infusion therapy. In patients receiving 5-FU as an IV bolus, incidence was 13% (Lokich & Moore, 1984). In a study of patients with colorectal cancer (CRC) receiving daily capecitabine oral chemotherapy (a prodrug of 5-FU that converts enzymatically to 5-FU in vivo), the incidence of HFS was 68%, and 11%–17% of patients experienced severe grade 3 toxicity with moist desquamation, ulceration, blistering, and severe pain interfering with activities of daily living (Abushullaih, Saad, Munsell, & Hoff, 2002). Fifty-six percent of patients with breast cancer experienced PPES associated with capecitabine in a study (Blum et al., 1999).

PPES incidence is highest in patients receiving PEG doxorubicin (doxorubicin encapsulated in PEG-coated liposomes), estimated at greater than 50% in those receiving doses of 50 mg/m², with highest grade 3–4 severity occurring in 23.8% of patients at this dose level. Incidence and severity are dose dependent and occur with less frequency and intensity at lower doses (Janssen Products, LP, 2013). Liposomal daunorubicin has been cited to cause PPES when given in higher doses with infusion rates longer than commonly used (Hui & Cortes, 2000).

Xerosis

Xerosis is often referred to as dry skin and can evolve into xerotic dermatitis or eczema. Abnormal epidermal keratinocyte differentiation in patients receiving chemotherapy or tar-
geted therapy leads to a deteriorated stratum corneum with a decrease in loricrin, which is the main protein holding together the scaffolding of the epidermis. This process results in an epidermis that cannot preserve moisture, leading to dryness (Tsimboukis, Merikas, Karapanagiotou, Saif, & Syrigos, 2009). For treatment, frequent application of emollients with 5%–10% urea, ammonium lactate 12%, and salicylic acid 3%–6% twice daily and within 15 minutes of showering or bathing can substantially improve skin dryness (Robert et al., 2012). It also is important to use fragrance-free detergents and soaps to avoid irritation.

**Pruritus**

Pruritus is defined as localized or generalized itching caused by irritation of sensory nerve endings and is a frequent occurrence in patients receiving targeted cancer therapies (Ensslin, Rosen, Wu, & Lacouture, 2013). A systematic review and meta-analysis of 17,368 patients revealed an incidence of up to 30.7% for all grades of pruritus, with up to 44% of patients reporting a negative impact on their quality of life as a result (Ghandi, Oishi, Zubal, & Lacouture, 2010). Figure 23-6 presents a treatment algorithm for pruritus.

**Rash**

**Pemetrexed-Induced Rash**

Pemetrexed is a multitargeted antifolate and is active as a single agent or in combination with cisplatin or carboplatin in both NSCLC and malignant pleural mesothelioma (Adjei, 2004). Current research also supports the usefulness of pemetrexed in other solid tumors such as colorectal cancer (Hochster, 2002), small cell lung cancer (Socinski, 2005), and breast cancer (Llombart-Cussac et al., 2007). Skin rash is one of the principal toxicities of pemetrexed. Routine use of prophylactic oral dexamethasone appears to lessen the frequency of severe rash (Socinski, 2005). A typical dose regimen of dexamethasone is 4 mg administered twice daily for three days beginning the day prior to pemetrexed administration for grade 2–3 rash. For grade 1 rash, topical steroids are usually sufficient (Socinski, 2005).

**Targeted Therapy-Induced Rash**

The EGFRIs known as the epidermal growth factor receptor tyrosine kinase inhibitors are oral agents that target members of the human epidermal growth factor receptor (HER) family. In accordance with National Comprehensive Cancer Network treatment guidelines (www.nccn.org), they are used alone or in combination for the treatment of lung (erlotinib), pancreatic (erlotinib in combination with gemcitabine), breast (lapatinib in combination with capecitabine or anastrozole), head and neck (cetuximab in combination with radiation therapy), and colorectal cancers (cetuximab or panitumumab). Generally, the acneform rash appears in the first weeks of treatment with an EGFRi (Albanell et al., 2002; Balagula et al., 2011; Hidalgo et al., 2001).

EGFRi therapies are associated with dermatologic toxicity of varying severity. The Br.21 trial of erlotinib (N = 731) revealed skin toxicity as the most common AE, with any grade rash occurring in 76% of patients treated. The most severe grade 3 or 4 rash occurred in 9% of patients. Additionally, 12% of patients had rash severe enough to warrant dose reduction, and
**Definition:** A disorder characterized by an intense itching sensation

**Causative agents**
- Chemotherapies and targeted therapies: Actinomycin, all-trans-retinoic acid, arsenic trioxide, asparaginase, bexorotene, bleomycin, capecitabine, cetuximab, chlorambucil, cladribine, cyclophosphamide, cytarabine, dasatinib, daunorubicin, docetaxel, doxorubicin, erlotinib, etoposide, gefitinib, gemcitabine, ibritumomab, imatinib, interferon alfa, interleukin-2, ipilimumab, irinotecan, lenalidomide, mechlorethamine, melphalan, mercaptopurine, methotrexate, nilotinib, nilutamide, octreotide, paclitaxel, panitumumab, pazopanib, pemetrexed, procarbazine, retinoic acid, rituximab, romidepsin, sargramostim, sorafenib, streptozocin, temozolomide, thalidomide, thioguanine, thiotepa, tositumomab, vincristine, vinorelbine, vorinostat
- Hormone therapies: Anastrozole, bicalutamide, estramustine, exemestane, fluoxymesterone, letrozole, leuprolide, medroxyprogesterone, megestrol, tamoxifen, toremifene
- Blood thinners: Dalteparin, enoxaparin, tinzaparin, warfarin
- Blood stimulants: Darbepoetin alfa, epoetin alfa, filgrastim, fondaparinux, pegfilgrastim
- Morphine, codeine, or other opioid derivatives
- Nonsteroidal anti-inflammatory drugs: Aspirin, ibuprofen, naproxen

<table>
<thead>
<tr>
<th>Severity Grading (CTCAE)</th>
<th>Description</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>–</td>
<td>Provide gentle skin care instructions.</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Mild or localized; topical intervention indicated</td>
<td>Continue drug at current dose and monitor for change in severity.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Topical moderate/high potency strength steroid OR topical antipruritics (pramoxine 1%, doxepin 5% cream) applied BID.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reassess after 2 weeks (either by healthcare professional or patient self-report); if reactions worsen or do not improve proceed to the next step.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Intense or widespread; intermittent; skin changes from scratching (i.e., edema, population, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL</td>
<td>Continue drug at current dose and monitor for change in severity.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apply topical moderate-/high-potency steroid OR topical antipruritics (pramoxine 1%, doxepin 5% cream) BID AND oral antipruritics.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reassess after 2 weeks (either by healthcare professional or patient self-report); if reactions worsen or do not improve, proceed to the next step.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Intense or widespread; constant; limiting self-care ADL</td>
<td>Dose-modify as per protocol, obtain bacterial/cultures if infection is suspected, and continue treatment of skin reaction with the following.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Oral antipruritics AND oral corticosteroids (prednisone 0.5–1 mg/kg or equivalent for 5 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Oral gabapentin or pregabalin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reassess after 2 weeks; if reactions do not improve, discontinuation of drug per protocol may be necessary.</td>
</tr>
</tbody>
</table>

*Note.* From “Dermatologic Toxicities” (p. 375), by E. Balagula and M.E. Lacouture in I.N. Olver (Ed.), *The MASCC Textbook of Cancer Supportive Care and Survivorship*, 2011, New York, NY: Springer. Copyright 2011 by the Multinational Association of Supportive Care in Cancer. Adapted with permission.
erlotinib dosing was interrupted in 14% of patients because of intolerable rash (Shepherd et al., 2005). When severe, dermatologic rash can lead to dose modification or discontinuation of therapy by 36% and 72% of healthcare providers, respectively (Boone et al., 2007).

Cetuximab is an EGFRI antibody given by IV infusion. Rash occurred in 88% of patients treated with cetuximab in combination with irinotecan and in 90% of patients treated with cetuximab monotherapy (ImClone Systems Inc. & Bristol-Myers Squibb Co., 2013; Saif & Kim, 2007).

Other tyrosine kinase inhibitors include sorafenib and sunitinib, which target two different signaling pathways. The first pathway is vascular endothelial growth factor, which plays a critical role in the proliferation, migration, and survival of endothelial cells involved in angiogenesis. The second pathway is platelet-derived growth factor. By blocking this pathway, sorafenib and sunitinib disrupt the stability and maturation of existing blood vessels around tumors. Rash and desquamation related to sunitinib occurs in 40% of patients receiving this therapy. Of those receiving sorafenib, HFSR occurs in 30% (Wood, 2006).

Pathophysiology

Rash is the most common, the earliest, and the most bothersome side effect of EGFRIs, occurring in more than 75% of patients after two weeks of therapy (Robert et al., 2012). It is sometimes described as “acneform” because it appears as follicular papulopustules located on the face, scalp, and trunk. However, the lack of cystic lesions or comedones discerns this AE from routine acne (Lacouture et al., 2010). The stratum corneum of the epidermis also has been noted to be thinner and without the characteristic basketweave pattern in the skin of patients treated with cetuximab or gefitinib (Pérez-Soler et al., 2005). The rash usually develops in cosmetically sensitive areas and affects the majority of treated patients. Pruritic and tender erythematous papules and pustules develop in skin containing a high density of sebaceous glands (face, scalp, upper chest, and back). Histologic analyses reveal superficial inflammatory cell infiltrate with surrounding hyperkeratosis or florid neutrophilic suppurative folliculitis with rupture of the epithelial lining (Lacouture, 2006a).

EGFRIs are novel treatments for cancer, and, therefore, their associated dermatologic AEs are still being rigorously studied and evaluated. Accurate clinical assessment is difficult at present because terminology and grading systems are not consistent among healthcare providers. Rash generally is mild (grade 1) to moderate (grade 2), with severe rash (grade 3 or 4) occurring less commonly. Inconsistent use of various scales to grade rash and terms to describe rash makes it difficult to compare severity of rash among trials and agents.

Skin rash typically presents initially as erythema within a week or two of beginning treatment (Shepherd et al., 2005; Soulieres et al., 2004). Grade 1 rash appears sooner with scattered maculopapular lesions that may have slight erythema occurring on the patient’s face, neck, scalp, anterior chest, or back (see Figure 23-7). Discomfort at this stage typically is minimal, with patients reporting mild, localized pruritus and tenderness that may worsen to severe discomfort. Although the AE is mainly dermatologic, skin toxicities result in significant physical and emotional discomfort; thus, it is imperative to maximize supportive measures for both prevention and amelioration (see Table 23-3 for prevention of EGFRI-associated rash).

Interventions

Over-the-counter emollients and cleansers: Patients should be encouraged to cleanse skin with mild, hypoallergenic emollient soaps such as Basis® or Cetaphil® (Morse & Cala-
<table>
<thead>
<tr>
<th>FIGURE 23-7</th>
<th>Epidermal Growth Factor Receptor Inhibitor (EGFRI)–Associated Rash</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Image 1]</td>
<td>EGFRI-associated rash, mild (grade 1)</td>
</tr>
<tr>
<td>![Image 2]</td>
<td>EGFRI-associated rash with symptoms of pruritus and tenderness (grade 2)</td>
</tr>
<tr>
<td>![Image 3]</td>
<td>EGFRI-associated rash with associated local superinfection (grade 3)</td>
</tr>
</tbody>
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Note. Photos courtesy of Pamela Hallquist Viale, MS, ANP, AOCNP®. Used with permission.
TABLE 23-3 Prevention for Epidermal Growth Factor Receptor Inhibitor–Associated Rash*  

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Recommended</th>
<th>Not Recommended</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical</td>
<td>Hydrocortisone 1% cream with moisturizer and sun-screen BID</td>
<td>Pimecrolimus cream</td>
<td>Tazarotene cream</td>
</tr>
<tr>
<td>Systemic</td>
<td>Minocycline 100 mg daily Doxycycline 100 mg BID</td>
<td>Tetracycline 500 mg BID</td>
<td>Doxycycline is preferred in patients with renal impairment. Minocycline causes less photosensitivity.</td>
</tr>
</tbody>
</table>

* Weeks 1–6 of epidermal growth factor receptor inhibitor initiation

Note. Based on information from Balagula & Lacouture, 2011.

If pruritus persists, systemic antihistamines may relieve symptoms (Halpern & Thomas, 2005). The rash can cause distress regarding body image and appearance. A dermatologist-approved cover-up such as Cover FX® may be helpful cosmetically, although any type of foundation that does not cause irritation may be used to cover erythema or lesions. Rash may be aggravated by sunlight, so patients should be advised to use a broad-spectrum sunscreen such as Vanicream® or a nonirritating sunscreen with a sun protection factor (SPF) of 15 or higher (Pérez-Soler et al., 2005) applied every two hours when outside. Female patients should be encouraged that coverage makeup can be safely applied and improve appearance (Robert et al., 2005).

**Topical corticosteroids:** Topical steroids have an important role, especially if used early in therapy for mild rash or after antibiotics to abate inflammation and prevent infection. However, no clinical trials have been conducted thus far to prove this hypothesis. Current evidence does support the relative safety of using intermittent corticosteroids on the face, as the risk of skin thinning or atrophy occurs only after prolonged use and reverses once treatment has stopped (Pérez-Soler et al., 2005). Topical immunomodulatory agents such as pimecrolimus and retinoids such as adapalene gel should be avoided because they may exacerbate skin dryness and pruritus (Lacouture et al., 2011; Pérez-Soler et al., 2005).

**Systemic antibiotic prophylaxis or mitigation:** Patients can be informed that randomized clinical trials support the prophylactic use of systemic tetracyclines in preventing EGFRI-induced cutaneous AEs. Initiating dermatologic treatment early can potentially avoid interrupting or dose-reducing life-prolonging cancer treatment (Baas et al., 2012; Burtness et al., 2009), thereby improving quality of life and adherence to the therapeutic doses of EGFRIs.

**Systemic antibiotic treatment:** Patients who develop a rash related to any agent may develop secondary infection with associated pustules, inflammation, and worsening erythema. These can worsen the rash, particularly in appearance. To reduce the likelihood of secondary infection of nasal mucosa, twice-daily application of intranasal mupirocin should be considered. Secondarily infected rash that is confined to a localized area (e.g.,
chin or paranasal area) may be effectively managed with topical agents such as clindamycin, but bacterial cultures are always recommended (Eilers et al., 2010). Generalized infected rash over larger areas or follicular pustules may respond well to a short course of oral antibiotics. Tetracyclines (minocycline) have been suggested because of their proposed weak anti-inflammatory effects combined with their activity against *Staphylococcus aureus* (Jatoi et al., 2008). However, many different oral antibiotics may be effective. The agent should be continued for at least six weeks, and if no improvement occurs, cultures should be obtained and an antibiotic with a broader spectrum should be used (Pérez-Soler et al., 2005).

Skin rash can rapidly deteriorate to grade 2 or 3; therefore, patients should be evaluated regularly during the first two months of therapy. Clinicians with available secure patient portals can encourage patients to send photographs of their rash for triage over the telephone. Patients may report severe generalized pruritus or itching, with acute areas of painful breakout on their face, neck, or scalp making them feel overwhelmed by the change in their appearance. Patients may require psychosocial support to continue with their treatment. Figure 23-8 presents a treatment algorithm for EGFRI-associated rash.

<table>
<thead>
<tr>
<th>Severity Grading (CTCAE)</th>
<th>Description</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>–</td>
<td>Implement prophylactic therapy with hydrocortisone 2.5% cream or alclometasone cream AND an oral antibiotic (i.e., doxycycline, minocycline*) for the first 6 weeks.</td>
</tr>
</tbody>
</table>
| Grade 1                  | Papules and/or pustules covering < 10% BSA, which may or may not be associated with symptoms of pruritus or tenderness | Continue anticancer agent at current dose and monitor for change in severity.  
Treat with hydrocortisone 2.5% cream and clindamycin 1% gel every day.  
Reassess after 2 weeks (either by healthcare professional or patient self-report); if reactions worsen or do not improve, proceed to the next step. |
| Grade 2                  | Papules and/or pustules covering 10%–30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL | Continue anticancer agent at current dose and monitor for change in severity.  
Treat with hydrocortisone 2.5% cream and doxycycline (100 mg) or minocycline (100 mg BID).*  
Reassess after 2 weeks (either by healthcare professional or patient self-report); if reactions worsen or do not improve, proceed to the next step. |

(Continued on next page)
FIGURE 23-8  Epidermal Growth Factor Receptor Inhibitor–Associated Rash (Papulopustular, Acneform) Treatment Algorithm (Continued)

| Grade 3 | Papules and/or pustules covering > 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated |
|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
|         | Modify dose per PI; obtain bacterial/viral cultures if infection is suspected.                                                                                                                                 |
|         | Treat with hydrocortisone 2.5% cream and doxycycline (100 mg) or minocycline (100 mg BID)* plus prednisone (0.5 mg/kg) for 5 days.                                                                 |
|         | Reassess after 2 weeks (either by healthcare professional or patient self-report); if reactions worsen or do not improve, dose interruption or discontinuation per PI may be necessary.                  |

| Grade 4 | Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences |
|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
|         | Modify dose per PI; obtain bacterial/viral cultures if infection is suspected.                                                                                                                                 |
|         | Treat with hydrocortisone 2.5% cream and doxycycline (100 mg) or minocycline (100 mg BID)* plus prednisone (0.5 mg/kg) for 5 days.                                                                 |
|         | Reassess after 2 weeks (either by healthcare professional or patient self-report); if reactions worsen or do not improve, dose interruption or discontinuation per PI may be necessary.                  |

* For patients who are allergic or intolerant to doxycycline or minocycline, other antibiotics such as cefadroxil, amoxicillin/clavulanic acid, or sulfamethoxazole/trimethoprim may be used.

ADL—activities of daily living; BSA—body surface area; CTCAE—Common Terminology Criteria for Adverse Events, version 4.0; PI—package insert.

Note. From “Dermatologic Toxicities” (p. 365), by E. Balagula and M.E. Lacouture in I.N. Olver (Ed.), The MASCC Textbook of Cancer Supportive Care and Survivorship, 2011, New York, NY: Springer. Copyright 2011 by the Multinational Association of Supportive Care in Cancer. Adapted with permission.

**Patient Teaching Points**

Patient education prior to the initiation of a drug that causes dermatologic toxicity is imperative. Nurses provide this education so that patients can recognize the early signs of skin rash and seek timely intervention with management to minimize the progression to a high-grade, bothersome rash. Nurses should educate patients receiving EGFRIs that rash may be an indication of response to therapy and that patients should not stop taking their medications without consulting their treatment team first. This reinforcement may encourage patients to remain on a therapy despite experiencing low-grade, cosmetically challenging skin changes. It may help for patients to decide what degree of rash is tolerable in relation to a positive outcome in their response to treatment (Oishi, 2008). Nurses should teach patients the elements of skin care as discussed in this chapter, including regular use of mild cleansers and emollient moisturizers. Skin irritants, for example, alcohol-based cleansers, should be avoided. Nurses should educate patients regarding the increased risk of irritation with sun exposure associated with these agents and the necessity of using products with SPF 15 or greater. Also, it is important to emphasize that the
rash peaks around four to six weeks and then improves, so patients will not suffer with rash throughout their entire treatment.

Need for Future Research

Randomized clinical trials are needed to test these interventions and determine those that best manage dermatologic AEs. Oncology nurses are an important part of the treatment team and can lead the way in future research. The cosmetic challenges encountered by patients with facial and body rash can be daunting. Nurses should use the evidence-based technique of active and empathetic listening while patients convey their psychological concerns (Oishi, 2008). Future studies should examine the impact of nursing interventions and measure the effectiveness of the guidelines recommended by clinical experts.

Conclusion of Case Study

M.C.’s case illustrates the importance of considering interventions that can improve patients’ ability to tolerate targeted therapies despite adverse side effects. Nurses assess and grade skin toxicities and provide education and recommendations for prevention and management of cancer therapy–related skin changes. The nurse’s treatment plan in this case should have included education regarding the potential for an acneform rash that will likely peak at around four to six weeks and decrease after about eight weeks of therapy. Prevention techniques including prophylactic therapy with broad-spectrum sunscreen with SPF of at least 15 and gentle skin care instructions including hydrocortisone 1% combined with gentle moisturizer should have been reviewed. Barring any contraindications, the patient could also have prophylactically begun a regimen of doxycycline 100 mg BID, which appears to have a more favorable safety profile than minocycline, especially in patients with renal dysfunction. Minocycline 100 mg daily is also effective with less photosensitivity, but all patients taking any tetracycline therapy should be educated regarding potential photosensitivity and the importance of sunscreen (Lacouture et al., 2011). EGFR-associated rashes tend to present on the most cosmetically challenging areas of the face, nose, and neck (see Figure 23-7). Makeup camouflage may be beneficial for M.C.

When M.C. returns with a grade 2 rash after 14 days of erlotinib therapy, the nurse discusses treatment options with the team and educates the patient regarding topical application of a higher potency steroid cream, such as alclometasone 0.05%, or an antibiotic, such as fluocinonide 0.05% BID. The nurse supports the patient and instructs her to continue on the same dose of tetracycline and erlotinib therapy. The nurse reassures M.C. that the rash dissipates over time in most patients.

If the rash worsens or persists, the team may decide to dose-reduce the erlotinib, but only when all supportive measures have failed to make this toxicity tolerable for the patient. Postinflammatory skin alterations of erythema and hyperpigmentation are long-term sequela that can last for several months or years if patients continue erlotinib. Nursing education and support of patients suffering from painful and cosmetically challenging rash are imperative to maintain adherence with treatment regimens that are likely to ameliorate symptoms of cancer and prolong patients’ lives.
Conclusion

Novel targeted cancer agents have unique dermatologic AEs. Only limited research has been conducted to help nurses in developing strategies for treating rash and changes associated with targeted agents. More randomized controlled trials are necessary to develop new strategies to discern the optimum treatment for skin effects of anticancer agents. Until then, current interventions are based on prior clinical experience and patient response. The recommendations contained in this chapter are based on knowledge of the rash’s inflammatory nature and the experience of nurses and dermatologists. As the use of these agents becomes more widespread, evidence-based guidelines for rash management will be imperative.

Nursing education for patients prior to the initiation of treatments that may alter their skin or nails is imperative to help patients recognize early onset of these changes and ensure prompt intervention to prevent worsening or intolerable skin changes. This, in turn, may enable patients to tolerate higher doses of cancer therapies for longer durations, thus leading to better control of their illness.

References


Case Studies

Adult Case Study

S.M. is a 48-year-old woman, married, and the mother of three children, ages 21, 17, and 14. She works full time in retail and is very involved in her children’s lives. She was diagnosed with stage IIA breast cancer and has recovered from a mastectomy with reconstruction. Based on the pathology of the tumor, treatment of four cycles of dose-dense chemotherapy (every 14 days) with doxorubicin and cyclophosphamide (AC), followed by four cycles of paclitaxel, has been prescribed. She is perimenopausal, having irregular periods for the past eight months, and has been experiencing daily hot flashes.

S.M. comes to the clinic today for her second dose of chemotherapy. Using 0–10 visual analog scales, she reports her pain as a 4 and her fatigue as a 6. She has missed three days of work in the past 14 days because she felt she could not carry out her responsibilities because of daytime fatigue and sleepiness. S.M. rates her distress as a 5 because she has “not been a very good wife or mother” since her first chemotherapy treatment. Her most frequent problem has been sleep maintenance. She reports waking up at least 8–10 times a night and having problems falling back to sleep almost every time. On the days she has missed work and on weekends, she stayed in bed until after 9 am, which is three hours later than her usual get-up time. She also took daytime naps because she felt fatigued and sleepy.

Factors contributing to S.M.’s sleep disturbances include

- Caucasian, perimenopausal, female
- Works full-time outside the home
- Stimulating home environment with three adolescent and young adult children
- Daytime naps
- Feelings of distress and low self-worth
- Recent mastectomy with reconstruction surgery; started chemotherapy three weeks later
- Highly emetogenic chemotherapy regimen associated with abrupt menopausal symptoms.

Young Adult Case Study

B.R. is a 24-year-old man who was attending graduate school when he was diagnosed with stage IV Hodgkin lymphoma two and a half months ago. B.R. was hospitalized for one week at the time of diagnosis because of a pericardial effusion with left ventricular
compromise. His treatment regimen is to initially receive four cycles of ABVD chemotherapy, consisting of IV administrations of doxorubicin, bleomycin, vinblastine, and dacarbazine every two weeks. He has now completed two cycles, and his symptoms of shortness of breath, night sweats, and itching are relieved. B.R. also reports improved stamina. At present, B.R. lives alone, has taken the semester off from school, and is ready to return to work part-time as a research assistant.

Currently, B.R.’s most bothersome symptoms include fatigue and trouble sleeping. He is most bothered by difficulty falling asleep. He typically watches late-night sports programs, hoping to feel sleepy. He frequently falls asleep on the couch, then wakes up to go into his bed for the night and cannot fall back asleep. After he falls asleep, he reports waking several times during the night. Because he is not on a work or school schedule, B.R. usually wakes up naturally around 11 am, but upon arising feels tired and not refreshed. During the day, he admits he is bored and lonely because his girlfriend and other friends are at work or school. He has felt too tired to concentrate much on reading or resuming his usual physical activities. B.R. watches a lot of sports on television because there is nothing else to do. He frequently falls asleep during the day, sometimes sleeping for more than an hour. He is “annoyed” at being idle, and he admits he is worried about this new cancer diagnosis. He and his girlfriend agree that his mood has been irritable.

Factors contributing to B.R.’s sleep disturbances include

- Lack of daytime activity
- Long daytime naps
- Worry
- Watching late-night television
- Falling asleep in a setting outside the bedroom.

Overview

A sufficient amount of quality sleep is essential for the health and well-being of every person. Insufficient or disrupted sleep can lead to a number of negative health, safety, cognitive, and psychosocial outcomes. Recent evidence also suggests that long durations of sleep may be associated with increased morbidity and mortality (Cappuccio, D’Elia, Strazzullo, & Miller, 2010). Unfortunately, sleep problems and their daytime consequences, especially those related to insufficient sleep, commonly affect many healthy adults and children in today’s 24/7 culture (Berger, 2009). A diagnosis of cancer, its associated symptoms, various treatments, and side effects add further disruptions to a patient’s quantity and quality of sleep. Troubling cancer-related symptoms, difficult and time-consuming therapies, and the emotional distress caused by cancer frequently keep patients from getting a good night’s sleep and feeling rested upon awakening. Sleep difficulties also add to the distress caused by other symptoms and compromise daily functioning and quality of life (Berger, 2009; Fleming, Gillespie, & Espie, 2010; Palesh et al., 2010). Although sleep problems are common in people with cancer, these symptoms only recently have become the focus for evidence-based prevention and management strategies by oncology caregivers (Berger, 2009; Sateia & Lang, 2008).

Oncology care providers across all settings need adequate knowledge about sleep physiology and sleep-wake disturbances to effectively assess their patients for these troubling symptoms. Primary sleep disorders are medical diagnoses defined by the American Academy of Sleep Medicine (AASM) in the International Classification of Sleep Disorders (AASM, 2014), whereas sleep-wake disturbances are more general complaints that can be assessed and addressed by all
providers. Oncology clinicians need to add emerging evidence from sleep research to practice so that they can prescribe interventions to promote sleep and enable patients to achieve optimal rest, energy levels, and function. Likewise, sleep researchers need to partner with oncology clinician colleagues when designing interventions to reduce sleep disturbances.

This chapter provides an overview of sleep physiology and the sleep-wake disturbances that are most prevalent in people with cancer. The chapter content includes strategies and instruments for clinical sleep screening and assessment, as well as diagnostic approaches when medical sleep disorders are suspected. Finally, evidence-based interventions for sleep-wake disturbances from the Oncology Nursing Society (ONS) Putting Evidence Into Practice (PEP) program are recommended to improve sleep-wake outcomes (Berger, Desaulniers, Matthews, Otte, & Page, 2014). Although the focus of the chapter is on symptom management of patients with cancer, the authors recognize that family members, caregivers, and direct care providers also may experience sleep disturbances. (See Chapter 7 for information on caregiver burden.)

Sleep Physiology

Functions of Sleep

Sleep is an active behavioral state of disengagement and unresponsiveness to the environment and is associated with physiologic processes vital to life (Carskadon & Dement, 2011). Although the exact purposes of sleep remain unknown, ongoing research finds that sleep plays a critical role in a variety of physiologic processes that include energy conservation, memory consolidation and learning, regulation of metabolism, hormone production, and immune function (Bonnet, 2011; Vassalli & Dijk, 2009). Sleep is a basic drive to restore and rejuvenate the individual to achieve an optimal state of alertness, ability to function, and well-being during waking hours.

Sleep Architecture

The sleep-wake cycle in humans follows a diurnal circadian rhythm of approximately 24 hours (Carskadon & Dement, 2011). Sleep alternates with a state of wakefulness characterized by readiness of the brain to respond to outside stimuli. Individual variances in circadian rhythms and sleep-timing preferences lead some individuals to possess a preference for early bedtimes and wake times (“early birds” or “larks”), whereas others prefer later bedtimes and wake times (“night owls”) (Dijk & Archer, 2010).

Sleep is divided into two alternating states: rapid eye movement (REM) and non–rapid eye movement (non-REM). Non-REM sleep is further divided into four stages with recently modified nomenclature. Stages vary from light sleep (stage N1 and N2) to deep sleep (stage N3) (Carskadon & Dement, 2011). The slower electroencephalogram (EEG) waves of deep sleep are most associated with the restorative function of sleep (Berger, 2006). Non-REM sleep is associated with minimal brain activity and a moderate amount of body activity. REM sleep includes bursts of rapid brain waves associated with dreaming and muscle atonia interrupted with episodes of muscle twitching. A typical night of sleep begins with the onset of sleep in stage N1, followed by several alternating cycles of various stages of non-REM and REM sleep, which average 90–110 minutes in length (Carskadon & Dement, 2011). Early episodes of REM sleep are short but become longer as the night progresses. Deep sleep (stage N3) occurs and cycles more frequently early in the sleep period. Lighter
sleep (stages N1 and N2) and more frequent periods of REM sleep occur later in the sleep period (Carskadon & Dement, 2011).

**Model of Sleep Regulation**

The two-process model of sleep regulation has been historically proposed to explain how individual sleep and wake times are determined by the interaction of a circadian timing system (process C) and a sleep-wake homeostasis process (process S), each controlled by separate mechanisms (Achermann & Borbély, 2011). Process C is controlled by an internal “clock” located in the suprachiasmatic nucleus in the anterior hypothalamus, which synchronizes an elaborate feedback system of multiple oscillators located in tissues throughout the body to establish a 24-hour sleep-wake rhythm. The process C system incorporates stimuli from the environment, especially related to lightness and darkness, and regulates the production of neuropeptides, which promote feelings of sleepiness in the evenings and wakefulness in the mornings. Process S is influenced by the individual’s sleep-wake behaviors, including the duration and quality of prior episodes of wakefulness and sleep. Homeostatic sleep propensity, or the drive to sleep, rises during the waking hours and peaks just prior to bedtime, followed by a steady decline during sleep to its lowest level at wake time (Achermann & Borbély, 2011; Landis, 2011).

When the two regulatory processes of sleep-wake homeostasis and circadian timing are ideally coordinated, outcomes include robust rhythms of sleeping and waking associated with optimal wake-time performance and better-quality sleep and bodily functions (Berger, 2006; Kyriacou & Hastings, 2010). Changes that affect processes C and S occur as a result of normal aging as well as lifestyle behaviors, such as rotating shift work and changing sleep and nap schedules. These changes influence the timing of sleep and wakefulness, as well as the duration and structure of sleep, and may result in problems such as difficulty falling asleep (sleep latency), difficulty staying asleep (sleep maintenance), and excessive daytime sleepiness.

The Conceptual Model of Impaired Sleep (Lee, 2003) emphasizes the effects of health-related issues and developmental and lifestyle factors that result in sleep deprivation and sleep disruption. This model, illustrated in Figure 24-1, identifies the adverse health outcomes associated with insufficient sleep, including impairments in immune function, metabolism, daytime functioning, mood, and social interactions. Lee’s model is especially useful for clinicians and researchers who are interested in patients with sleep problems. Nurses can use the model to conceptualize and organize the multiple factors that may contribute to a patient’s sleep problems as well as to consider the multiple consequences of insufficient sleep on the patient’s health and well-being. For example, the nurse may assess a 50-year-old woman with newly diagnosed colon cancer and find existing causes of insufficient sleep, such as family and work responsibilities and perimenopausal symptoms, which cause nighttime awakenings. The patient’s recent diagnostic tests and anxiety about her health contribute further disruptions to her activity and sleep schedules. The nurse considers the effects of insufficient sleep on the patient’s complaints of increased fatigue, depressed mood, and irritability.

**Sleep-Wake Disturbances in Patients With Cancer**

**Pathogenesis of Sleep-Wake Disturbances**

Potential etiologic factors for sleep-wake disturbances in patients with cancer are numerous because cancer is not a single disease but rather many different disease processes that cause
a variety of symptoms. Additionally, various cancer treatments, including surgery, chemotherapy, and radiation therapy, may increase a person’s likelihood of having risk factors for sleep-related problems. These factors can be organized into demographic, lifestyle and psychological, disease-related, and treatment-related categories (Matthews & Berger, 2014) (see Figure 24-2).

Demographic factors that increase the risk for sleep-related problems include being older, female, and Caucasian (Morin & Benca, 2012). Lifestyle factors that increase risk include
daytime napping patterns and excessive environmental stimulation. Sleep patterns are influenced by psychological health threatened by ongoing concerns and worries about the disease. Anxiety and depression are common and are believed to affect sleep in patients with cancer. Disease-related factors include the presence of other symptoms, such as pain and fatigue; changes in activity and rest patterns; and alterations in hormone and cytokine production.

Treatments such as chemotherapy and hormonal therapy create estrogen deficiency and often result in premature menopause or aggravated menopausal symptoms, particularly hot flashes, that interfere with sleep (Otte, Carpenter, Russell, Bigatti, & Champion, 2010; Savard, Savard, et al., 2011). Cancer and cancer treatment also influence circadian rhythms (Block, Hrushesky, & Blask, 2009). Blunted or erratic production of cortisol, melatonin, and other substances has been identified in patients with cancer and affects sleep (Payne, Piper, Rabinowitz, & Zimmerman, 2006; Rich et al., 2005). Cancer and medical, surgical, and radiation treatments are known to increase the production of inflammatory cytokines, including interleukin-1, that may be related to daytime sleepiness and longer sleep times (Bower et al., 2011; Liu et al., 2012). Increased knowledge is needed about the relationships among sleep and neuroendocrine and metabolic patterns associated with various types of cancer and treatment (Langford, Lee, & Miaskowski, 2012).

**Common Sleep-Wake Disturbances**

Common sleep disorders in adults include insomnia, sleep-related breathing disorders, sleep-related movement disorders, and parasomnias (AASM, 2014) (see Table 24-1). The term *insomnia* refers to complaints of difficulty initiating or maintaining sleep or nonrestorative sleep that lasts for at least one month and causes clinically significant distress or impairment in social, occupational, or other important areas of functioning (AASM, 2014). Primary insomnia, for which no other cause is known, has been termed *psychophysiologic* (heightened arousal and learned sleep-preventing associations), *physiologic* (subjective reports confirmed by objective sleep measures), or *idiopathic* (linked to childhood onset and a chronic inability to obtain adequate sleep). The prevalence of each type of primary insomnia has not been routinely assessed or reported in patients with newly diagnosed cancer, with recurrent disease, or at the end of life.

Another group of insomnias, referred to as *secondary* or *comorbid insomnias*, are associated with other medical disorders, including cancer (Savard, Ivers, Villa, Caplette-Gingras,
### TABLE 24-1  Common Sleep Disorders in Adults

<table>
<thead>
<tr>
<th>Sleep Disorder</th>
<th>Definition</th>
<th>Presenting Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>Difficulty initiating or maintaining sleep that causes significant daytime impairment or distress for 3 months or more</td>
<td>Patient complains of difficulty falling asleep or staying asleep or early morning awakening that impairs daytime function.</td>
</tr>
<tr>
<td>Obstructive sleep apnea-hypopnea syndrome</td>
<td>Recurrent episodes of partial or complete upper-airway obstruction despite ongoing respiratory effort during sleep</td>
<td>Patient wakes with breath-holding, gasping, or choking; bed partner reports habitual snoring.</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>Uncontrollable sleepiness and intermittent signs of rapid eye movement sleep that interrupt normal wakefulness</td>
<td>Patient reports repeated episodes of need to sleep and suddenly falling asleep during usual daytime activities.</td>
</tr>
<tr>
<td>Restless legs syndrome</td>
<td>Urge to move legs with unpleasant and uncomfortable sensations in legs at night that are relieved by movement of limbs</td>
<td>Patient describes feelings of creeping, tingling, or cramping pain in legs that is worse when patient is lying down.</td>
</tr>
<tr>
<td>Periodic limb movement disorder</td>
<td>Periodic or random leg-kicking or arm movements during sleep</td>
<td>Bed partner reports kicking or arm movements by patient during sleep.</td>
</tr>
<tr>
<td>Circadian rhythm disorder</td>
<td>Advanced or delayed major sleep episode in relation to desired clock time that results in undesired insomnia or sleepiness</td>
<td>Patient reports inability to fall asleep or awaken relative to conventional sleep-wake times.</td>
</tr>
<tr>
<td>Parasomnias</td>
<td>Undesirable physical events or behaviors that occur during sleep</td>
<td>Bed partner reports behaviors by patient such as sleepwalking, sleep talking, or sleep terrors.</td>
</tr>
<tr>
<td>Hypersomnias</td>
<td>Constant or recurrent episodes of extreme sleepiness and lapses into sleep</td>
<td>Patient reports excess sleeping at night plus hour-long naps during the day and still feels sleepy.</td>
</tr>
</tbody>
</table>

*Note. Based on information from American Academy of Sleep Medicine, 2014.*

Because cancer is more prevalent in older individuals, many patients are likely to have one or more medical or psychological conditions that increase their risk for insomnia (Extermann & Hurria, 2007). Depression is a frequent condition seen in the cancer population and is accompanied by complaints of changes in sleep patterns and fatigue (Akechi et al., 2012; Alfano & Rowland, 2006; Bardwell et al., 2008). Insomnia can be transient (occasional nights), transient recurring (occasional nights whenever stress level is high), or chronic in nature (lasting six months or longer) (AASM, 2014). Problems with sleep latency and sleep maintenance are common complaints of people with cancer (Enderlin et al., 2011; Sanford et al., 2013).

Daytime sleepiness is described as the likelihood of a person falling asleep during activities of daily living because of a physiologic need for sleep (Roehrs, Carskadon, Dement, & Roth, 2011). A healthy person is unlikely to fall asleep during usual daytime activities such as eating or reading, but illness can increase the likelihood of increased sleepiness while performing these activities. Patients with cancer frequently report daytime sleepiness to clinicians, but few studies have described the prevalence and consequences of daytime sleepiness in these patients (Enderlin et al., 2011; Gibbins et al., 2009).
Associated Symptoms and Clusters

Other symptoms commonly occur concurrently with sleep-wake disturbances in people of all ages who have a diagnosis of cancer. The concept of coexisting symptoms is frequently studied as a “symptom cluster”—defined as “two or more symptoms that are related to each other that occur together” (Kim, McGuire, Tulman, & Barsevick, 2005, p. 278). Clusters of symptoms may share an underlying causative biologic mechanism and may have one predominant symptom (Barsevick, Whitmer, Nail, Beck, & Dudley, 2006). In many studies of adults with cancer, sleep-wake disturbances are most commonly associated with fatigue and depression (Dodd et al., 2010) but also with pain, gastrointestinal disturbances, and cognitive disturbances (Dirksen, Epstein, & Hoyt, 2009; Donovan & Jacobsen, 2007; Kim, Barsevick, Fang, & Miaskowski, 2012; Liu et al., 2009; Matthews, Schmiege, Cook, & Sousa, 2012). Studies with children and adolescents also have provided evidence that sleep-wake disturbances cluster with fatigue and depression (Yeh et al., 2008) and with nausea, vomiting, and limitations in performance (Hockenberry, Hooke, McCarthy, & Gregurich, 2011). In a study with 131 children and adolescents who were receiving myelosuppressive chemotherapy, Baggott, Cooper, Marina, Matthay, and Miaskowski (2012) concluded that insomnia fit in the “neuropsychological discomforts” cluster, along with pain, drowsiness, irritability, dizziness, and headache, all symptoms associated with proinflammatory cytokines. Symptom clusters that include sleep disturbances have been documented to occur in patients as they start cancer treatment, and these symptom clusters may persist during and after the treatment period (Liu et al., 2009). Kim et al. (2012) described a psychoneurologic symptom cluster (depressed mood, cognitive disturbance, fatigue, insomnia, and pain) in women with breast cancer undergoing chemotherapy or radiation therapy. Subgroups of women were classified by the severity of symptoms (low, medium, high), and these subgroups remained consistent throughout the treatment period. Women in the “all-high symptom” group experienced serious limitations in functional performance (Kim et al., 2012). Sleep-wake disturbances do not occur as isolated symptoms; therefore, clinicians need to consider the dynamic and complex interactions between multiple concurrent symptoms when planning optimal assessment and management strategies.

Assessment

Because sleep-wake disturbances may bother up to half of all patients with cancer at some time in their disease trajectory (Berger, 2009), oncology caregivers in all settings need to incorporate routine screening and assessment of sleep-wake disturbances into their practice. When patients complain of difficulty sleeping, care providers need to conduct a comprehensive sleep assessment, with knowledge of which sleep variables to measure and how to access the information. To guide oncology clinicians and researchers in sleep assessment, a panel of oncology sleep experts proposed measurement of nine sleep parameters that provide a common language to use in symptom management discussions and comprehensive evaluations of sleep-wake disturbances (Berger, 2009). These sleep parameters and their definitions are listed in Table 24-2.

Self-Report Instruments for Clinical Use

Several helpful tools are available for nurses to use in assessing patients for sleep-wake disturbances. One tool recommended for use is the Clinical Sleep Assessment for Adults
TABLE 24-2 Nine Sleep Parameters Recommended for Evaluation of Sleep-Wake Disturbances

<table>
<thead>
<tr>
<th>Sleep Parameter</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time</td>
<td>Number of minutes of sleep in bed</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>Number of minutes between getting into bed and falling asleep</td>
</tr>
<tr>
<td>Awakenings</td>
<td>Number of awakenings during the sleep period</td>
</tr>
<tr>
<td>Wake after sleep onset</td>
<td>Number of minutes awake after initial sleep onset</td>
</tr>
<tr>
<td>Daytime napping</td>
<td>Number of minutes of sleep during daytime naps</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>Number of episodes of falling asleep without intention</td>
</tr>
<tr>
<td>Quality of perceived sleep</td>
<td>Subjective assessment of quality</td>
</tr>
<tr>
<td>Circadian rhythm</td>
<td>Biobehavioral phenomenon that repeats approximately every 24 hours</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>Number of minutes of sleep divided by the number of minutes in bed</td>
</tr>
</tbody>
</table>

Note. Based on information from Berger, 2009.

(Lee & Ward, 2005), which screens for sleep disturbances with seven questions that address the parameters of sleep quality, total sleep time, sleep latency, awakenings, daytime sleepiness, and use of sleep aids. The assessment can be shortened to four questions to use as a brief screening tool, and a children’s version is available. Results of the assessment indicate when referral to a sleep specialist should be considered, and the tool can be scored for research purposes.

“BEARS” is a practical mnemonic guide recommended for sleep screening and assessment that includes questions assessing five major sleep domains: B is for bedtime problems, E is for excessive daytime sleepiness, A is for awakenings, R is for regularity of sleep, and S is for sleep-disordered breathing (Owens & Dalzell, 2005). It also includes age-appropriate questions about sleep for children and parents.

Nurses can assess for specific sleep disturbances by using more focused assessment tools. For example, the Insomnia Severity Index (Savard, Savard, Simard, & Ivers, 2005) is a seven-item instrument that assesses for insomnia. The Epworth Sleepiness Scale (eight items) (Johns, 1991) can be used to identify patients who have excessive daytime sleepiness. For some patients, clinicians may need to obtain sleep information (e.g., snoring) from bed partners or parents, although these proxy reports will vary in reliability. Nurses also can obtain helpful sleep data from patients by suggesting that they keep a daily sleep diary in which they record selected sleep parameters, such as bedtime, wake time, number of nighttime awakenings, and number and length of daytime naps (Berger, Farr, Kuhn, Fischer, & Agrawal, 2007).

**Objective Sleep Evaluation**

Patients who complain of more severe sleep-wake disturbances may need a referral to a sleep disorders center, a medical facility staffed by trained sleep specialists that offers a multidisciplinary approach to the diagnosis and treatment of sleep disorders. The gold standard of objective sleep measurement is the comprehensive physiologic monitoring of polysomnography (Chervin, 2011). Polysomnography is an assessment that usually is per-
formed in an overnight sleep laboratory and includes neurologic and neuromuscular measurements recorded by EEG, electrooculogram, and electromyelogram, as well as assessment of cardiac and respiratory parameters (see Figure 24-3). Polysomnography is necessary to diagnose sleep-related breathing disorders and unusual sleep-related behaviors or parasomnias and to examine stages of sleep (Buysse, 2013; Matthews & Aloia, 2009).

A second approach to objective sleep measurement is actigraphy, which uses a small portable device that can estimate sleep and activity parameters over extended periods of time outside of a laboratory setting. An actigraph is a wristwatch-like device that senses and records movements in short periods of time during sleep and/or wake periods (see Figure 24-4). Computer algorithms then translate the movement data into numeric and graphic values (Boyne, Sherry, Gallagher, Olsen, & Brooks, 2013). Actigraphy does not analyze sleep stages, but it is helpful to evaluate patients with circadian rhythm disorders, to describe sleep patterns in healthy populations, and to document responses to sleep therapy (Sadeh, 2011). Actigraphy is used commonly for clinical and research purposes to objectively measure responses to sleep interventions in patients of all ages (Erickson, 2009; Langford et al., 2012).

Self-report and objective measures of sleep may not always give the same results. For example, patients who report few nighttime awakenings may show evidence of multiple awakenings from a sleep-related breathing disorder when monitored with polysomnography. Because each subjective and objective measurement approach has a unique set of benefits and limitations and yields complementary information, a combination of sleep measures using both approaches is recommended for a comprehensive sleep evaluation (Berger, 2009; Dhruva et al., 2012). Some sleep measures can be particularly useful for clinical research or quality improvement projects, such as the Insomnia Severity Index (Savard, Savard, et al., 2005) and an instrument to measure sleep disturbances from the Patient-Reported Outcomes Measurement Information System (PROMIS™) (Yu et al., 2012).

Evidence-Based Interventions

Oncology nurses’ scope of practice includes assessment and management of symptoms that are present with cancer and cancer treatment. ONS has identified patient outcomes that are sensitive to nursing intervention, known as nursing-sensitive patient outcomes (Given & Sherwood, 2005; Matthews & Berger, 2014). The ONS PEP Sleep-Wake Disturbances Team has rated the interventions that have been tested to reduce sleep-wake disturbances in people with cancer (see www.ons.org/practice-resources/pep/sleep-wake-disturbances). Clinical nurses can use this information to determine the strength of the evidence for various interventions.

Pharmacologic Interventions

The attempt to modify sleep-wake disturbances in patients with cancer with medications has been rated by the ONS PEP resource in the category of Effectiveness Not Established (Berger et al., 2014). This category indicates that insufficient supportive data exist to implement these interventions into practice (Berger et al., 2014).

Despite widespread prescribing of sedative-hypnotics to improve sleep, no experimental design study was found that examined the efficacy of using these drugs in patients with cancer. The drugs most commonly prescribed for short- and long-term use are in the benzodiazepine, nonbenzodiazepine, and benzodiazepine receptor agonist groups and vary in their
FIGURE 24-3 Polysomnography

**EEG Sleep Stages**

**Awake:** low voltage – random, fast

**Drowsy:** 8 to 12 cps – alpha waves

**Stage 1:** 3 to 7 cps – theta waves

**Stage 2:** 12 to 14 cps – sleep spindles and K complexes

**Delta sleep:** (stages 3 and 4) 1/2 to 2 cps – delta waves >75 µV

**REM sleep:** low voltage – random, fast with sawtooth waves

**Note.** Figure courtesy of the American Academy of Sleep Medicine. Used with permission.
half-lives (National Cancer Institute [NCI], 2014; Wilson et al., 2010). Medications with longer half-lives pose the risk of causing daytime sleepiness and may impair daytime functioning. Medications with shorter half-lives may wear off, resulting in problems with sleep maintenance during the second half of the night.

NCI (2014) lists agents that must be individually evaluated for their side effect profile (see Table 24-3). Benzodiazepines, nonbenzodiazepines, benzodiazepine receptor agonists, melatonin receptor agonists, tricyclic antidepressants, second-generation antidepressants, and antihistamines may be considered when attempting to improve sleep. Newer agents such as eszopiclone, ramelteon, zaleplon, and zolpidem are commonly prescribed. The risks for potential interactions between these and other medications, including prescription, over-the-counter, and herbal agents, must be weighed with the potential benefits to patients.

Herbal supplements, such as valerian, passionflower, kava, black cohosh, and St. John’s wort, have been assigned to the category Benefits Balanced With Harms based on the evidence. Studies have shown potential risks of herbal agents blocking the effects of chemotherapy and other common drugs, making herbal agents potentially dangerous for use in patients with cancer (Berger, 2009). Unless they consult and receive approval from the oncology team, patients receiving chemotherapy should not use these herbal supplements for sleep problems (Block, Gyllenhaal, & Mead, 2004). Oncology nurses are advised to routinely review each patient’s use of herbal agents (Anderson & Taylor, 2012; Moore, Berger, & Dizona, 2011). Routine oncology clinical practice should integrate assessment for the use of prescription, over-the-counter, and herbal agents. For more information, refer to ONS PEP resources.

**Nonpharmacologic Interventions**

Growing evidence shows that several nonpharmacologic interventions promote quality sleep and daytime functioning in patients with cancer. For ease of recall, these interventions can be organized into the categories of cognitive behavioral interventions/approaches, com-
<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Medication</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonbenzodiaze-</td>
<td>Zaleplon</td>
<td>5–20 mg</td>
<td>Useful for problems falling asleep only</td>
</tr>
<tr>
<td>pine benzodia-</td>
<td>Zolpidem tartrate</td>
<td>5–10 mg</td>
<td>Useful for problems falling asleep only</td>
</tr>
<tr>
<td>zpine receptor</td>
<td>Zolpidem tartrate</td>
<td>6.25–12.5 mg</td>
<td>Biphasic release; useful for problems both falling asleep and staying asleep; do not crush or split tablets.</td>
</tr>
<tr>
<td>agonist (&quot;Z-drugs&quot;)</td>
<td>Eszopiclone</td>
<td>1–3 mg</td>
<td>Useful for problems both falling asleep and staying asleep; do not take with or right after a meal.</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>Alprazolam</td>
<td>0.25–2 mg</td>
<td>Higher risk of withdrawal; side effects: lack of motor coordination, falls, and cognitive impairment</td>
</tr>
<tr>
<td></td>
<td>Lorazepam</td>
<td>0.5–4 mg</td>
<td>Side effects: lack of motor coordination, falls, and cognitive impairment</td>
</tr>
<tr>
<td></td>
<td>Clonazepam</td>
<td>0.5–4 mg</td>
<td>Side effects: lack of motor coordination, falls, and cognitive impairment</td>
</tr>
<tr>
<td></td>
<td>Temazepam</td>
<td>15–30 mg</td>
<td>Side effects: lack of motor coordination, falls, and cognitive impairment</td>
</tr>
<tr>
<td>Melatonin receptor agonist</td>
<td>Ramelteon</td>
<td>8 mg</td>
<td>Little negative effect on cognition, somnolence, motor coordination, or nausea; useful for problems falling asleep only</td>
</tr>
<tr>
<td>Antihistamine</td>
<td>Diphenhydramine</td>
<td>25–100 mg</td>
<td>Useful for problems falling asleep only; good side effect profile</td>
</tr>
<tr>
<td></td>
<td>Hydroxyzine</td>
<td>10–100 mg</td>
<td>Useful for problems falling asleep only; anticholinergic side effects</td>
</tr>
<tr>
<td>Tricyclic antidepressant</td>
<td>Doxepin</td>
<td>10–25 mg</td>
<td>Lower doses used for treatment of primary insomnia when antidepressant effect is not needed; risks include anticholinergic side effects and weight gain.</td>
</tr>
<tr>
<td></td>
<td>Amitriptyline</td>
<td>10–15 mg</td>
<td>Lower doses used for treatment of primary insomnia when antidepressant effect is not needed; risks include anticholinergic side effects and weight gain.</td>
</tr>
<tr>
<td></td>
<td>Nortriptyline</td>
<td>10–50 mg</td>
<td>Risks include anticholinergic side effects and weight gain.</td>
</tr>
<tr>
<td>Second-generation antidepressant</td>
<td>Trazodone</td>
<td>25–200 mg</td>
<td>Risks include orthostatic hypotension and falls.</td>
</tr>
<tr>
<td></td>
<td>Mirtazapine</td>
<td>7.5–45 mg</td>
<td>If depression is not a concern, 7.5–15 mg is best for sleep, hot flashes, increased appetite, and less morning sedation. Be aware of fall risk.</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>Quetiapine</td>
<td>25–100 mg</td>
<td>Risks include weight gain, metabolic syndrome, abnormal/involuntary movements, and possible cardiovascular effects (e.g., prolonged QT interval).</td>
</tr>
<tr>
<td></td>
<td>Chlorpromazine</td>
<td>10–50 mg</td>
<td>Risks include weight gain, metabolic syndrome, abnormal/involuntary movements, and possible cardiovascular effects (e.g., hypotension).</td>
</tr>
<tr>
<td>Chloral derivative</td>
<td>Chloral hydrate</td>
<td>0.5–1 g</td>
<td>Used mainly for sleep maintenance; risks include gastric irritation, dependence, and withdrawal; lethal in overdose.</td>
</tr>
</tbody>
</table>

*Note.* Based on information from National Cancer Institute, 2014.
plementary therapies, psychoeducation interventions, and exercise. The cognitive behavioral interventions/approaches have been classified as Likely to Be Effective (Berger et al., 2014). All of the interventions in the other categories have been classified as Effectiveness Not Established based on the evidence.

The most frequently tested interventions to improve patients’ sleep have been cognitive behavioral interventions/approaches and complementary therapies, but many of these studies have limitations. Study samples were small (N < 100), mostly Caucasian, and recruited from outpatient settings; interventions often were tested without using a comparison group; and outcomes may not have focused primarily on sleep (Berger et al., 2014). The knowledge base on sleep-wake disturbances will be advanced when results from several large (N > 100) randomized controlled trials (RCTs) are reported using sleep measurements with established reliability and validity and whose primary outcome variables are sleep-wake disturbances in people with cancer.

A variety of psychological and cognitive behavioral interventions/approaches can be used alone or in combination to improve sleep. They are used to change negative thought processes—attitudes and behaviors related to one’s ability to fall asleep, stay asleep, get enough sleep, and function during the day. Cognitive behavioral interventions/approaches that have been tested in patients with cancer include stimulus control, sleep restriction, relaxation therapy, and improving sleep hygiene (see Table 24-4). Overall results have shown sev-

### TABLE 24-4

<table>
<thead>
<tr>
<th>Nonpharmacologic Interventions That Have Been Tested for Disturbed Sleep in Patients With Cancer*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Likely to Be Effective—Cognitive Behavioral Interventions/Approaches</strong></td>
</tr>
</tbody>
</table>

Instruct patients in the following stimulus control techniques.
- Go to bed only when sleepy and at approximately the same time each night.
- Get out of bed and go to another room whenever unable to fall asleep; return to bed only when sleepy again.
- Use the bedroom for sleep and sex only.

Instruct patients in the following sleep restriction techniques.
- Maintain a regular bedtime and rising time each day.
- Avoid daytime napping. If needed, limit to 30–45 minutes.

Instruct patients in the following relaxation techniques.
- Use preferred relaxation technique within two hours of going to bed, such as a warm bath or shower, reading, or listening to music.

Instruct patients in the following sleep hygiene techniques.
- Avoid caffeine and other stimulants after noon; complete dinner three hours before bedtime; do not go to bed hungry.
- Replace mattress every 10–12 years and pillows more frequently; keep the bedroom cool and use light covers; do not watch television in the bedroom.

- Improved sleep quality (Berger, Kuhn, Farr, Lynch, et al., 2009; Epstein & Dirksen, 2007; Kwakkeboom et al., 2010; Ritterband et al., 2012; Savard, Simard, et al., 2005; Savard et al., 2010)
- Longer sleep duration (Epstein & Dirksen, 2007)
- Higher sleep efficiency (Berger, Kuhn, Farr, Lynch, et al., 2009; Davidson et al., 2001; Epstein & Dirksen, 2007; Espie et al., 2008; Quesnel et al., 2003; Ritterband et al., 2012; Savard et al., 2010; Tremblay et al., 2009)

- Maintenance of normal sleep patterns (Berger et al., 2002, 2003)
- Improved insomnia (Arving et al., 2007; Davidson et al., 2001; Farrell-Carnahan et al., 2010; Ritterband et al., 2012; Savard, Simard, et al., 2005; Savard et al., 2010)
- Shorter sleep latency (Epstein & Dirksen, 2007; Espie et al., 2008; Ritterband et al., 2012; Savard et al., 2010)
- Shorter waking after sleep onset (Davidson et al., 2001; Epstein & Dirksen, 2007; Espie et al., 2008; Quesnel et al., 2003; Ritterband et al., 2012; Savard et al., 2010)
- Longer time in bed (Epstein & Dirksen, 2007)

(Continued on next page)
TABLE 24-4  Nonpharmacologic Interventions That Have Been Tested for Disturbed Sleep in Patients With Cancer* (Continued)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcomes of Intervention on Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness Not Established—Complementary Therapies</td>
<td></td>
</tr>
<tr>
<td>Encourage patients to decrease stress by selecting</td>
<td>Improved sleep quality (Andersen et al., 2013; Carlson &amp; Garland, 2005; Carlson et al., 2003, 2004; Cerrone et al., 2008; Cohen et al., 2004; Demiralp et al., 2010; de Moor et al., 2002; Fobair et al., 2002; Haest et al., 2011; Shapiro et al., 2003; Soden et al., 2004; Stringer &amp; Donald, 2011; Sturgeon et al., 2009; Tang et al., 2010)</td>
</tr>
<tr>
<td>relaxation techniques that suit them, including</td>
<td></td>
</tr>
<tr>
<td>massage, individual muscle relaxation, mindfulness-</td>
<td></td>
</tr>
<tr>
<td>based stress reduction, and yoga.</td>
<td></td>
</tr>
<tr>
<td>Refer patients to practitioners in acupuncture,</td>
<td></td>
</tr>
<tr>
<td>electroacupressure/acupressure, biofeedback, and/or</td>
<td></td>
</tr>
<tr>
<td>healing touch therapies.</td>
<td></td>
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<tr>
<td>Encourage patients to keep a journal in which they</td>
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<td>document their deepest thoughts and feelings about</td>
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<td>their illness and treatment.</td>
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<td>Encourage patients to decrease stress by focusing on</td>
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<td>and isolating various muscle groups while moving</td>
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<td>progressively up and down the body. Encourage</td>
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<td>focused breathing, with all attention centered on the</td>
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<td>sensations of breathing, including the rhythm and</td>
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<td>rise and fall of the chest.</td>
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<td>Improved sleep quality (Andersen et al., 2013;</td>
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<td>Carlson &amp; Garland, 2005; Carlson et al., 2003, 2004;</td>
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<td>Cerrone et al., 2008; Cohen et al., 2004; Demiralp et</td>
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<td>al., 2010; de Moor et al., 2002; Fobair et al., 2002;</td>
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<td>Haest et al., 2011; Shapiro et al., 2003; Soden et</td>
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<td>et al., 2004; Stringer &amp; Donald, 2011; Sturgeon et</td>
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<td>al., 2009; Tang et al., 2010)</td>
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<td>Longer sleep duration (Carson et al., 2009; Cohen et</td>
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<td>al., 2004; de Moor et al., 2002; Simeit et al., 2004;</td>
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<td>Weze et al., 2004)</td>
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<td>Higher sleep efficiency (Simeit et al., 2004)</td>
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<td>Shorter sleep latency (Cannici et al., 1983; Cohen et</td>
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<td>al., 2004; Otte et al., 2011; Simeit et al., 2004;</td>
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<td>Wright et al., 2002)</td>
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<td>Less need for sleeping medication (Cohen et al., 2004;</td>
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<td>Simeit et al., 2004)</td>
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<td>Less daytime dysfunction (de Moor et al., 2002;</td>
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<td>Simeit et al., 2004)</td>
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<td>Less sleep difficulties (Cohen &amp; Fried, 2007)</td>
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<td>Improved insomnia (Bozczuk et al., 2006; Carlson &amp;</td>
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<td>Garland, 2005; Cohen et al., 2004; Weze et al., 2004)</td>
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<td>Less sleep disturbance (Carlson &amp; Garland, 2005;</td>
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<td>Carlson et al., 2003, 2004; Feng et al., 2011;</td>
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<td>Lengacher et al., 2012; Sturgeon et al., 2009)</td>
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<td>Shorter waking after sleep onset (Otte et al., 2011)</td>
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<td>Effectiveness Not Established—Psychoeducation Interventions</td>
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<tr>
<td>Provide patients with information regarding specifics</td>
<td>Fewer problems sleeping (Cleeland et al., 2011; Kim et al., 2002)</td>
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<td>of treatment and expected side effects, including sleep-</td>
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<td>wake disturbances.</td>
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<td>Repeat this information throughout the treatment.</td>
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<td>Teach patients basic information about sleep hygiene.</td>
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<td>Effectiveness Not Established—Exercise</td>
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<td>Rule out bone metastasis or exercise contraindication.</td>
<td>Improved sleep quality (Donnelly et al., 2011; Mock et al., 1997;</td>
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<td>Have patient complete moderate exercise (e.g., brisk</td>
<td>Payne et al., 2008; Rabin et al., 2009; Sprod et al., 2010; Tang et</td>
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<td>walking 20–30 minutes four to five times per week)</td>
<td>al., 2010; Young-McCaughan et al., 2003)</td>
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<td>at least three hours before bedtime.</td>
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<td>Encourage patients to perform strength and resistance</td>
<td>Longer sleep duration and improved sleep efficiency (Coleman et al.,</td>
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<td>training.</td>
<td>2003; Wang et al., 2011)</td>
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* Level of evidence from Oncology Nursing Society Putting Evidence Into Practice. More information can be found at https://www.ons.org/practice-resources/pep/sleep-wake-disturbances.
eral positive trends in sleep variables with cognitive behavioral interventions/approaches, including improved sleep quality, longer sleep duration, and higher sleep efficiency. Berger and colleagues demonstrated that an intervention using an individual sleep promotion plan maintained normal ranges of sleep variables except for excessive nighttime awakenings (Berger, Kuhn, Farr, Lynch, et al., 2009; Berger, Kuhn, Farr, Von Essen, et al., 2009).

A significant group by time difference between the intervention and the control group was found from baseline to 30 days after the last chemotherapy treatment \( [F(2,174) = 3.06, p < 0.049] \). Pairwise comparisons showed that these differences continued between the groups at 90 days \( (p = 0.002) \) but not at one year \( (p = 0.052) \). Baseline higher fatigue and anxiety, as well as a higher educational level, were associated with poorer sleep at one year.

Complementary therapies are a diverse group of medical and healthcare practices and products that are not generally considered to be part of conventional medicine. Many complementary therapy interventions have been tested in patients with cancer to improve sleep, with acupuncture, mindfulness-based stress reduction (MBSR), and yoga demonstrating positive outcomes (see Table 24-4). When one or more of the previously mentioned complementary therapies were employed, improvements in sleep disturbances included higher sleep quality, shorter sleep latency, longer sleep duration, higher sleep efficiency, less daytime dysfunction, and use of fewer sleep medications (Dhruva et al., 2012; Feng et al., 2011; Frisk, Kallstrom, Wall, Fredrikson, & Hammar, 2011; Winbush, Gross, & Kreitzer, 2007). Two of the strongest studies thus far testing a complementary therapy intervention in an RCT (Andersen et al., 2013; Lengacher et al., 2012) used MBSR to improve symptoms, including sleep disturbance in patients with breast cancer. Shortly after the MBSR interventions, both studies reported improved sleep in the experimental group. However, better sleep in the experimental group (versus the control group) did not persist at 12-month follow-up (Andersen et al., 2013).

Psychoeducational interventions provide patients with structured education and information about treatment and side effects via the use of a variety of media. These interventions also may include strategies to decrease psychological distress, such as anxiety, in order to help the patient learn. An RCT using a single-item sleep measure reported increased sleep duration using an educational, informational tape in 152 men receiving radiation for localized prostate cancer (Kim, Roscoe, & Morrow, 2002). Another RCT showed no change in sleep disturbances as measured by a daily sleep diary when using informational audiotapes in a study with 71 women with breast cancer undergoing chemotherapy (Williams & Schreier, 2005).

Exercise interventions include any planned, structured, and repetitive bodily movement that is performed to improve or maintain physical fitness, performance, or health. A variety of aerobic, strength, and resistance training interventions have been tested in people with cancer in an attempt to improve function and to prevent and manage symptoms, including sleep disturbances. While early studies were conducted with women with breast cancer (Mock et al., 1997), additional studies, although with small sample sizes, have since provided evidence about the feasibility and benefits of exercise for patients with other cancer diagnoses (Coleman et al., 2003; Donnelly et al., 2011; Tang, Liou, & Lin, 2010; Wang, Boehmke, Wu, Dickerson, & Fisher, 2011; Young-McCaughan et al., 2003). Mock et al. (1997) used a one-group experimental study to test a self-paced, progressive, home-based exercise program in women with breast cancer that resulted in participants reporting less difficulty sleeping. In an RCT with women with newly diagnosed breast cancer, Wang et al. (2011) found that women in a walking program had less sleep disturbances compared with those in the usual care group. Coleman et al. (2003) concluded that a home-based aerobic and resistance training program intervention was feasible for patients who were receiving high-dose chemotherapy and peripheral blood stem cell transplant for multiple myeloma.
In a study that tested the effect of a 12-week home-based physical activity intervention with women with gynecologic cancer, Donnelly et al. (2011) concluded that the intervention group had improved sleep outcomes compared with the control group. In other studies with patients with mixed cancer diagnoses, exercise programs improved self-reported sleep outcomes (Tang et al., 2010; Young-McCaughan et al., 2003). Nurse clinicians are urged to work with other interdisciplinary members who have expertise regarding exercise in patients with cancer to tailor physical activity interventions for patients throughout the cancer trajectory. Oncology clinicians can keep up to date with current evidence-based practice resources by consulting the ONS website (see www.ons.org/practice-resources/pep/sleep-wake-disturbances).

**Expected Patient Outcomes**

When nurses intervene with evidence-based interventions to improve sleep in patients with cancer, positive outcomes are anticipated (Berger et al., 2014). Positive sleep outcomes for patients include the ability to fall asleep easily, to stay asleep through the night, and to awaken feeling refreshed and rejuvenated with the use of fewer sleep aids. Other measurable outcomes during waking hours include less daytime sleepiness and napping, improved alertness and function, and fewer sick days from work. Because insufficient sleep can coexist with and exacerbate other symptoms, such as pain and mood disturbances, in patients with cancer, improving sleep may lead to improvement in these symptoms as well. Improved symptom management can lead to increased physical, emotional, social, and mental functioning and overall quality of life. Nurses are in an excellent position to help patients to deal with sleep disturbances.

**Patient Teaching Points**

Many opportunities exist to teach patients and families about how to improve their sleep. Basic information about the importance of sleep needs to be included along with recommendations for nutrition and physical activity as part of healthy lifestyle guidelines for all people. Many parents do not know about sleep needs and healthy sleep practices for their children or themselves (National Sleep Foundation, 2006; Owens, Jones, & Nash, 2011). Although sleep needs vary by age and by individual, nurses should encourage adults to receive at least 7 hours of sleep per night, teenagers to receive 8.5–9.25 hours per night, and school-age children to receive 10–11 hours per night for optimal performance (National Sleep Foundation, n.d.). Clinicians can reinforce the value of obtaining quality sleep by routinely screening their patients with cancer for sleep-wake disturbances and discussing the associations among sleep, other symptoms, and overall performance. Nurses are encouraged to use the ONS PEP resources to suggest evidence-based interventions that patients find acceptable and are willing to try to relieve insomnia and other sleep disturbances. Nurses can coach patients to increase adherence to the intervention and evaluate the outcomes of the intervention after six to eight weeks (Langford et al., 2012).

**Need for Future Research**

Although many recent studies have focused attention on sleep-wake disturbances in patients with cancer, more knowledge is needed to better understand the broad nature of
sleep-wake disturbances related to cancer and their consequences. More research is needed on the pathophysiology of sleep difficulties related to specific types and stages of cancer. Evidence is limited in high-risk groups, such as older adults, adolescents and young adults, and those at the end of life. More information is needed about how sleep problems interact with other cancer-related symptoms, including fatigue, mood disturbances, and pain. Nurses are in an optimal position to explore how factors related to cancer treatment contribute to sleep-wake disturbances. Treatment schedules and settings, for example, could be modified to promote improved sleep. Nurses can identify patients at high risk for sleep problems and intervene early in the treatment process to prevent and manage the distress attributed to these symptom clusters.

Additional work needs to be done to identify the most effective screening and assessment strategies for various oncology populations and in diverse clinical and research settings. Efficient screening techniques will enable nurses to identify common sleep problems that may go unrecognized or untreated in their patients. Although patients may volunteer reports of difficulty falling asleep, nurses may need to ask further questions to detect other common sleep-wake disturbances, such as excessive sleepiness or restless legs. Research is needed to test various sleep-promoting interventions for their effectiveness during the phases of the cancer trajectory, including the early diagnosis and treatment phases, survivorship, and the end of life. Plenty of opportunities exist to advance knowledge about the importance of refreshing and restoring sleep in this population. Because sleep is an excellent example of a clinical issue that crosses many disciplines and specialties, teams consisting of nurses, physicians, and other therapists are essential to maximize efforts in research and clinical care (Berger & Mitchell, 2011).

Conclusion of Case Studies

**Adult Case Study**

Recall that S.M. is a patient with stage IIA breast cancer who has been prescribed four cycles of dose-dense chemotherapy (every 14 days) with doxorubicin and cyclophosphamide, followed by four cycles of paclitaxel. S.M. has complaints of difficulty maintaining sleep at night, daytime sleepiness, fatigue, and distress. The clinic nurse recommends a number of interventions from the ONS PEP resources on sleep-wake disturbances and fatigue.

Recommendations to relieve S.M.’s sleep-wake disturbances include

- Use the bedroom for only sleep and sexual activity.
- If unable to fall back to sleep when awake during the night, go to a dark and quiet place to relax and return to bed only when sleepy; repeat if needed.
- Set a regular bedtime and wake time seven nights per week. Keep this schedule with seven to nine hours in bed as much as possible. S.M. can ask her husband to parent their teenagers after 10 pm.
- Get up, even if sleepy, at the same time each morning, and take 20–30-minute power naps during the day.
- Maintain daytime activity at the same level it was prior to starting chemotherapy unless febrile, experiencing lower blood counts, or vomiting. Choose a pleasant place to walk indoors as well as outdoors (weather permitting).
- Take time to unwind and enjoy a relaxing activity within two hours of bedtime.
- Discuss interventions for hot flushes with the oncology team. Avoid herbal remedies.
- Control other related symptoms (pain, fatigue, depression, nausea, and vomiting).
Young Adult Case Study

Recall that B.R. is a young man who was diagnosed with stage IV Hodgkin lymphoma two and a half months ago. His treatment is four cycles of ABVD chemotherapy, followed by reevaluation. B.R. was hospitalized for a brief period at the time of diagnosis but is now at home after completing two cycles of chemotherapy and continues his treatment on an outpatient basis. He has had significant improvement of many symptoms, including shortness of breath, night sweats, and itching. He has improving stamina and is ready to return to some of his usual activities. B.R.’s nurse in the oncology clinic recommended a number of interventions from the ONS PEP resources on sleep-wake disturbances and fatigue to address B.R.’s complaints of difficulty falling asleep, daytime sleepiness, fatigue, and mood disturbances.

- Increase daytime activity to include two 30-minute walks each day with his girlfriend and other friends. Gradually increase activity as tolerated to include light hiking and golf, which he previously enjoyed.
- If sleepy during the day, go to bed for a 30-minute nap.
- Sit, rather than lie, on the couch to watch sports programs in the evening. Go to bed when feeling sleepy to avoid falling asleep on the couch.
- Set consistent times for going to bed and waking up in the morning. Adhere to these times as much as possible, especially when returning to a schedule that includes part-time work.
- If unable to fall asleep in 20 minutes when in bed, go into the living room and read magazines or a book. Return to bed when feeling sleepy.
- Talk with healthcare providers if worry and anxiety continue to be troubling problems.

Conclusion

Sleep-wake disturbances are common and distressing symptoms for many patients throughout the cancer trajectory and can negatively affect their physical, social, and emotional health. With knowledge about sleep physiology, sleep assessment, and common sleep disorders, nurses can effectively intervene with patients with cancer who have problems with disrupted and insufficient sleep. Patients who are considered to be at increased risk for primary sleep disorders should be referred to a sleep disorders center for evaluation. Nurses can implement a number of pharmacologic and nonpharmacologic interventions based on current evidence-based recommendations for patients with more general sleep-wake disturbances. Nurses need to efficiently translate evidence from ongoing research to new clinical interventions for optimal sleep-wake outcomes in their patients.

References


Case Study

M.L. comes to the cancer genetics clinic for an evaluation and possible genetic testing. The nurse obtains a fairly extensive family history of cancer, inclusive of M.L.’s history of breast cancer seven years prior and her youngest sister’s recent diagnosis of stage IV ovarian cancer. As she is providing the information about her sister’s diagnosis, M.L. talks about how unfair it is that her sister will not survive the ovarian cancer when M.L. is doing so well after her own treatment. Her sister still has children in the primary and middle grades, but M.L.’s children are raised and independent.

Overview

“What do we live for, if not to make the world less difficult for each other?”
—Mary Ann Evans (George Eliot), *Middlemarch: A Study of Provincial Life*

The Joint Commission (2010) has recommended that spiritual care be integrated as part of the initial patient assessment, treatment, and end-of-life care. Spiritual care by oncology nurses involves the process of making the world of cancer (physical, social, psychological, and spiritual) less difficult for patients. Yet, spiritual care often is not experienced or at least recognized by patients, or even by the nurses themselves. The reasons for this lack of recognition or experience are many, but one of the major ones is definitional.

Meaning of Spirituality

In our diverse society, the human spirit is defined quite differently by Christians, Jews, Muslims, agnostics, New Age followers, Native Americans, and so on. Therefore, what is meaningful to a New Age follower may not be meaningful to a Christian unless there is a willing-
ness to look for the common ground while respecting the differences. This is what makes spiritual care challenging and also rewarding. Oncology nurses may reap the rewards if willing and able to meet the challenge.

A definition of spirit that would likely be acceptable for most is the essence of a human being, the source of life, what makes an individual uniquely human. It is all that a person is except for the physical body and yet is inextricably united with the body. It is what connects one human with all others. For those who believe in God or a higher power, the spirit is defined first as what connects with God or that higher power. As opposed to popular portrayal of the heart as the seat of love, it is the spirit that connects one with another and with God in love. The differing beliefs about a connection with a higher power mandate that nursing care for the human spirit be based on a respect for both the patient’s and the nurse’s beliefs.

Because of the inextricable union of spirit and body, the pain of the body can be the source of pain of the soul, and vice versa (Mako, Galek, & Poppito, 2006). Therefore, care for the body and care for the spirit are inseparable in nursing care. Within the realm of nursing, the activities of this care renew, uplift, comfort, heal, and inspire patients, their families, and the nurses themselves. Among others, these activities include a focus on the individuality of patients, supportive activities, advocacy, and referral. All nurses should be competent to assess the need for and provide these interventions.

What Patients Have to Say About the Spirit

A brief review of what patients with cancer, survivors, and high-risk individuals have said about their experience is an essential starting point for a consideration of spiritual care. At the time of diagnosis, women with breast cancer experienced shock, fear of dying, and a frightening sense of vulnerability and aloneness while trying to maintain self-identity (Coward & Kahn, 2004). The women turned inward to mobilize their inner resources. Reliance on God and their own internal resources increased their hope for survival. They reached outward to connect with family, friends, caregivers, and faith communities for support to relieve the fear and isolation. Helping others and meeting their commitments at home and work helped to maintain their sense of identity. As the women passed through the cancer trajectory toward survivorship, they regained a sense of normalcy, but it was different than before diagnosis; their bodies were different and their life values had changed (Coward & Kahn, 2004).

Isolation was identified in another study of women newly diagnosed with breast cancer, but it was a self-imposed isolation in which the women focused their attention on what was happening and mustering their inner strength (Logan, Hackbusch-Pinto, & De Grasse, 2006). They sought comfort selectively from those who could provide it. For many, this search for comfort included prayer and their relationship with God and the prayers of others. For others, nature was a source of comfort. Some wanted the offer of a referral to a chaplain in the outpatient setting and others did not, but as one participant said, “Someone needs to ask the questions” (Logan et al., 2006, p. 124).

In contrast with the experience of women, Kronenwetter et al. (2005) found that men with early-stage prostate cancer rarely discussed spirituality in relation to their cancer diagnosis. When they did, they were equally likely to view the diagnosis as having no change or as having a positive relationship with their spirituality. However, others have found that prayer was highly valued by African American prostate cancer survivors (Jones et al., 2007). This may reflect a difference in the cancer trajectory or a difference in ethnicity. Krupski et al. (2005) found that among low-income men with prostate cancer, African American and Hispanic men scored significantly higher than Caucasian men did on the Functional Assessment of
Chronic Illness Therapy–Spiritual Well-Being (FACIT-Sp). The implication from these studies is that nurses should be aware of variances among ethnicities and between the sexes, and generalities cannot be assumed with any one patient.

Patients with advanced cancer have identified spiritual concerns or spiritual pain in multiple studies (Alcorn et al., 2010; Delgado-Guay et al., 2011; Mako et al., 2006; Winkelman et al., 2011). In the 2010 study by Alcorn et al., 65% of the 86 patients, especially the younger, more religious, and more spiritual, identified concerns related to one or more of the following themes: coping, practices, beliefs, transformation, and community. Winkelman et al. (2011) found a significant association between spiritual concerns and a lower psychological quality of life among their 69 patients. Most of these patients believed it is important for healthcare professionals to attend to their concerns. Delgado-Guay et al. (2011) defined spiritual pain as “a pain deep in your soul (being) that is not physical” (p. 988) and was inversely correlated with religiosity and spiritual quality of life. Using the same definition for spiritual pain, Mako et al. (2006) found that the intensity of spiritual pain was correlated with depression. These studies indicate that spiritual pain or concern is common among patients with advanced cancer and is frequently associated with depression and decreased quality of life.

Among parents of children with cancer, the support of their ministers was an important source of support (Schneider & Mannell, 2006). These parents found that the act of having faith in God and prayer were essential sources of support and comfort throughout their child’s illness, despite occasional periods of doubt. They described their confidence in God’s presence and how that bolstered their ability to keep going. Those who were part of a church appreciated and found the prayers of their faith communities to be a source of comfort and hope. Parents with theistic beliefs and those without them also found spiritual comfort and a source of strength in the beauty of nature (Schneider & Mannell, 2006).

Families have described the support from church communities in many forms, including assistance in meeting the daily needs for meals, transportation, and child care, as well as prayer chains and healing services. One woman with breast cancer described her experience of physical and spiritual support from her church community that continued after moving to another part of the country.

“We had more food than we could eat. Some women came and packed my entire kitchen and did a lot of other packing because I couldn’t lift any weight. They were supportive in every sense of the word: prayer, person, visiting, bringing food. After I moved, it was a very lonely time, but I could feel the wave up from Texas. I was still in their thoughts and prayers there and I was very aware of that. I could feel it.” (Tinley, 2006, pp. 89–90)

A Gallup poll indicated that 73% of Americans expressed a firm belief in God (Newport, 2011). As a belief in God is not universal among patients or providers, an awareness and appreciation of how alternative beliefs affect coping with potential, existing, and past cancer experiences is essential to providing spiritual care. A young woman with a BRCA1 mutation identified her spirituality as a belief in a balance in life with a purpose for everything that happens, but not belief in a god. In describing how that belief has helped her to cope with her family history, she said the following.

“I think it helps to know that maybe there is a reason for this. This might open another door and I am one of those annoying people that always say there has got to be a silver lining. I believe that out of the bad things, something good could happen, so you just have to deal with it and hope that something good comes along. So I think that helps me cope with it.” (Tinley, 2006, p. 91)
Prerequisites and Self-Care for Engagement in Spiritual Care

“Be at peace with yourself first and then you will be able to bring peace to others.”

—Thomas à Kempis

Many nurses have a desire to be active, to make a difference, and to apply their skills to enhance the care experience for patients. When a patient needs undivided attention and time, nurses must be able to quiet the need for activity and the chatter in their mind (Miller, 2001). To provide this kind of caring presence, nurses have identified the need to develop and care for their own internal space: a space where the nurse can examine beliefs, resolve personal issues, cultivate a desire to connect with others, and develop a comfort with the spiritual (Kirkham, Pesut, Meyerhoff, & Sawatzky, 2004).

The nurse’s tools for spiritual care are personal. They include sensitivity, intuition, presence, altruism, openness, genuineness, and vulnerability. These tools require a depth of personal knowledge and comfort with one’s past journey and with the uncertainty of the future. In a study involving nurses who provide spiritual care, additional requisites to providing spiritual care that were identified included a willingness to connect, comfort with spiritual matter, a conviction that spiritual care is part of nursing care, integration of spiritual care with all aspects of patient care, and a sincere desire to understand another’s spiritual beliefs (Kirkham et al., 2004). Although some knowledge of different religious practices and beliefs, especially as they relate to health, illness, and treatment, can be beneficial, mostly nurses need to have respect for others’ beliefs and an openness to being taught by patients while being true to their own beliefs. It is not a kind of expert care in which the nurse teaches or advises. Most of the time, there will be as much, if not more, for the nurse to learn from the patient.

For nurses to develop competency in spiritual care, they must also be aware of potential barriers to this care. External barriers can include the emphasis on cure even when beyond the possible, the secularism of our society, an institutional focus on financial matters, and the dilution of specific religious beliefs by trying to accommodate everyone in the same way, thus meeting no one person’s needs. Furthermore, workloads and lack of education in spiritual care are significant barriers to nurses’ ability to discuss the spiritual concerns of their patients (Chan, 2010; McSherry & Jamieson, 2011). Depending on the setting, these barriers can be more or less of a problem. When problematic, they require nurses to be advocates for the care that patients deserve by educating other nurses and administrators about the benefits of spiritual care and to be creative in care delivery through incorporating the spiritual with the physical care.

The nurse’s internal barriers include the chatter of one’s mind and burnout. Corso (2012), a chaplain, has identified a need for oncology nurses to intervene on behalf of themselves to prevent compassion fatigue and replenish their resources. This self-care needs to be provided within the work environment and on the individual level of the nurse, such as a mindfulness intervention described. It should include meditation and prayer. Nurses may additionally benefit from a relationship with a certified spiritual director. A spiritual retreat also can enhance the development of an internal space and the ability to quiet the mental chatter. In a randomized controlled study, a retreat for nurses was assessed for long-term effects among the 87 participants and 110 controls. The retreat topics included self-awareness, self-care, and normalization of feelings that accompany critical care nursing. Over a six-month time period, the intervention group had significantly greater experiences of spirituality (p = 0.05) and greater spiritual well-being (p = 0.04) than the control group (Bay, Ivy, & Terry, 2010). Retreats may or may not be religious in nature, can be somewhere else or in one’s
own backyard, may be conducted by another or alone, and can occur over a weekend or during whatever time the participant or participants can afford. The retreat allows for nurses to reexamine what is happening internally and replenish resources. Innumerable websites are available to assist in the process and can be found by searching for spiritual retreat or online spiritual retreat.

General consensus in the nursing literature recognizes that spiritual care is an essential part of the nurse’s role (Cavendish et al., 2004; Pesut, 2006; Reimer-Kirkham et al., 2012; Taylor, 2002). The most outspoken exception comes from John Paley (2009), who has written that not only is it unnecessary for nurses to provide spiritual care, but that avoidance of spiritual care is a requirement to preserve the separation of church and state. However, patients’ opinions in this matter always take precedence. In the words of one group of patients, spiritual care requires that nurses have an established relationship with patients and have some training in spiritual care. It was less important to these patients that they and the nurse share similar spiritual or religious beliefs or similar life experiences (Taylor, 2007). Patients in other studies have clearly indicated that they do not perceive nurses as having any role in their spiritual care. In a survey about what patients with cancer and family caregivers want from nurses, the desires varied widely. The greatest agreement among patients and families was for interventions that allowed personal spiritual development in independent ways and not wanting overtly religious interventions or those that involved a very personal approach by the nurse (Taylor & Mamier, 2005). Clearly, one of the prerequisites to providing spiritual care is that nurses be open to and honor the wishes of individual patients.

Assessment of Spiritual Needs

Religion is a widely understood term among patients, but spirituality is not. For many, the distinction between religion and spirituality will be not only artificial but perhaps offensive. When nurses are attempting to assess patients’ needs and desires, especially those related to the theistic aspect of spirituality, nurses and patients must ensure they are talking about the same concepts.

Who can define another’s spiritual needs related to that individual’s connection with God? Is a Jewish nurse competent to assess the spiritual needs of a Lutheran, Catholic, Muslim, or agnostic patient? For that matter, are most nurses competent to assess the spiritual needs of a patient, especially those who relate to another’s connection with a higher being? If this is so, then spiritual assessment has to be open-ended, allowing patients to tell nurses what they need. However, this does not mean that nurses have no role in spiritual care beyond being open to what patients choose to share and making referrals to the appropriate religious advisors or leaders. Rather, there is a role in nursing care for supporting the spirit of all patients, no matter what their religious views.

For the sake of clarity, an artificial line can be drawn between spiritual care for the “human” and the “theistic” needs of patients. The human needs refer to those that can be met through human connections, one spirit to another, and the connections made through nature and the environment. These needs generally are less sensitive, and nurses feel more competent in assessing them. Human needs are not always seen by nurses or patients as being spiritual. They include the fears, anxieties, pain, and discomforts that are associated with cancer and its treatment. Although these needs are almost universally recognized as part of the cancer experience, they often are overlooked in the busyness of an oncology unit or are treated with the latest and greatest drugs.
The theistic needs refer to those needs related to patients’ connection with God or a higher power. In addition to being uniquely couched in the patients’ beliefs, theistic needs are personal and private. Because of patients’ vulnerability, spiritual care designed to meet these needs has the potential to be harmful, ranging from being intrusive to being destructive to patients’ belief system (Pesut, 2006; Pesut & Sawatzky, 2006; Winslow & Winslow, 2003). Nurses entering into this level of spiritual care need to be very cautious and aware of their limitations.

Nurses utilize the self more than any other kind of assessment tool when assessing patients’ spiritual needs. This use of self includes intuition, active listening, and an ability to communicate empathy, trustworthiness, and acceptance that allows patients to feel safe and free to share.

Without ever overtly discussing a patient’s theistic needs, nurses often can gather information from the admission page about religious affiliation and visual cues in the patient’s room, such as the presence of a Bible, prayer book, icons, prayer shawl, or other items. The level of rapport established with the patient and the nurse’s intuition also should be components in the nurse’s decision about how direct to be in assessing the patient’s needs that might be met by theistic spiritual care.

Competency in assessing and meeting the theistic needs will vary among nurses, as will the degree to which nurses and their patients are open to each other because the nurse relies primarily on the subjective perspective of the patient. Pesut and Sawatzky (2006) advocated for the use of an open-ended assessment tool that allows the patients to decide what to reveal. Another important element of the assessment is an inquiry about how patients want the nurses to support their beliefs and practices (Taylor & Mamier, 2005).

Puchalski (2006) has defined a mnemonic, FICA, to assist healthcare providers in conducting an open-ended spirituality assessment that will help to identify religious preferences in a nonthreatening manner. Faith signifies whether patients have religious or spiritual beliefs that help with coping and, if not, what does help them with coping. Important refers to how important their belief system is and how they see it relating to their health and decisions for treatment. Community relates to a church or spiritual community or group of individuals that are important in patients’ lives and provide support for them. Address represents a discussion of how patients want healthcare providers to address these issues while caring for them. Findings of a correlational evaluation of the FICA with spirituality indicators of the City of Hope quality-of-life tool suggest that FICA is a feasible tool for assessing spirituality (Borneman, Ferrell, & Puchalski, 2010).

In an integrative review of tools measuring spirituality, Draper (2012) found two quantitative tools that had undergone rigorous evaluation that were capable of assessing patients’ current spiritual state in a clinical setting: the FACIT-Sp and the Spirituality Index of Well-Being. He concluded, “The point of assessment is to identify patients’ needs and to represent them in numbers (in the case of quantitative approaches) or words (for qualitative ones)” (p. 976).

**Application of FICA to Case Study**

A return to the case study presented at the beginning of this chapter can demonstrate the application of FICA as defined by Puchalski (2006) and evaluated by Borneman et al. (2010). When completing the family history, the nurse asks M.L. how she has coped with the cancers, her own and her sister’s. M.L. explains that after years of being away, she had resumed regular church attendance when she was diagnosed with breast cancer. She says that she thought her religion had been an important support for her at that time. However, she describes herself as a “CEO”—Christmas and Easter only—Christian for the past few years. She expresses
feelings of anger at God for allowing her sister to suffer. The nurse asks if M.L. thinks it is OK for her to be angry with God, and M.L. laughs and says yes, she thinks he is big enough to bear her anger without retribution. As M.L. discusses her sorrow over her sister’s diagnosis, she also expresses a desire to have half the faith that her sister has. She talks of her sister’s faith and participation in a church community as a source of a calm and trusting acceptance of her future.

The nurse is constantly aware of M.L.’s responses and is cautious to never push, but to allow M.L. to reveal what she wants to discuss. With just a couple of open-ended questions following M.L.’s lead, the nurse learns that her belief system includes a faith in God that had been a source of support in the past. Her faith has not been so important in recent years, but she expresses a desire to possess a faith and trust in God similar to her sister’s. She also had derived support from participation in a church community in the past but not recently. Yet, she expresses an admiration for her sister’s consistent participation in her church community. Because of M.L.’s potential ambivalence about her faith in God and church attendance, the nurse assesses how M.L. wants her to address her spiritual care by allowing M.L. to take the lead in their discussion and by asking if she would like a referral to a minister.

**Interventions**

“We can make our minds so like still water that beings gather about us that they may see, it may be, their own images, and so live for a moment with a clearer, perhaps even with a fiercer life, because of our quiet.”

—William Butler Yeats, *The Celtic Twilight: Faerie and Folklore*

Interventions in spiritual care in nursing often are supportive in nature. It can be ethically problematic for nurses to go beyond that role to one of actively intervening in the theistic aspect of a patient’s spirituality (Pesut & Sawatzky, 2006). The exception would be those few nurses who have the additional education that allows them to be spiritual directors, and even with that educational preparation, the nurse/spiritual director needs to be transparent as to which role is being offered to a patient.

Spiritual care has been described as having four attributes: intuitive, interpersonal, altruistic, and integrative (Sawatzky & Pesut, 2005). The *intuitive* attribute requires a way of knowing beyond rational thought and a connection between the patient and nurse that allows the nurse to intuitively discern when the patient provides the opportunity for discussion. The nurse’s intuition always requires validation by the patient. The *interpersonal* attribute refers to the nurse’s therapeutic use of self. It means that the nurse needs to accept a degree of personal vulnerability in engaging with the patient. The characteristics for this attribute include warmth, nonjudgmental acceptance, compassion, and the ability to communicate those qualities. *Altruism* implies a willingness to place the patient first. Altruism in spiritual care is necessary to avoid even an inadvertent taking advantage of the patient’s vulnerability to meet the nurse’s agenda. Lastly, spiritual care is *integrative* in that physical, social, psychological, and spiritual realms are integrated.

In an ethnographic study of spiritual care, nurses described the need to keep spiritual care in the forefront while interacting with the patient in order to be open to the patient’s cues (Kirkham et al., 2004). Without such a conscious effort, it was too easy for the nurses to get caught up with everything else and lose sight of the patient as a whole. The nurses also described a purposeful avoidance of imposing one’s own beliefs and maintenance of awareness of the potential for harm.
Presence

“The only gift is a portion of thyself.”
—Ralph Waldo Emerson

In a concept analysis of spiritual care, presence was found to be almost universally identified in a comprehensive literature review (Ramezani, Ahmadi, Mohammadi, & Kazemnejad, 2014). It is an intervention in and of itself, but it also is an essential component of every other spiritual intervention. One nurse described her intentional and purposeful presence:

“The challenge and the discipline of that was to go in and leave my own self outside the door, just walk in, available . . . it’s discipline and hard work to really be in tune. You leave the room realizing if you believed your traditional things, I didn’t provide spiritual care because we didn’t talk about God, read any Bible verses, and I didn’t even pray with him. So how did I provide spiritual care? Well, I was aware of his spirituality. I was present for him.” (Kirkham et al., 2004, p. 158)

Miller (2001) identified the following seven steps in the art of being present.

- Preparation of self as provider by being open to yourself, being honest and accepting of your history
- Intentional aspiration to be present with the patient
- Preparation of a physical space if possible and a mental space within yourself; clearing out your own needs, expectations, and the chatter in your mind
- Honor and respect for the one to whom your presence is being offered
- The gift of what you have to offer, with no strings attached and a sincere realization that it is the patient’s choice whether to accept it
- Gratitude and acceptance of any gifts that flow from being present to your patient, such as a new relationship or lessons learned from the patient’s stories, joy, and laughter
- Replenishment of your spirit, especially when there is grief, disappointment, failure, or an inability to connect. The last step requires acknowledgment of your own needs and allowing others to be a healing presence to you.

Sometimes there is only a moment for presence, whereas other times, there may be an opportunity to be truly present for longer periods of time. The nurse’s full and undivided attention is focused on the patient, and yet the nurse also may be performing routine care tasks at the same time. Listening and really focusing on what the patient has to say, not on how to respond and not jumping ahead or making assumptions, is part of being present. Sometimes it is not easy to be truly present, and nurses need to be able to acknowledge when it is not possible and never try to fake it.

Human Connections

Oncology nurses can foster human connections directly with patients or indirectly through family members and friends. As noted previously, some of the research has shown that there may be times when patients need to focus on their own inner resources (Coward & Kahn, 2004; Logan et al., 2006). However, at many other times, the connections with friends and family are essential. Nurses can play an important role in coaching and encouraging family members to provide those connections. Among other interventions, nurses caring for older adult patients have identified the intervention of assisting patients to connect with family or significant others by encouraging these individuals to visit frequently and helping the patients to complete unfinished business (Narayanasamy et al., 2004).
Often, older adult patients are eager to share the story of their life. Asking about photos, cards, or memorabilia in the room can serve as an encouragement. A written or recorded history can provide an important legacy for families while also providing the impetus for patients to recollect their life’s history. A study of the efficacy of life review interviews on the spiritual well-being of terminally ill patients with cancer (N = 68) found significantly higher scores in the intervention group compared to the control group on the FACIT-Sp (p < 0.001) (Ando, Morita, Akechi, & Okamoto, 2010), thus providing support for the efficacy of life review as a mechanism of spiritual care.

**Humor**

Humor produces physiologic, psychological, social, and spiritual effects (James, 1995). Most people can identify with the positive effects that laughter can have by relieving tension and providing or deepening a connection between people. In a qualitative study with women who had breast cancer, participants identified humor as an important element of their coping and their spirituality (Johnson, 2002). In describing how spirituality affected her adjustment to breast cancer, one woman described how she and her two sisters, also affected with breast cancer, laughed at and with each other as they experimented with various prostheses. She questioned if this was spiritual and then answered her own question affirmatively because it strengthened the bond between the sisters and aided in their acceptance of a drastically altered body image (Tinley, 2006). The daughter of another patient with breast cancer described how her mother incorporated humor as part of her spirituality when she uplifted herself, her family, and the staff at the cancer center with the clown wigs and silly hats she would wear while going through chemotherapy (Tinley, 2006). Sometimes, the nurse’s humor intervention may be merely connecting with the patient as they share in laughter about something one has said or done. Nurses can intervene more actively by sharing jokes, cartoons, and amusing tales with their patients. Oncology units or clinics can make available humorous tapes, DVDs, and reading materials. Carefully encouraging patients to find humor in some of the disruptions in their lives can facilitate their ability to cope. For some patients with a theistic view, the connection between spirituality and humor may not be as apparent, but for others, attribution of humor to their god can demystify and encourage a more intimate relationship. As with other forms of spiritual care, nurses need to assess patients’ receptivity, the timing, and the content prior to using humor as an intervention.

**Hope**

The ability to look with confidence to the future is a sign of spiritual well-being. Hope can be elusive but is vital to coping for patients with cancer. Times when it may be especially difficult for patients to maintain hope include the time of diagnosis, when the side effects of treatment cannot be adequately managed, when metastasis or other signs of disease progression are present, and when the patient is dying. Oncology nurses can help their patients to cultivate a realistic sense of hope during any of these times with presence, humor, listening, helping them to establish and use support systems, affirming personal worth, recalling positive memories, or providing information in an honest, respectful, and compassionate manner. There should always be a sense of hope. Even when cure is no longer realistic, patients can have hope for time to do those things they have always wanted to do, to make peace with loved ones, or to have a peaceful death (Puchalski, 2006). Hope can be supported and enhanced through religious ritual and prayer when appropriate to the patient. The study by Ando et al. (2010) revealed significantly greater hope (p < 0.001) among the group of
terminally ill patients with cancer who had participated in a short life review interview than among the control group.

**Prayer and Ritual**

For many individuals, prayer and ritual are important aids to coping with health issues. In a national poll conducted by the Pew Research Center’s Forum on Religion and Public Life (2009), 58% of Americans reported they pray at least once a day. However, the treatment of cancer, including hospitalizations, surgeries, and medications, can present challenges in the patient’s ability to focus attention on prayer. There may be times when patients would welcome the assistance of their nurses in praying. If, in the process of caring for a patient, the nurse assesses a commonality in religious beliefs through the presence of a religious symbol or based on something said by the patient, it is appropriate for the nurse to offer, with no hint of persuasion, to share in a religious practice. Nurses must always take care when intervening with a religious practice or discussion. First of all, evangelization of a patient by a nurse is unethical because of the imbalance of power in their relationship and the potentially offensive nature of this type of approach. The ethical considerations of praying with a patient can be subsumed under two broad categories—respectful care of the patient and the integrity of the nurse (Winslow & Winslow, 2003). Respect for the patient includes a constant awareness that the patient is a unique individual with his or her own values. A nurse always asks for permission before introducing prayer and never urges or pressures the patient in any way. If the patient requests the nurse’s assistance or company in a religious practice, the nurse can accommodate the patient as long as the action is acceptable within the nurse’s belief system. Spiritual care also requires the integrity of the nurse. If participation in prayer is meaningful to the patient but not to the nurse, the nurse should refer to a chaplain or offer to contact a minister, priest, rabbi, shaman, or another individual as appropriate.

A nursing student wrote about the following experience in her clinical journal. She was caring for an older adult female patient who was becoming increasingly anxious the morning she was to go to surgery. The student assessed her patient’s increasing anxiety as having a potentially negative impact on her physical state going into surgery. The student noticed that the patient had a rosary laid out on her bedside stand. Being a Catholic herself, the student offered to pray with the patient. The patient indicated that praying a portion of the Rosary would be nice if the student knew how. The student then led the patient through the prayers of the Rosary. The patient became visibly more relaxed as they prayed. When they had completed the prayers, the patient thanked the student and expressed a readiness to go to surgery.

Nurses may also want to pray for their patients. In a blinded, randomized study of intercessory prayer for 667 patients with cancer, the intervention group had significantly better scores over time than the control group on spiritual (p = 0.03) and emotional well-being (p = 0.04). The participants were all Christian, and the prayers were offered by a Christian prayer group (Olver & Dutney, 2012). Because this was part of a study, the participants provided informed consent. In a clinical setting, it would be advisable for nurses to ask for permission to pray for a specific patient.

**Psychospiritual Integrative Therapy**

Psychospiritual integrative therapy (PSIT) incorporates mindfulness and passage meditation with cognitive behavioral therapy to address psychological and spiritual needs. PSIT is provided in a small-group format of eight sessions. The first four focus on one’s purpose in life, identifying adaptive and maladaptive belief patterns and mindful (secular) meditation,
and the last four focus on incorporation of spirituality in the pursuit of life’s purpose. Preliminary research in this type of group intervention with women who have breast cancer has provided evidence of improved quality of life, mood, and psychological and spiritual well-being (Corwin, Wall, & Koopman, 2012).

**Chaplains**

Professional healthcare chaplains are individuals who have graduate education in theology or divinity, have postgraduate training in clinical pastoral education, and have demonstrated competency in chaplaincy. Their role includes providing supportive spiritual care that crosses religious boundaries. They lead nondenominational ceremonies of worship and ritual and participate on healthcare teams and ethics committees. They are an excellent resource for nurses, especially when the patient’s spiritual needs exceed the nurse’s competency. Chaplains also can cross disciplinary lines to provide care for staff members experiencing the stress of patient care (Geevarghese, n.d.).

**Community-Based Spiritual Care**

A community-based intervention was organized and conducted by oncology providers from a secular healthcare system and interdenominational community clergy (Dann, Higby, & Mertens, 2005). Physicians, nurses, patients, survivors, and caregivers participated; the services were structured around the themes of fear, hope, peace, feeling God’s love, and importance of community. The authors identified the benefit of the collaborative effort in the message to patients that the religious community was concerned with their physical health and the medical community was concerned with their spiritual health.

Spirituality/religion may be an essential resource for families just as it is for individuals. Sometimes it can be the vehicle for resolving rifts within a family and leading to cohesion, but there is also the possibility that individual members may have differing views of spirituality that result in disagreements or isolation. Nurses need to carefully assess whether conflicts exist among family members because of differing views of religion or spirituality (Tanyi, 2006). It also can be helpful to patients if the nurses provide opportunities for spouses and family members to meet their own needs so that they, in turn, are in a better position to meet the patients’ needs. Nurses may need to offer family members reassurance or encouragement to leave so that they can get the rest and nourishment they need. Kim, Carver, Spillers, Crammer, and Zhou (2011) examined individual and dyadic associations of spiritual well-being with the quality of life of couples dealing with cancer. Each individual’s spiritual well-being was the strongest correlate to his mental health, but it was also correlated with the partner’s physical health. The investigators concluded “that both survivors and caregivers may benefit from interventions that enhance their ability to find meaning and peace in the cancer experience” (p. 769).

**Conclusion of Case Study**

The nurse’s assessment and interventions on M.L.’s behalf require the nurse’s openness and respect for M.L.’s vulnerability. The nurse is able to assess M.L.’s needs by utilizing the FICA assessment principles, and at the same time providing the intervention of presence by attending solely to what M.L. had to say and conveying a sense of acceptance and understanding. This provides an opportunity for M.L. to express her response to her
sister’s diagnosis in a way that helped her to sort out some of her spiritual ambivalence. Although the nurse does not introduce humor as an intervention, she shares in M.L.’s laughter as well as her distress. Because M.L. has expressed a desire to have a faith like that of her sister and recounted how her faith community had been a source of comfort in the past, the nurse offers a referral to a chaplain or minister, sensing M.L.’s willingness to reconnect with her faith community. M.L. decides to go back to the minister who had helped her in the past. At the end of her time with the nurse, M.L. says that although her sister’s cancer was not something she would have chosen, she thought it would be a privilege to accompany her sister in the journey ahead.

Conclusion

Spiritual care can enable coping, diminish negative feelings, provide connection between nurses and patients, reduce suffering, and promote growth and greater self-understanding. “Spirituality, then, must be acknowledged, appreciated, and included. It may not be the law, but it is the ethically appropriate course of action” (Puchalski, 2006, p. 38). However, not all patients want a theistic type of spiritual care from nurses, nor are all nurses comfortable or competent in providing it. Nurses who are providing spiritual care need to tread lightly, always keeping the patient’s needs and values in the forefront. Nurses may not be able to provide spiritual care within a religious framework, but they can always be open to connecting with their patients on the plane of one human spirit to another. It is imperative that oncology nurses provide this latter type of care to their patients regardless of the patient’s spiritual outlook, age, language, or culture. Without the spiritual connection, patients will be deprived of the best that nurses have to offer—themselves.

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