

Putting Evidence Into Practice[®]: Interventions for Depression

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Depression and depressive symptoms are prevalent in people with cancer, yet interventions for depression are a low priority for most oncology care providers. Barriers to diagnosis and treatment include beliefs by patients and providers that depression is an expected correlate of cancer diagnosis, the reluctance of patients to share psychological concerns, and the reticence of some professionals to assess patients with cancer for depressive symptoms in the midst of busy oncology settings. Intervening to diminish depressive symptoms in people with cancer is important because depression has been associated with poorer quality of life, recovery, and possibly survival. This article reviews and summarizes the evidence for pharmacologic and nonpharmacologic interventions for people with cancer and depression and identifies opportunities for future research and practice change.

The Oncology Nursing Society (ONS) has led efforts to identify patient outcomes that are influenced by nursing interventions. Nursing interventions must be within the scope of nursing practice, integral to the processes of nursing care (Given & Sherwood, 2005), and selected based on research examining intervention effectiveness. The 2006 ONS Putting Evidence Into Practice[®] (PEP) Depression Intervention Project Team reviewed, critiqued, and summarized the research evidence for nursing interventions related to depression in people with cancer. This article is an evidence-based review of pharmacologic and non-pharmacologic nursing interventions used to treat adult patients with cancer and depression.

Oncology care providers long have recognized that patients and their families experience emotional distress associated with cancer and its treatment. Emotional distress is an important problem in cancer survivorship because it significantly influences cancer recovery (Alferi, Carver, Antoni, Weiss, & Duran, 2001; Helgeson, Snyder, & Seltman, 2004; Manne et al., 2003; Osborne, Elsworth, & Hopper, 2003; Owen, Klapow, Roth, Nabell, & Tucker, 2004), quality of life (QOL) (Heiney et al., 2003; Vega et al., 2002; Vos, Garssen, Visser, Duivenvoorden, & de Haes, 2004), and possibly even long-term survival (Maunsell, Brisson, & Deschenes, 1995; Weihs, Enright, Simmens, & Reiss, 2000). Depression, the most common emotional distress experienced, is estimated to have prevalence from 1.5%–50% in breast cancer survivors (Massie, 2004; Trask, 2004; Zabora, BrintzenhofeSzoc, Curbow, Hooker, & Piantadosi, 2001), depending on how depression is defined.

Much has been written about depression, although the term's many definitions may contribute to the lack of under-

At a Glance

- ◆ Depression is a prevalent, comorbid condition for people with cancer, but barriers often prevent appropriate assessment and intervention.
- ◆ Evidence shows that psychoeducational and psychosocial interventions, particularly cognitive behavioral therapy, are beneficial in managing depressive symptoms in patients with various types of cancer.
- ◆ Complementary therapies are gaining popularity, but currently no sufficient, high-quality studies support the use of such therapies in people with cancer.

standing of the seriousness of depressive symptoms and can provide barriers to its treatment. Styron (1990) wrote in *Darkness Visible: A Memoir of Madness* that it was “a noun with

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a bland tonality and lacking any magisterial presence, used indifferently to describe an economic decline or a rut in the ground, a true wimp of a word for such a major illness" (p. 37). Depression is defined for this review as the entire range of feelings and emotions expressed by individuals with cancer as they manage personal and illness-related problems; it includes normal sadness in response to loss as well as chronic, depressed emotional affect and clinical depression that meets specific criteria for a psychiatric disorder (Barsevick, Sweeney, Haney, & Chung 2002). Patients suffering with depressive symptoms that fail to meet the criteria for diagnosis or with sufficient symptoms to meet a diagnosis are at risk for poor health outcomes (Zabora et al., 2001).

One barrier to effective assessment and intervention for depression is the belief of many providers and patients that depression is a natural reaction to the diagnosis of cancer rather than a comorbid and serious condition (Passik et al., 1998). This myth limits identification of depression as a condition that can be treated. Another barrier is the reluctance of many patients to share their emotional symptoms with busy healthcare professionals; conversely, providers often are uncomfortable probing into patients' psychological distress.

To overcome these barriers, standards and guidelines such as the National Comprehensive Cancer Network (NCCN) Standards of Care for Distress Management (NCCN, 2008) call for screening, evaluating, and treating depression in all patients with cancer (see Figure 1). Oncology nurses can play a significant role in (a) recognizing visual and verbal cues of anxiety and depression, (b) screening for depressive symptoms with the many valid screening tools available, and (c) integrating evidence-based interventions into their practice.

Descriptions of screening tools for depression can be found on the ONS Outcomes Resource Area (www.ons.org/outcomes/measures/summaries.shtml#dep). Oncology nurses can advocate for patients and their families to improve recognition and treatment of depressive symptoms and depression and collaborate with mental health professionals to ensure comprehensive care. Figure 2 provides signs and symptoms of depression.

The ONS PEP Depression Intervention Project Team explored the evidence on interventions to answer the question, "What can oncology nurses do to assist people with cancer who also have depressive symptoms or major depressive disorder?"

Methods

The workgroup searched MEDLINE®, CINAHL®, PubMed®, and PsycINFO using the search terms *interventions, psycho-social interventions, psychoeducational interventions, supportive counseling, and cancer and depressive symptoms or depression or major depressive disorder*. Years searched were 2001–2006, and the search ended September 30, 2006. In some cases, earlier articles were reviewed in an attempt to comprehensively cover appropriate literature.

Articles were eliminated if they did not involve an intervention targeted for depressive symptoms or major depressive disorder, or if they were exclusively about caregivers or pediatric patients. A health services librarian was consulted to assist in the search.

- Distress should be recognized, monitored, documented, and treated promptly at all stages of disease.
- All patients should be screened for distress at the initial visit, at appropriate intervals, and as clinically indicated, especially with changes in disease status.
- Screening should identify the level and nature of the distress.
- Distress should be assessed and managed according to clinical practice guidelines.
- Multidisciplinary institutional committees should be formed to implement standards for distress management.
- Educational and training programs should be developed to ensure that healthcare professional and pastoral caregivers have knowledge and skills in the assessment and management of distress.
- Licensed mental health professionals and certified pastoral caregivers experienced in psychosocial aspects of cancer should be readily available as staff members or by referral.
- Medical care contracts should include reimbursement for services provided by mental health professionals.
- Clinical health outcomes measurement should include assessment of the psychosocial domain (e.g., quality of life, patient and family satisfaction).
- Patients, families, and treatment teams should be informed that management of distress is an integral part of total medical care and provided with appropriate information about psychosocial services in the treatment center and the community.
- Quality of distress management should be included in institutional continuous quality-improvement projects.

Figure 1. Standards of Care for Distress Management

Note. From "Distress Management Clinical Practice Guidelines in Oncology (version 1.2008)," *The Complete Library of NCCN Clinical Practice Guidelines in Oncology*, 2008, Jenkintown, PA: National Comprehensive Cancer Network (NCCN). Copyright 2008 by NCCN. Reprinted with permission. To view the most recent and complete version of the guideline, go to www.nccn.org. These guidelines are a work in progress that will be refined as often as new significant data become available. NCCN guidelines are to be used with independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by NCCN. All rights reserved. The guidelines and illustrations herein may not be reproduced in any form for any purpose without written permission from the NCCN.

Highlights of Reviewed Literature

Nine systematic reviews or meta-analyses from the identified time period found the highest evidence in support of psychosocial and psychoeducational interventions and pharmacologic interventions. The detailed ONS PEP card can be found in the Appendix. Each study and review was rated on strength of evidence as identified by the ONS Weight-of-Evidence Classification Schema (see Table 1). The system critically appraises evidence sources from strongest (multiple, well-designed, randomized, controlled trials with samples more than 100 subjects) to weakest (e.g., qualitative designs, case studies, opinions). From there, interventions were classified using a weight-of-evidence schema (Mitchell & Friese, n.d.), which

- A depressed mood for most of the day and on most days
- Diminished pleasure or interest in most activities
- Significant change in appetite and sleep patterns
- Psychomotor agitation or slowing
- Fatigue
- Feelings of worthlessness or excessive, inappropriate guilt
- Poor concentration
- Recurrent thoughts of death or suicide

Figure 2. Signs and Symptoms of Major Depression

Note. Based on information from National Cancer Institute, 2007.

ranged from Recommended for Practice for those with strong supportive evidence to Likely to be Effective, Benefits Balanced With Harms, Effectiveness not Established, Effectiveness Unlikely, or Not Recommended for Practice. Interventions reviewed are psychosocial and psychoeducational, pharmacologic, and complementary.

Psychoeducational and Psychosocial Interventions

Evidence at the highest level (Barsevick et al., 2002; Bennett & Badger, 2005; Given et al., 2004; Newell, Sanson-Fisher, & Savolainen, 2002; Osborne et al., 2003; Pirl, 2004; Uitterhoeve et al., 2004; Williams & Dale, 2006) supports the benefit of psychoeducational and psychosocial interventions in the management of depressive symptoms during and following cancer treatment in patients with different types of cancer. Psychoeducational and psychosocial interventions include cognitive-behavioral therapy, patient education and information, counseling and psychotherapy, behavioral therapy, and supportive interventions. Cognitive-behavioral therapy is defined as any specific psychological or psychosocial intervention that is relatively brief, goal oriented, based on learning principles of behavior change, and directed at effecting change in a specific clinical outcome (Osborn, Democada, & Feuerstein, 2006). It teaches problem-solving skills and challenges “black and white” thinking to help reframe attitudes. Counseling and psychotherapy refer to interactive verbal interventions, including nondirective, psychodynamic, existential, supportive, and crisis interventions; nurses who provide such interventions have advanced education and training. Of the interventions studied, the most evidence is for cognitive-behavioral therapy. Patient education, therapeutic social support, and information take many forms but clearly are important and essential actions for oncology nurses.

Barsevick et al. (2002) examined scientific studies, qualitative or quantitative systematic reviews, and practice guidelines published from 1980–2000, and concluded that psychoeducational interventions reduced depressive symptoms in patients with cancer. Behavior therapy or counseling alone or in combinations with cancer education was found to be beneficial. The same recommendations were made in a meta-analysis by Williams and Dale (2006), which also included pharmacologic interventions. Although considerable variability exists in frequency, duration, and type of psychosocial intervention, most studies support that

the interventions are effective for reducing depressive symptoms; thus, they are recommended for practice. Although less evidence shows that psychosocial interventions are effective for treating those with depression, the ONS PEP Weight-of-Evidence Classification Schema indicates that enough evidence exists to recommend such interventions for practice.

Pharmacologic Interventions

Antidepressant Medications

Although much has been written about antidepressant use in patients with depression and cancer, few randomized, controlled trials have examined the effectiveness of antidepressants. Treatment studies of patients with cancer and depression support use of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), mianserin (atypical antidepressant not available in the United States), and others (Goodnick & Hernandez, 2000; Lan Ly, Chidgey, Addington-Hall, & Hotopf, 2002; Pirl, 2004; Schwartz, Lander, & Chochinov, 2002). Four reviews were identified that supported the benefits of antidepressant medication in patients with cancer (Pirl; Schwartz et al.), other comorbid medical illness (Goodnick & Hernandez), and palliative care (Lan Ly et al.). Studies measuring depression at less than five weeks showed less benefit, likely because the time to reach therapeutic effect may be four to eight weeks. No differences were found in effectiveness between TCAs and SSRIs; however, the lower incidence of side effects with SSRIs makes them preferable in patients with cancer. Although no studies have specifically examined the newer serotonin-norepinephrine reuptake inhibitor duloxetine in patients with depression and cancer, its similarity to venlafaxine makes it likely to be similarly effective.

Patients with malignant melanoma, traditionally treated with interferon alfa, are known to experience depression as a side effect of treatment. Musselman et al. (2001) prescribed paroxetine two weeks prior to the initiation of interferon alfa and continued it for the first 12 weeks of therapy in a double-blind study of 40 patients. Dosage ranged from 10–40 mg daily. Major depression developed in only 2 of the 18 patients in the paroxetine group compared to 9 of the 20 on placebo. Paroxetine treatment also significantly decreased the likelihood that interferon would have to be discontinued because of severe depression.

Clinical practice guidelines, another comprehensive, evidence-based tool to assist healthcare professionals in providing optimal care, support the benefit of medication interventions. The National Health and Medical Research Council, Australia (2003), which published *Clinical Practice Guidelines for the Psychosocial Care of Adults With Cancer*, concluded that the treatment of depression should incorporate psychotherapeutic and medication interventions. Although clear evidence supports the efficacy of antidepressant medication in treating depression in patients with cancer, no evidence exists that any particular antidepressant is superior to another. Antidepressant selection should be based on side-effect profiles and patient needs. For example, the sedating properties of the TCAs may be beneficial for some patients, and TCAs may potentiate opioid analgesia in those with pain. The long half-life of fluox-

Table 1. Putting Evidence Into Practice® Weight-of-Evidence Classification Schema

WEIGHT-OF-EVIDENCE CATEGORY	DESCRIPTION	EXAMPLES
Recommended for practice	Effectiveness is demonstrated by strong evidence from rigorously designed studies, meta-analyses, or systematic reviews. Expected benefit exceeds expected harms.	At least two multisite, well-conducted, randomized, controlled trials (RCTs) with at least 100 subjects Panel of expert recommendation derived from explicit literature search strategy; includes thorough analysis, quality rating, and synthesis of evidence
Likely to be effective	Evidence is less well established than for those listed under recommended for practice.	One well-conducted RCT with fewer than 100 patients or at one or more study sites Guidelines developed by consensus or expert opinion without synthesis or quality rating
Benefits balanced with harms	Clinicians and patients should weigh the beneficial and harmful effects according to individual circumstances and priorities.	RCTs, meta-analyses, or systematic reviews with documented adverse effects in certain populations
Effectiveness not established	Data currently are insufficient or are of inadequate quality.	Well-conducted case control study or poorly controlled RCT Conflicting evidence or statistically insignificant results
Effectiveness unlikely	Lack of effectiveness is less well established than those listed under not recommended for practice.	Single RCT with at least 100 subjects that showed no benefit No benefit and unacceptable toxicities found in observational or experimental studies
Not recommended for practice	Ineffectiveness or harm clearly is demonstrated, or cost or burden exceeds potential benefit.	No benefit or excess costs or burden from at least two multisite, well-conducted RCTs with at least 100 subjects Discouraged by expert recommendation derived from explicit literature search strategy; includes thorough analysis, quality rating, and synthesis of evidence
<i>Note.</i> Based on information from Mitchell & Friese, n.d.		

etine makes it less desirable in patients with hepatic or renal dysfunction; in such cases, another antidepressant is preferable (Health and Medical Research Council, Australia; National Cancer Institute, 2007). Other guidelines for the treatment of depression also provide useful information about medication management in the treatment of depression in adults (American Psychiatric Association, 2000; Ministry of Health, Singapore, 2004). Those guidelines contain information about selecting antidepressants, adjusting doses, assessing response, switching medications, managing the continuation and maintenance phases of antidepressant treatment, and discontinuing treatment. The guidelines are not specific to depression in patients with cancer. Although the guidelines document that depression can coexist with medical conditions, they are not specific for the physical impairments of many patients with cancer. In contrast, the National Comprehensive Cancer Network (2008) has published guidelines detailing algorithms describing care of patients with cancer and mood disorders or adjustment disorders with depressed mood. Pharmacology with antidepressants is an effective intervention and is recommended for practice.

Methylphenidate

One phase II study (Homsí et al., 2001) and one systematic review (Rozans, Dreisbach, Lertora, & Kahn, 2002) explored methylphenidate (Ritalin®, Novartis) in patients with depression in advanced cancer (cancer sites studied included breast, esophagus, pancreas, colorectal, and other). The advantage of

the central nervous system stimulant is its reported safety and rapid onset of action. It is used most often in advanced cancer and palliative situations, when doses typically are prescribed twice a day starting at 5 mg and titrated until a response is obtained or side effects dictate discontinuance. Giving the dose early in the day with food is recommended to increase absorption and decrease insomnia. Homsí et al. found that the maximum daily dose needed for resolution of depression was 20 mg. In the Rozans et al. systematic review of nine studies, methylphenidate was useful in treating depression in a variety of malignancies, with more than 80% of patients responding favorably and less than 20% reporting side effects. Methylphenidate also is used to address opioid-induced somnolence, augment opioid effects, improve cognitive functioning in patients with cancer, and decrease pain scores. Those benefits may contribute to mood improvement. Using the ONS PEP Weight-of-Evidence Classification Schema, the team concluded that methylphenidate is likely to be effective.

Complementary Interventions

Complementary and alternative therapies used to treat depression in patients with cancer are gaining popularity and prevalence. Unfortunately, few randomized, controlled studies of complementary interventions have been conducted in people with cancer and depression. Included in this category are massage therapy, relaxation therapy, hypnotherapy, and many others.

Massage Therapy

Massage is the manipulation of soft-tissue areas of the body, offered to assist in relaxation, aid in sleep, and relieve muscle tension and pain (Cassileth & Vickers, 2004). Studies examining the effect of massage therapy on depression are beginning to emerge, but effectiveness has not been established. The most consistent effect on symptom relief in patients with cancer was reduction in anxiety (Fellowes, Barnes, & Wilkinson, 2004). Some short-term reduction in depression has been demonstrated; self-report symptom scores of depression reduced by about 50% 2–48 hours after massage (Cassileth & Vickers), but more and better-quality studies are needed to recommend this intervention.

Relaxation Therapy

Relaxation therapy refers to techniques that focus on inducing a relaxed physical and mental state, such as progressive muscle relaxation with or without guided imagery, hypnosis, and autogenic training (Leubbert, Dahme, & Hasenbring, 2001; Sloman, 2002). Leubbert et al.'s meta-analysis evaluated 15 randomized, controlled studies conducted from 1980–1995. Relaxation training was found to have a significant impact on reducing cancer treatment-related side effects, including emotional adjustment variables (e.g., depression, anxiety, hostility). In a study of 56 people with advanced cancer, progressive muscle relaxation and guided imagery were taught to patients; a reduction in depression was found in all three treatment groups (Sloman). Findings from the review included a small but significant benefit on treatment-related side effects, including depression. According to the ONS PEP Weight-of-Evidence Classification Schema, relaxation as a method is likely to be effective in managing depressive symptoms.

Hypnotherapy

Hypnotherapy is a behavior therapy to induce heightened concentration, receptivity, and relaxation (Sadock & Sadock, 2003). Rajasekaran, Edmonds, and Higginson's (2005) systematic review reported results of 27 studies prior to 2003. Terminally ill adult patients with cancer obtained relief from depression, anxiety, and pain, but only 1 of the 27 was a randomized, controlled study. Although few adverse effects were reported overall, reports were made of patients who were unable to enter a deep trance or who were frightened by the treatment (Rajasekaran et al.). Most studies were considered of poor quality with very small sample sizes. Therefore, according to the ONS PEP Weight-of-Evidence Classification Schema, effectiveness is not established for hypnotherapy in managing depression; further research is needed.

Other Complementary Interventions

St. John's wort, an herb known to treat mild to moderate depression, should be avoided during chemotherapy or radiation or when surgery is planned because it can adversely impact the efficacy of some chemotherapeutic agents and prescription medications (Deng & Cassileth, 2005). Other complementary interventions such as nutritional and herbal supplements, yoga, acupuncture, aromatherapy, Healing Touch, exercise, and meditation have not been studied specifically in people with cancer,

Table 2. Selected Screening Tools for Depression

TOOL	DOMAINS OR FACTORS
Beck Depression Inventory (BDI; short form: BDI-SF)	Behavioral, cognitive, and somatic components of depression; focuses on negative attitudes of the patient toward self
Center for Epidemiological Studies–Depression Scale (CES-D; short form: CES-D-SF)	Frequency of depressive symptoms. Four factors: negative affect and mood, positive mood or well-being, somatic, interpersonal
Hamilton Rating Scale for Depression (HAM-D)	Rates severity of depression
Hospital Anxiety and Depression Scale (HAD)	Self-screen to rate severity of depression and anxiety
Geriatric Depression Scale (GDS; short form: GDS-SF)	Positive and negative affective domains of depression
Profile of Mood States (POMS; short form: POMS-SF)	Six subscales: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment

Note. Based on information from Badger, 2005.

or insufficient studies have demonstrated effectiveness to recommend for practice (Pirl, 2004). Although some studies (Post-White et al., 2003; Sloman, 2002) show promising results and benefits of such methods to reduce mood disturbance, stress, pain, and other symptoms, effectiveness in decreasing depressive symptoms in patients with cancer has not been established; therefore, the method cannot be recommended.

Implications

The evidence documenting the ill effects of depression as a comorbid symptom or diagnosis supports the need for improved recognition and intervention. Oncology nurses are well positioned to assess for depression during the cancer treatment trajectory. A routine including questions about patient concerns, difficulties, hopes, and expectations with supportive responses and information leads to further education or referral. Nurses must educate themselves about depression as a symptom and an illness and can select one of many, well-established depression assessment tools to incorporate into their practices (see Table 2). In addition, each practice setting must develop methods to provide or make referrals for psychosocial, psychoeducational, and pharmacologic interventions. Oncology nurses with additional expertise may do so or can collaborate with other professionals to improve cancer care.

Conclusions

Depression, whether classified as depressive symptoms or diagnosis, is prevalent and distressing for many patients with cancer and their families. Depression can contribute to

negative health outcomes, including increased morbidity and mortality (Manne et al., 2003; Osborne et al., 2003; Owen et al., 2004; Vega et al., 2002; Vos et al., 2004; Weihs et al., 2000). Although many of the interventions used to treat depression may be effective in patients with cancer and depression, patients with cancer are not offered the interventions routinely. Depression remains underdiagnosed and undertreated.

The strongest evidence exists for psychosocial and psychoeducational interventions. Further research is needed to examine intervention dosage (frequency and duration) and combinations of psychosocial interventions and medications with diverse cancer populations. Pharmacologic interventions also have been found to be effective, and clinical practice guidelines recommend the combination of psychosocial interventions and medication. Finally, initial studies of some types of complementary and alternative interventions have shown promise. Lack of evidence does not equate lack of efficacy, but more studies are needed in patients with cancer and diverse diagnoses before practice recommendations can be made.

Oncology nurses are ideally situated not only to assess for depressive symptoms in their patients, but also to provide education about depression and its effects, offer support, and make appropriate referrals when needed. Such actions will augment a holistic approach to high-quality care for patients with cancer.

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Put Evidence Into Practice

The Putting Evidence Into Practice® (PEP) resource card for chemotherapy-induced peripheral neuropathy (CIPN) appears on the following pages. For more information about evidence-based interventions for CIPN, including different versions of the card, definitions, evidence tables, and a complete list of references, visit www.ons.org/outcomes/volume2/peripheral.shtml. PEP resources for several other nursing-sensitive patient outcomes are available at www.ons.org/outcomes.

The *Clinical Journal of Oncology Nursing* wants to hear how you use the PEP resources to improve the quality of cancer care that you deliver. E-mail CJONEditor@ons.org to share your experiences with nurses everywhere.

Appendix. Putting Evidence Into Practice® Card on Depression in Patients With Cancer

What can nurses do to assist people with cancer who also have depression or depressive symptoms?

RECOMMENDED FOR PRACTICE

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

Psychoeducational or Psychosocial Interventions

Psychoeducational or psychosocial interventions include cognitive-behavioral therapy, patient education and information, counseling or psychotherapy, behavioral therapy, and social support. Cognitive-behavioral therapy is defined as any specific psychological or psychosocial intervention that is relatively brief, goal oriented, based on learning principles of behavior change, and directed at effecting change in a specific clinical outcome.⁵ Patient education and information are defined as sensory, procedural, or medical information about cancer or cancer therapy regarding illness or symptom(s), symptom management, and/or discussion of treatment options; may include the use of booklets, videos, or other education materials; and do not include active rehearsal of new behaviors.^{1,5} Counseling or psychotherapy is defined as interactive verbal interventions, including nondirective, psychodynamic, existential, supportive, general, or crisis interventions; no specific behavioral or coping skills, including social support, are taught by professionals.¹ Social support is defined as supportive interventions provided by patients with cancer, family members, or laypeople but not professionals.¹ With the exception of patient education and information, the other types of intervention require advanced education and training.

Evidence at the highest level¹⁻⁸ supports the benefit of psychoeducational or psychosocial interventions in the management of depressive symptoms during and following cancer treatment in patients with different types of cancer. Although variability in frequency and duration of the interventions is considerable, most studies support that such interventions are effective for reducing depressive symptoms; fewer studies support that such interventions are effective for a diagnosis of depression.⁸ A small study²⁵ concluded that nurses could be trained to provide problem-solving therapy to outpatients with cancer that resulted in reduced symptoms of a major depressive disorder. Of the psychosocial interventions studied, the strongest evidence is for cognitive-behavioral therapy. More research is needed to systematically examine the intervention "dosage" (frequency, duration) required for effectiveness among the different types of psychoeducational or psychosocial interventions for diverse cancer subpopulations.

Pharmacologic Interventions

Antidepressant Medications

Articles describing the effectiveness of antidepressant medications in the treatment of depression abound. However, fewer randomized, controlled trials (RCTs) are available describing the medications' effectiveness in patients with cancer and depression. Four reviews were identified that supported the benefits of antidepressant medication in patients with cancer,^{6,11} other comorbid medical illness,⁹ and palliative care.¹⁰ Treatment studies of depression in patients with cancer have been completed using tricyclic antidepressants (TCAs) as well as selective serotonin reuptake inhibitors (SSRIs) and mianserin. Studies measuring depression at less than five weeks showed less benefit, perhaps because the time to reach therapeutic effect may be four to eight weeks. No differences were found in the effectiveness between TCAs and SSRIs; however, the lower incidence of side effects in the SSRIs and serotonin-norepinephrine

reuptake inhibitors (SNRIs) makes them preferable in patients with cancer. No studies have specifically examined the newer SNRI, duloxetine, in patients with depression and cancer, but its similarity to venlafaxine makes it likely to be similarly effective.

Patients with malignant melanoma, traditionally treated with interferon alfa, are well known to experience depression as a side effect of their treatment. In a double-blind study,¹² 40 patients were prescribed paroxetine two weeks prior to the initiation of interferon alfa and continued for the first 12 weeks of therapy. Dosages ranged from 10–40 mg daily. Major depression developed in only 2 of the 18 patients in the paroxetine group as opposed to 9 of the 20 on placebo. Paroxetine treatment also significantly decreased the likelihood that interferon would have to be discontinued because of severe depression.

Clinical practice guidelines are another comprehensive, evidence-based tool to assist healthcare professionals in providing optimal care. The National Health and Medical Research Council¹³ published *Clinical Practice Guidelines for the Psychosocial Care of Adults With Cancer*, concluding that the treatment of depression should incorporate psychotherapeutic and medication interventions. The guidelines state that evidence clearly indicates the efficacy of antidepressant medication in treating depression in patients with cancer, but no evidence suggests that any one antidepressant is superior to another. The sedating properties of the tricyclics and the potentiation of opioid analgesia in those with pain may be beneficial to some patients. The guidelines also state that patients with cancer may respond to a lower dose of tricyclic antidepressants. The long half-life of fluoxetine makes it less desirable in patients with hepatic or renal dysfunction; in such cases, sertraline or paroxetine is preferable. Other guidelines for the treatment of depression exist and provide useful information about medication management in the treatment of depression in adults.^{15,16} Provided information includes antidepressant selection, dose adjustment, response assessments, switching medications, continuation and maintenance phases of antidepressant treatment, and discontinuation of treatment. The guidelines are not specific to depression in patients with cancer, and although they recognize that depression can coexist with medical conditions, they do not take into consideration the physical impairments of many patients with cancer; therefore, they must be applied with caution. The National Comprehensive Cancer Network¹⁴ published guidelines for distress management that contain algorithms describing the care of patients with cancer and mood disorders as well as adjustment disorders with depressed mood. Pharmacology is recommended as an effective intervention.

Antidepressant Medications Used in Patients With Cancer

Selective serotonin reuptake inhibitors:

- Fluoxetine (Prozac®)
- Fluvoxamine (Luvox®)
- Sertraline (Zoloft®)
- Paroxetine (Paxil®)
- Citalopram (Celexa®)
- Escitalopram (Lexapro®)

Tricyclic antidepressants:

- Amitriptyline (Elavil®)
- Imipramine (Tofranil®)
- Desipramine (Norpramin®)
- Nortriptyline (Pamelor®)
- Doxepin (Sinequan®)

Serotonin-norepinephrine reuptake inhibitors:

- Venlafaxine (Effexor®)
- Duloxetine (Cymbalta®)

Other Antidepressants:

- Mirtazapine (Remeron®)
- Bupropion (Wellbutrin®)
- Trazodone (Desyrel®)
- Mianserin (This drug has not been approved by the U.S. Food and Drug Administration for use in the United States.)

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

Methylphenidate (Ritalin®)

One phase II study¹⁷ and one systematic review¹⁸ explored methylphenidate in patients with depression in advanced cancer. The advantage of this central nervous system stimulant is its reported safety and rapid onset of action. It is used more often in advanced cancer and palliative situations. Doses are typically prescribed twice daily starting at 5 mg and titrated until response is obtained or side effects dictate discontinuance. Administering methylphenidate before breakfast and lunch is recommended because food increases the absorption rate and early administration lessens insomnia. Various cancer sites studied include breast, esophagus, pancreas, and colorectal. The maximum daily dose needed to resolve depression was 20 mg in a study of 40 patients.¹⁷ In a review of nine studies, methylphenidate was concluded useful in treating depression in a variety of malignancies, with more than 80% of patients responding favorably and less than 20% reporting side effects.¹⁸ Methylphenidate also is used to address opioid-induced somnolence, augment opioid effects, and improve cognitive functioning in patients with cancer; in addition, some have found a decrease in pain scores. These benefits may contribute to mood improvement.

Complementary and Alternative Therapy

Relaxation Therapy

Techniques that focus on inducing a relaxed physical and mental state include progressive muscle relaxation with or without guided imagery, hypnosis, and autogenic training.^{19,20} A meta-analysis¹⁹ evaluated 15 RCTs that were conducted from 1980–1995. Relaxation training was found to have a significant impact on reducing cancer treatment-related side effects, including emotional adjustment variables (depression, anxiety, and hostility). In a study of 56 people with advanced cancer, progressive muscle relaxation and guided imagery techniques were taught to patients as single techniques or as a combined technique. Patients in the three treatment groups showed a reduction in depression as measured by the Hospital Anxiety and Depression Scale (HADS) three weeks later; those randomized to the control group did not.²⁰

EFFECTIVENESS NOT ESTABLISHED

Interventions for which there are currently insufficient or conflicting data or data of inadequate quality, with no clear indication of harm

Complementary and Alternative Therapy

Massage Therapy

Massage is the manipulation of soft tissue areas of the body, offered to assist relaxation, aid in sleep, and relieve muscle tension and pain.²¹ One systematic review²² evaluated 8 RCTs and 10 reports from 1966–2002 regarding the effect of massage for symptom relief in patients with cancer. Approximately one of three studies in the review found a beneficial

effect on cancer-related depression. The patients with cancer experienced the most consistent relief on postintervention anxiety.²² Two studies evaluated the effect of massage therapy. A randomized study²³ evaluated 34 female participants with breast cancer who were at least three months post treatment. They received massage three times weekly for five weeks and depressed mood was reduced at pre- and post-session and first-last days.²³ In a nonrandomized study of 1,290 patients looking at symptoms relief from massage therapy, patients chose one of three types of massage treatments in which sessions lasted 20–60 minutes.²¹ Baseline scores were self-rated for common symptoms: pain, fatigue, stress or anxiety, nausea, depression, and “other.” The rating scale was 0 (not at all bothersome) to 10 (extremely bothersome). Patients again self-rated 5–15 minutes after massage therapy. Symptoms scores were reduced by approximately 50%, with those reporting depression demonstrating 48.9% improvement in their scores.²¹ The researchers attempted to follow some of the patients up to 48 hours post treatment; even so, the results reflect only short-term benefit.

Hypnotherapy

Hypnotherapy is a behavioral therapy that uses hypnosis to induce heightened concentration, receptivity, and relaxation. One systematic review²⁴ reported results of 27 studies conducted from 1974–2003 using hypnotherapy in terminally ill adult patients with cancer for symptom relief. Of the 27 studies reported, most were of poor quality and only one was a randomized control study involving 50 subjects. In that study, a statistically significant reduction in depression and anxiety scores was demonstrated for patients’ assigned hypnotherapy compared with the standard group.²⁴ Overall, few adverse effects were reported; however, reports indicated that patients were unable to enter a deep trance or were frightened by the treatment.²⁴

Special Consideration: The use of other complementary methods such as St. John’s wort, nutritional and herbal supplements, yoga, acupuncture, aromatherapy, exercise, and meditation has not been studied specifically in the setting of patients with cancer and depression. Although some promising studies show benefit of the methods on stress, pain, and other symptoms, at this time, effectiveness for depression in patients with cancer has not been established.

EXPERT OPINION

Low-risk interventions that are (a) consistent with sound clinical practice, (b) suggested by an expert in a peer-reviewed publication (journal or book chapter), and (c) for which limited evidence exists. An expert is an individual with peer-reviewed journal publications in the domain of interest.

Experts^{26–28} have recommended the following interventions for patients experiencing depressive symptoms and/or depression during and following cancer treatment.

- Assess patients and family members for depression and depressive symptoms at every encounter.
- Assess patient’s and family’s understanding of depression and its role in cancer recovery, as well as the meaning of depression to the patient and his or her family.
- Provide education and information to patients and families about depression and its management.

Although no evidence exists on combination of antidepressant medication plus psychoeducational or psychosocial therapy in patients with cancer and depression, clinical practice guidelines for the treatment of depression do recommend combined therapy for severe and chronic depression, finding it more effective than either alone.^{15,16}

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Definitions of the interventions and full citations: www.ons.org/outcomes
Literature search completed through September 2006.

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