

Practical Approaches to Pharmacologic Management of Pain in Older Adults With Cancer

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The literature lacks a strong evidence base regarding the use of analgesics in older adults (aged 65 years or older). Most of the current recommendations on treating older adults with analgesics are based on clinical practice and expert opinions. Hence, to make good decisions about pain management when developing treatment plans for older adults, healthcare providers should focus on the pharmacokinetic and pharmacodynamic properties of drugs in the context of the physiologic changes that occur with aging. This article describes the pharmacologic management of pain in older adults, drawing from research on cancer pain and other types of persistent painful conditions.

Physiologic Changes Associated With Aging

Age-related altered pharmacokinetic and pharmacodynamic properties of drugs (Pergolizzi et al., 2008), as well as comorbidities, can increase the risk of pharmacologic toxicity and narrow the therapeutic window. Additionally, older adults have a greater risk of polypharmacy issues, in part because approximately 20% of adults aged 70 years or older take five or more medications (Milton, Hill-Smith, & Jackson, 2008), thereby increasing their risks for adverse events associated with interactions between medications or their metabolites. Although overmedicating can increase the risks of adverse events, undermedicating may inadequately treat a patient's pain.

When medications are administered, the effect on the body is altered by age-related changes in the gastrointestinal tract, fat and lean body mass, body water volume, and renal and hepatic function. Those physiologic changes may lead to reduced absorption, altered drug distribution, and modified metabolism and elimination.

The age-related changes in absorption are associated with an increased risk of constipation because of reduced gastric and intestinal motility. Also, individuals can be affected detrimentally by increased

Purpose/Objectives: To identify appropriate strategies for pharmacotherapeutic agents in the management of pain in older adults with cancer.

Data Sources: PubMed literature searches, personal reference collection, and clinical experience.

Data Synthesis: To make good decisions about pain management when developing treatment plans for older adults, healthcare providers should focus on the pharmacokinetic and pharmacodynamic properties of drugs in the context of the physiologic changes that occur with aging.

Conclusions: Unrelieved pain can have a detrimental effect on older adults; conversely, overmedicating can lead to an increased risk of adverse events. With advancing age, physiologic changes alter the pharmacokinetic and pharmacodynamic properties of drugs by reducing their absorption, changing their distribution, and modifying their metabolism and elimination. Also, common comorbidities increase the risk of pharmacologic toxicity and narrow the therapeutic window. In addition, polypharmacy—an issue more common in older adults—increases the complexity of prescribing and risk of adverse events. Consequently, older adults require individualization of their pharmacotherapies. Healthcare providers should consider carefully the risks and benefits of nonsteroidal anti-inflammatory drugs, opioids, and adjuvants before initiating an analgesic trial. The 2009 guidelines published by the American Geriatrics Society described several key principles for prescribing analgesics to older adults and offered specific recommendations and caveats for each drug class.

Implications for Nursing: Current guidelines support appropriate management of cancer pain in older adults with specific recommendations for each class of analgesics as well as general prescribing principles.

pH, decreased digestive enzyme activity, and mucosal atrophy. The potential consequences of these physiologic alterations include prolonged colon transit times, frequent constipation, gastrointestinal distress, and a higher risk for opioid-induced constipation. Slowed gastrointestinal transit times affect the oral administration of medications and can lead to decreased and even inadequate absorption of drugs. Swallowing difficulties and cancer-associated complications can make oral medications difficult to ingest, if not unmanageable.

The distribution of fat and water in the body is affected by age—an increased ratio of fat to lean body mass and a reduction of total water in the body. The combination of increased fat and reduced water leads to a higher distribution volume of lipophilic (“fat-loving”) drugs, resulting in a delayed onset of effect and a delayed rate of elimination of such agents (Pergolizzi et al., 2008). In particular, the changes can affect the lipophilic opioids (fentanyl and its derivatives) (Sinatra, Hyde, & Harrison, 1988), potentially leading to greater drug toxicity. On the other hand, the changes may aid in more global distribution of drugs. Concomitantly, a decreased distribution volume of hydrophilic (“water-loving”) agents occurs, leading to increased plasma levels (Pergolizzi et al., 2008). This can change the dosing of hydrophilic medications. Reduced body water also puts older adults at higher risk for dehydration, hypoalbuminemia, and anemia. Because many drugs require protein binding for distribution, with reduced serum protein, such medications are retained systemically for longer periods in older adults with anemia. Hence, hypoalbuminemia and anemia can lead to increased serum levels of drugs and, ultimately, toxicities (Pergolizzi et al., 2008).

Furthermore, hepatic function is reduced with age. Although reports of reductions in the amounts of cytochrome P450 (CYP450) enzymes in liver biopsies from older adults have been noted in the literature (Hurria & Lichtman, 2008), the effects of aging on those metabolic pathways are not well understood. However, within populations of all ages, the potential for adverse effects from drug-drug interactions increases when patients are coadministered medications processed by the CYP450 enzyme system, which metabolizes 40%–50% of all medications (Rogers, Nafziger, & Bertino, 2002). The consequences of the hepatic age-related changes are prolonged drug half-lives, leading to extended periods of drug circulation, uptake, and distribution.

Similarly, the kidneys undergo a reduction in mass and blood flow, resulting in lower renal clearance and glomerular filtration rate (< 60 ml per minute) (Chau, Walker, Pai, & Cho, 2008). Hence, the half-lives of drugs eliminated primarily by the kidneys can become longer in older adults (Pergolizzi et al., 2008). The reduced clearance of a drug or its metabolites increases the potential for the accumulation of drug metabolites; in turn, the risk of toxicity and the severity of adverse events escalate. Table 1 summarizes pharmacokinetic changes in older adults.

Analgesic Options for Older Adults

Nonopioid Analgesics

Acetaminophen: The 2009 American Geriatrics Society (AGS) guidelines recommended acetaminophen as a first-line agent for persistent pain in older adults because of its effectiveness and safety profile (AGS Panel on the Pharmacological Management of Persistent Pain in

Older Persons, 2009). Long-term use of acetaminophen is not associated with significant gastrointestinal bleeding, adverse renal effects, or cardiovascular toxicity, with the exception of some renal toxicity when used in high doses over many years. Typically, the maximum daily dosage is 4 g, including any combination products that contain acetaminophen. Acetaminophen is contraindicated for individuals with liver failure and should be used only with caution in patients with hepatic insufficiency or chronic alcohol abuse or dependence.

Nonsteroidal anti-inflammatory drugs: Conversely, according to AGS recommendations, nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors should be used with extreme caution in selected individuals (AGS Panel on the Pharmacological Management of Persistent Pain in Older Persons, 2009). NSAIDs exert an analgesic effect by reversibly inhibiting cyclooxygenase and thereby halting the synthesis of prostaglandins. NSAIDs are used commonly when people self-medicate for pain, and their overuse occasionally leads to toxicities associated with high doses. NSAIDs require serum protein binding for transport and distribution. In older age, less serum albumin and, hence, decreased binding sites for NSAIDs are available; thus, these drugs tend to linger systemically for longer periods. Higher NSAID blood levels can lead to a higher risk for the triad of adverse effects commonly associated with NSAID use: gastrointestinal disturbances (such as upper gastrointestinal tract dyspepsia, peptic ulceration, hemorrhage, and perforation), renal failure, and bleeding (Brater, Harris, Redfern, & Gertz, 2001; Griffin, 1998).

Older adults have a higher risk for gastrointestinal complications from NSAID use as noted in black box warnings on all traditional NSAID product labels (Antman et al., 2007). Hence, prophylaxis for gastrointestinal complications should be provided for older adult patients taking NSAIDs, such as an H₂ antagonist or proton-pump inhibitor. As highlighted in the 2002 Beers criteria for inappropriate prescribing in older adults, conventional NSAIDs are contraindicated for individuals with a history of gastric or duodenal ulcers (van der Hooft et al., 2005).

NSAID toxicity is more prevalent in older adults because they tend to have reduced renal clearance. Therefore, NSAIDs should be used with caution, and renal status should be monitored. In addition, chronic NSAID use can exacerbate hypertension and affect the central nervous system by inhibiting prostaglandin synthesis, leading to confusion and dizziness. More falls have been noted in older patients taking NSAIDs, a problem that can have a substantial impact on the health of an older adult (Hegeman, van den Bemt, Duysens, & van Limbeek, 2009).

Cyclo-oxygenase-2 inhibitors: COX-2 inhibitors can be alternatives to NSAIDs; however, their side effects

Table 1. Pharmacokinetic Effects in Older Adults

Pharmacokinetic Process	Changes in Older Adults	Consequences
Absorption	• Increased gastric pH • Reduced gastric motility • Reduced intestinal motility • Decreased digestive enzyme activity • Mucosal atrophy	• Prolonged colon transit times • Frequent constipation and more risk for opioid-induced constipation • Gastrointestinal distress • Decreased absorption of oral agents
Distribution	• Reduced body fat to lean body mass • Reduced total body water • Higher risk for dehydration • Hypoalbuminemia • Anemia	• Increased distribution volume of lipophilic agents – Delays in onset of action – Delays in rate of elimination • Decreased distribution volume of hydrophilic agents – Increased plasma levels • Hypoalbuminemia and anemia lead to increased serum levels of drugs that bind to protein or hemoglobin.
Metabolism	Hepatic alterations • Reduced hepatic function • Reduced cytochromes (particularly P450) Renal alterations • Decreased renal mass • Decreased renal blood flow • Reduced renal clearance and glomerular filtration rate	Consequences of hepatic alterations • Prolonged drug circulation • Prolonged uptake • Prolonged distribution • Impact of CYP450 reduction is controversial. Consequences of renal alterations • Increased drug half-life • Accumulation of drug metabolites increases risk of toxicity and severity of adverse events.

can outweigh the benefits in older populations (AGS Panel on the Pharmacological Management of Persistent Pain in Older Persons, 2009). Specifically, such agents may increase the risk of potentially fatal cardiovascular thrombotic events, myocardial infarction, and stroke (Antman et al., 2007). Therefore, in exchange for a reduced risk of gastrointestinal complications, an increased potential for cardiovascular complications exists (Grosser, Fries, & FitzGerald, 2006).

Opioid Analgesics

Opioids are the mainstay of managing cancer pain in patients with cancer, including older adults. According to the Beers criteria for inappropriate medications for older adults, the opioids meperidine and propoxyphene should be avoided (Fick et al., 2003). Several other opioid options can provide relief of moderate to severe cancer or noncancer pain with tolerable or manageable side effects in older adults (Aiello-Laws et al., 2009; American Pain Society, 2008; National Comprehensive Cancer Network, 2010) (see Table 2).

Morphine: Morphine, the gold standard for comparison of all other opioids, is a hydrophilic drug used widely in the management of pain. The availability of many different formulations (e.g., oral controlled release, immediate release, subcutaneous, IV, per rectum, epidural, intrathecal) makes morphine a versatile opioid. However, morphine metabolites can accumulate in older adults and cause toxicity. Morphine-6-glucuronide

is potently analgesic and contributes to the pain relief produced overall, whereas morphine-3-glucuronide (M3G) paradoxically causes neuroexcitatory effects and counteracts analgesic effects. High concentrations of M3G can lead to sedation, confusion, delirium, respiratory depression, and myoclonic reactions (Morita, Tei, Tsunoda, Inoue, & Chihara, 2002). Considering other options or lowering the dose of morphine may be appropriate for older adult patients, particularly those with renal insufficiency.

Hydromorphone: Hydromorphone is a potent lipophilic opioid and is now available in a long-acting oral formulation. In addition, the high solubility of the opioid enables its use subcutaneously and via IV, routes of administration that are viable at home and in hospice care. The active metabolites of hydromorphone are hydromorphone-3-glucuronide and hydromorphone-6-glucuronide, although few studies have demonstrated the effect of those metabolites. The lack of CYP450 drug-drug interactions with hydromorphone can be advantageous in older adults taking multiple medications (Kadiev et al., 2008). Hydromorphone also is considered a safe drug to use for patients with hepatic or renal compromise, albeit generally with a lowered dose in older adults (Pergolizzi et al., 2008).

Oxymorphone: Oxymorphone is a semisynthetic opioid, with a potency 10 times that of IV morphine and 3 times that of oral morphine (Guay, 2007). Furthermore, oxymorphone is more lipophilic than morphine, but much less lipophilic than fentanyl and its analogs

Table 2. Opioid Choices for Older Adults With Severe Cancer Pain

Opioid	Characteristics	Recommendations for Older Adults
Fentanyl	• Lipophilic (Gutstein & Akil, 2006) • Availability: transdermal, transmucosal, IV, epidural, and IT • Metabolized by CYP450 3A4 isoenzyme but implications controversial (Kadiev et al., 2008) • Transdermal formulations for persistent pain in opioid-tolerant patients (Ortho-McNeil-Janssen Pharmaceuticals Inc., 2009). No pharmacokinetic differences are noted with age (Ortho-McNeil-Janssen Pharmaceuticals Inc., 2009). • Transmucosal formulations for breakthrough pain in patients tolerant to around-the-clock opioid therapy for persistent pain (Cephalon Inc., 2009)	• Lower the oral dose and increase monitoring in older adults who have reduced clearance. • Those on CYP450 inhibitors should be monitored carefully (Pergolizzi et al., 2008). • Consider delayed onset and delayed elimination (accumulation). • Transdermal administration system may be advantageous for some older adults.
Hydromorphone	• Lipophilic (Gutstein & Akil, 2006) • Duration of action: 10–16 hours (Gutstein & Akil, 2006) • Availability: oral CR, IR, SC, IV, epidural, and IT • No CYP450 drug-drug interactions (Kadiev et al., 2008) • Active metabolites: hydromorphone-3-glucuronide (Pergolizzi et al., 2008). Little data on the effect of these metabolites	• Start low and go slow in older adults. • Beware of high potency: 1.5 mg IV hydromorphone = 10 mg IV morphine (Knotkova et al., 2009) • An option in patients with polypharmacy issues because of a lack of CYP450 interaction (Pergolizzi et al., 2008)
Methadone (Gallagher, 2009)	• Lipophilic • Significant tissue distribution • Highly protein bound, particularly to alpha-1-acid glycoprotein • Long duration of action (12–24 hours) • Long half-life (20–35 hours, range = 5–130 hours) may lead to drug accumulation. • Large interindividual variations • Variations in individual patients from day to day and week to week • Availability: oral, buccal, and SC formulations • High oral bioavailability—parenteral form may not be an advantage. • NMDA activity may decrease tolerance and inhibit neuropathic pain. • Cost effective • Metabolized by CYP 3A4, 2B6, and 2D6 • No known active metabolites • Drug-drug interactions through competitive binding	• Should be prescribed only by providers with experience with methadone • Should be used with caution in older adults • Start low and go slow. • Consider delayed onset and delayed elimination (accumulation). • Reduce dose in patients with renal failure. • Because of metabolism by CYP450 and an associated increased risk of drug-drug interactions, may want to avoid use in patients with polypharmacy issues
Morphine (Pergolizzi et al., 2008)	• Hydrophilic • Standard for comparison • Availability: oral CR and IR, SC, IV, PR, epidural, and IT • Metabolized by UGT 2B7 and 1A3 • Metabolites can accumulate in older adults. – Morphine-3-glucuronide that can cause paradoxical central neuro-excitatory effects – Morphine-6-glucuronide that is a potent analgesic; contributes to overall analgesic effect • Oral dosing is higher to account for marked presystemic elimination (first-pass effect, a phenomenon of drug metabolism when a drug is broken down into metabolites and reduced before reaching systemic circulation).	• Lower dose in older adults and in those with renal dysfunction • Other opioid options may be preferred in those with renal compromise.

(Continued on next page)

AUC—area under the curve; C_{max}—maximum concentration of a drug after administration; CR—controlled release; IR—immediate release; IT—intrathecal; NMDA—N-methyl-D-aspartate; PR—per rectum; SC—subcutaneous

(Sinatra et al., 1988). Pharmacokinetic data obtained from older adult populations have helped establish appropriate dosing. The extended-release formulation of oxymorphone is dosed every 12 hours, and an immediate-release version is available for acute and breakthrough pain. Oxymorphone should be administered on an empty stomach one hour before a meal or two hours after a meal because coingestion with food has been shown to increase the C_{max} (maximum concentration of a drug after administration) and the area under the curve (AUC: total drug concentration

in the blood plasma over a period of time) by approximately 38% (Endo Pharmaceuticals, 2006). Alternatively, some clinicians have suggested reducing the dose and directing patients to take their doses with meals. In addition, oxymorphone should not be taken with alcohol because an average increase of 31% in the C_{max} occurs, and certain individuals have even more profound effects (although the AUC is not significantly different) (Endo Pharmaceuticals, 2006; Guay, 2007).

The steady-state plasma concentrations of the metabolites of oxymorphone—primarily oxymorphone-

Table 2. Opioid Choices for Older Adults With Severe Cancer Pain (Continued)

Opioid	Characteristics	Recommendations for Older Adults
Oxycodone (Pergolizzi et al., 2008)	- Hydrophilic (Kalso, 2007) - Availability: oral CR and IR, and in combination with acetaminophen - Active metabolite: oxymorphone - No cumulative effects are known. - Metabolized by CYP450 but implications are not clear.	- Lower the dose in older adults - Plasma concentrations tend to be 15% greater in older adults, with large inter-individual variation. - Safe drug to use in hepatic and renal insufficiency at lowered dosages - Beware of potential interaction with CYP450 inhibitors.
Oxymorphone (Endo Pharmaceuticals, 2006)	- Semisynthetic opioid; more lipophilic than morphine, but many-fold less lipophilic than fentanyl and its analogs (Sinatra et al., 1988) 10 times stronger than IV morphine and 4 times stronger than oral morphine (Knotkova et al., 2009) - Availability: oral CR and IR, IV, SC, and PR - Administer oral dose on an empty stomach (one hour before or after a meal). - Food increases C_{max} and AUC by ~38%. - Do not administer with alcohol. 7%–110% increase in C_{max} when taken orally; AUC not significantly changed (Endo Pharmaceuticals, 2008) - No CYP450 drug-drug interactions	- Oxymorphone contraindicated in moderate and severe hepatic impairment - Steady-state plasma concentrations from oral dose are approximately 40% higher in older adults - Initiate with a low oral dose (5 mg) in patients with a creatinine clearance less than 50 ml per minute, mild hepatic impairment, and in older adults - Consider for older adults with polypharmacy issues

AUC—area under the curve; C_{max} —maximum concentration of a drug after administration; CR—controlled release; IR—immediate release; IT—intrathecal; NMDA—N-methyl-D-aspartate; PR—per rectum; SC—subcutaneous

3-glucuronide from conjugation and to a lesser extent 6-hydroxyoxymorphone from reduction—along with the parent compound, are 40% higher in individuals aged 65 years and older (Endo Pharmaceuticals, 2008); still, the metabolites have not been demonstrated to have significant effects. Oxymorphone is metabolized hepatically but through metabolic pathways that do not involve the CYP450 enzyme family, thus obviating those common types of drug-drug interactions (Adams & Ahdieh, 2005). For that reason, as well as the reduced dosing associated with the extended-release formulation, oxymorphone can be considered an option for older adults with polypharmacy concerns. Oxymorphone is contraindicated for individuals who have moderate or severe hepatic impairment (Endo Pharmaceuticals, 2006). When prescribing oxymorphone, healthcare providers should initiate with a low dose (5 mg) and titrate slowly in older patients and in those with mild hepatic impairment or a creatinine clearance of less than 50 ml per minute (Endo Pharmaceuticals, 2008). Individuals with cirrhosis should not receive oxymorphone, and the opioid should be used with caution in patients with elevated liver enzymes.

Oxycodone: Oxycodone is another semisynthetic hydrophilic opioid available in controlled-release and immediate-release formulations, as well as in combination with acetaminophen. The controlled-release formulation has a biphasic peak of absorption and effects that are attained an hour after ingestion and then again six hours later, which can provide analgesia for as long as 12 hours (Cairns, 2001). Oxycodone is extensively metabolized primarily to noroxycodone and, to a lesser

extent, oxymorphone (Pergolizzi et al., 2008). Although the latter metabolite has activity itself, the active drug, rather than the metabolite, is responsible for the analgesic effects (Pergolizzi et al., 2008).

The metabolism of oxycodone is mediated by the CYP450 enzyme family (Pergolizzi et al., 2008), but the implication of this is not clear, and drug-drug interactions with medications that share this pathway have not been demonstrated. The dose of oxycodone should be lowered for older adult patients. The opioid is considered safe for individuals with renal insufficiency (Cairns, 2001).

Fentanyl: Fentanyl is an opioid currently available in transdermal, transmucosal, IV, epidural, and intrathecal formulations, and effects vary by route of administration. This lipophilic opioid distributes throughout the body well and has quick effects when administered via IV. The transdermal formulation is used commonly to treat older adults because of ease in dosing. However, because of the lipophilicity of fentanyl, transdermal fentanyl may have a delayed onset of action and a delayed rate of elimination in older adults who have a higher body-fat ratio (Pergolizzi et al., 2008). In addition, once the fentanyl binding sites are saturated, sedation can result. For those without sufficient fat stores, no research exists regarding the onset, elimination, and efficacy of transdermal fentanyl. Fentanyl may be best for treating stable pain without episodic breakthroughs because the opioid takes time to titrate. The administration system of the transdermal formulation can be advantageous for older adults who already are burdened with multiple tablets in their medication regimens. Transmucosal

fentanyl has a rapid onset and no change in pharmacokinetic parameters with age, making the buccal and transmucosal formulations adequate for treatment of breakthrough and procedural pain (Kharasch, Hoffer, & Whittington, 2004).

Fentanyl is metabolized by the CYP450 3A4 isoenzyme, but the implications of this are controversial. As with other opioids, the dose of fentanyl should be reduced in older adults and individuals who have reduced clearance. Transdermal fentanyl should not be prescribed for opioid-naïve patients, as 25 mcg of transdermal fentanyl is approximately equivalent to 50–75 mg morphine per day. When administering fentanyl, patients taking CYP450 inhibitors should be monitored carefully, and the opioid's delayed onset and elimination periods should be considered.

Methadone: Methadone has increased in popularity in treatment of pain because of its cost effectiveness. Beyond the price advantage, methadone is lipophilic with high bioavailability and a wide tissue distribution (Shaiova, 2005). Methadone also has no known active metabolites (Shaiova, 2005) and has N-methyl-D-aspartate (NMDA) activity (Lugo, Satterfield, & Kern, 2005), which may decrease opioid tolerance and potentially inhibit neuropathic pain (Yennurajalingam, Braiteh, & Bruera, 2005). Methadone inherently has a long duration of action, about four to eight hours (Shaiova, 2005), but it is not controlled released. Rather, methadone is highly protein bound (range = 81%–97%), leading to an extended half-life ranging from 5–130 hours (Lugo et al., 2005). This long half-life can lead to the significant accumulation of methadone, resulting in common opioid side effects such as sedation, constipation, and nausea; QTc prolongation and death are other possible adverse outcomes (Hartung et al., 2007; Shaiova, 2005). Older populations are particularly prone to developing the latter outcomes because of large interindividual variations in methadone half-life, in part because of the effects of polypharmacy. Other highly protein-bound drugs, including some anticonvulsants and many tricyclic antidepressants, compete for binding sites with methadone, leading to higher systemic concentrations of both medications. Additionally, drugs that require the CYP450 pathway for metabolism may compete with methadone for processing (Shaiova, 2005). Methadone should be used with caution, particularly with frailer, older adults, although the opioid may be appropriate at lower doses for individuals with renal impairment (Chou et al., 2009; Shaiova, 2005). Because of the long half-life of methadone, the American Pain Society and American Academy of Pain Medicine recommend initiating with a low dose and titrating very slowly, keeping in mind the delayed onset of effect and delayed elimination of the opioid. Familiarity with the clinical pharmacology and associated risks of methadone is needed for safe pain management with methadone (Chou et al., 2009).

Managing Adverse Effects of Opioids

Opioid adverse effects of most concern in older adults are sedation and confusion. They are observed commonly in that population, particularly in those with preexisting cognitive dysfunction or dehydration, or in those who concomitantly take other drugs that affect the central nervous system, such as barbiturates, benzodiazepines, antidepressants, and antipsychotics (Chau et al., 2008). Also, the accumulation of metabolites can lead to adverse opioid effects, as happens in individuals with renal or hepatic dysfunction. Delirium can result from opioid use, but other potential causes such as benzodiazepines and muscle relaxants should be ruled out first. Sedation can be counteracted with methylphenidate or dextroamphetamine.

Constipation is a common opioid adverse effect that, unlike most opioid side effects, is not reduced or eliminated with the development of tolerance (Chau et al., 2008). Older adults in particular have an increased risk for developing opioid-induced constipation, an outcome that can have serious complications. Opioid peptides and receptors are distributed throughout the gastrointestinal tract and can cause constipation by reducing fluid in the bowel, decreasing peristalsis, and increasing anal sphincter tone. Constipation should be managed with prophylaxis in all patients taking opioids. Prophylaxis for constipation includes the prescription of a stool softener and a stimulant, along with adjuvants if needed, such as polyethylene glycol 3350, milk of magnesia, and magnesium citrate. Methylnaltrexone can be prescribed for refractory constipation (Chamberlain et al., 2009).

Drug-drug interactions are another potential cause of opioid adverse events. Inhibitors of the CYP450 enzyme family, such as diazepam and some antibiotics, antidepressants, and antiviral agents, reduce the clearance rate of medications metabolized through this pathway, thereby prolonging elimination time and increasing plasma levels of opioids processed by the CYP450 family. Consequently, CYP450 inhibitors have the potential to induce a surge in effects of medications that are inactivated by this metabolic pathway as the drug accumulates over time. Conversely, inducers of CYP450, such as grapefruit juice, rifampin, and some anticonvulsants and corticosteroids, can cause an increase in the clearance rate, leading to peaks and troughs in the drug plasma concentrations and concomitant periods of pain between doses as the opioid is processed more quickly than expected. Primarily, these CYP450 drug interactions may be a concern for patients prescribed oxycodone, fentanyl, or methadone, as well as antidepressants; however, more research in this area is needed to elucidate the specific role that these interactions have on analgesia and drug levels.

Dose Titration

A lack of appropriate pain control despite aggressive titration or intolerable and unmanageable adverse

effects prompt opioid dose adjustments or changes. Depending on the specific situation, options may include dose reduction, opioid rotation, or a change in the route of opioid administration (Chau et al., 2008; Cherny et al., 2001). Oftentimes, lowering the dose is not an option with cancer pain, so changing to another formulation with a different administration method or adding a treatment for side effects may be more viable. New opioid rotation guidelines with best practices for switching from one opioid to another provide direction for managing a poor response to an opioid (Fine & Portenoy, 2009). When rotating between opioids, healthcare professionals should reference the equianalgesic dose table to determine a broad estimate of the starting dose based on the difference in relative potencies between the current opioid and the new one. Numerous equianalgesic tables are available online (e.g., http://endoflife.northwestern.edu/pain_management/table.pdf) and through the American Pain Society. Then further adjustment is needed to determine a safe dose tailored to the needs of the individual patient (see Figure 1). After calculation of an equianalgesic dose, a first adjustment is recommended to account for the potency of the new opioid. Subsequently, a second dose adjustment is applied to account for an individual's presentation, including pain severity, medical factors, and psychosocial characteristics. The presence of vulnerabilities such as older age, renal insufficiency, and cognitive impairment suggests a decrease in dose by 10%–30%, whereas severe pain may indicate an increase in the dose. For a baseline opioid dose that controls pain but induces adverse effects, minimal, if any, adjustments to the dose are needed after the first safety step.

Coanalgesics

Coanalgesics are a group of drugs that enhance the efficacy of opioids or NSAIDs, have independent analgesic properties themselves, or counteract the adverse effects of analgesics (American Pain Society, 2008). This diverse group of pain relievers has many different mechanisms of action that can assist in overall pain management plans.

Anticonvulsants

Gabapentin: Gabapentin stimulates the release of noradrenaline in the brainstem to evoke descending inhibition and thereby provide analgesia for neuropathic pain (Hayashida, Obata, Nakajima, & Eisenach, 2008). At the molecular level, gabapentin hinders neuronal hyperactivity by inhibiting calcium influx through voltage-gated ion channels embedded within the membranes of neurons (McDonald & Portenoy, 2006). Indeed, anticonvulsants have been used to treat noncancer-related and cancer-related neuropathic pain and have been recommended as first-line treatment for neuropathic pain (Dworkin et al., 2007).

Step 1. An Automatic Safety Factor Adjustment

- Calculate the equianalgesic dose of the new opioid based on the equianalgesic dose table.
- If switching to any opioid other than methadone or fentanyl, apply an additional “automatic dose reduction” 25%–50% lower than the calculated equianalgesic dose (see the last three bullets).
- If switching to methadone, apply an additional automatic dose reduction of 75%–90% lower than the calculated equianalgesic dose. For individuals on very high opioid doses (e.g., 1,000 mg morphine equivalents per day or higher), great caution should be exercised in converting to methadone at doses of 100 mg or greater per day; consider inpatient monitoring, including serial electrocardiography monitoring.
- If switching to transdermal fentanyl, calculate dose conversions based on the equianalgesic dose ratios included in the package insert for these formulations.
- Select a dose closer to the lower bound (25% reduction) or the upper bound (50% reduction) of the automatic dose reduction on the basis of a clinical judgment that the equianalgesic dose table is relatively more or less applicable, respectively, to the specific characteristics of the opioid regimen or patient.
- Select a dose closer to the upper bound (50% reduction) of the reduction if the patient is receiving a relatively high dose of the current opioid regimen, is not Caucasian, or is elderly or medically frail.
- Select a dose closer to the lower bound (25% reduction) of the reduction if the patient does not have these characteristics or is undergoing a switch to a different route of systemic drug administration using the same drug.

Step 2. An Additional Dose Adjustment Based on Patient Characteristics

- Perform a second assessment of pain severity and other medical or psychosocial characteristics to determine whether to apply an additional increase or decrease of 15%–30% to enhance the likelihood that the initial dose will be effective for pain, or conversely, unlikely to cause withdrawal or opioid-related side effects.
- Have a strategy to frequently assess initial response and titrate the dose of the new opioid regimen to optimize outcomes.
- If a supplemental “rescue dose” is used for titration, calculate at 5%–15% of the total daily opioid dose and administer at an appropriate interval; if an oral transmucosal fentanyl formulation is used as a rescue dose, begin dosing at one of the lower doses irrespective of the baseline opioid dose.

Figure 1. Guidelines for Opioid Rotation

Note. From “Establishing ‘Best Practices’ for Opioid Rotation: Conclusions of an Expert Panel,” by P.G. Fine & R.K. Portenoy, 2009, *Journal of Pain and Symptom Management*, 38, p. 422. Copyright 2009 by Elsevier. Reprinted with permission.

Gabapentin dosing can be complicated. Patients with compromised renal systems and older adults should be initiated at a low dose (100–300 mg) and slowly titrated (McDonald & Portenoy, 2006). Indeed, a consensus guideline issued by an expert panel of geriatric clinical pharmacists in 2009 recommended that the maximum gabapentin dose be limited to 600 mg taken twice daily for patients with a creatinine clearance rate of 30–59 ml per minute, 300 mg taken twice daily for 15–29 ml per minute, and 300 mg per day for less than 15 ml per minute (Hanlon et al., 2009). The dose can be escalated every three days by as much as 50%–100% to reach an effective level. However, in older adults, the

optimal dose is variable and dependent on the state of the transport system within each individual's gastrointestinal tract, creating the potential for reduced oral bioavailability with increasing doses. Somnolence is the most common dose-limiting toxicity encountered (McDonald & Portenoy, 2006). Other side effects associated with gabapentin are dizziness, ataxia, edema, weight gain, dyspepsia, and leucopenia. Still, gabapentin is minimally protein bound and not metabolized hepatically, potentially reducing the risk of drug-drug interactions (McDonald & Portenoy, 2006).

Pregabalin: Pregabalin has a similar mechanism of action to gabapentin and has demonstrated effectiveness for relieving neuropathic pain as well (McDonald & Portenoy, 2006). The anticonvulsant is efficiently absorbed through the gastrointestinal tract and yields a rapid onset of analgesia. The titration of pregabalin is more straightforward than that of gabapentin, often reaching an effective dose in two or three steps. Typically, pregabalin is initiated with a daily dose of 150 mg in older adults and then escalated to a usual effective dose of 150–300 mg taken twice per day (McDonald & Portenoy, 2006). Adverse effects of the anticonvulsant include somnolence, dizziness, peripheral edema, ataxia, headache, confusion, and diarrhea (McDonald & Portenoy, 2006).

Antidepressants

Antidepressants have a role in pain management; however, their side effects can outweigh their benefits for many older adults. Notably, the Beers criteria of medications that are contraindicated for use in older adults have listed amitriptyline, an older-generation tricyclic antidepressant (TCA), as a drug to avoid because of its anticholinergic and sedative properties (Fick et al., 2003). In addition, the cardiovascular adverse effects of TCAs include orthostatic hypotension and atrioventricular heart block. Instead, other tricyclic antidepressant options such as the secondary amines (including nortriptyline) have better tolerability. Still, the potential for drug-drug interactions should be considered with secondary amines (e.g., nortriptyline is metabolized by CYP2D6) (McDonald & Portenoy, 2006).

The newer antidepressant drug class, serotonin and norepinephrine reuptake inhibitors (SNRIs), also has analgesic properties. The SNRI duloxetine was the first antidepressant approved by the U.S. Food and Drug Administration for treatment of neuropathic pain (McDonald & Portenoy, 2006). The initial dose for duloxetine is 20 mg per day with a usual effective dose of 60 mg per day. Duloxetine is usually well tolerated, and the most common adverse event encountered is nausea. Venlafaxine, another SNRI, has demonstrated benefit in neuropathic pain at doses of 150–225 mg per day. One study reported electrocardiogram changes in 5% of patients who took venlafaxine; therefore, cardiac monitoring is recommended in high-risk patients with a history

of cardiac disease (Dworkin et al., 2007). Although less evidence exists supporting the use of SNRIs compared to TCAs, SNRIs may be advantageous because of their tolerability (American Pain Society, 2008).

Topical Agents

The topical route often is preferred by older adults, a population known for polypharmacy issues, because topical formulations eliminate the need to take “another” oral agent. Lidocaine patch 5% is a local analgesic that acts as a membrane stabilizer, preventing the influx of sodium ions in neurons prone to hyperexcitability, such as in various neuropathic pain syndromes and inflammatory states (Amir et al., 2006). The patch is indicated for postherpetic neuralgia—an often undertreated syndrome that tends to affect older adults more than younger populations (Hempstead, Nurmikko, Johnson, A'Hern, & Rice, 2005). Minimal systemic absorption of lidocaine occurs when it is administered topically, thus a low potential exists for serious systemic effects or drug-drug interactions (Gammon, Alvarez, & Galer, 2002).

NSAID topical agents, such as diclofenac gel, also can be effective for treating local inflammatory pain while lowering the risk of systemic side effects (Cooper & Jordan, 2004). Diclofenac gel is indicated for treatment of pain associated with osteoarthritis of the joints, a common pain syndrome in older adults.

Capsaicin, the component in chili peppers that makes them hot, reduces the production of substance P, a neurotransmitter in the pain pathway (Altman & Barkin, 2009; Caterina et al., 1997). Thereby, neurons become desensitized to pain; however, the desensitization phase is associated with the sensation of burning at the site of application of the capsaicin cream, which can last for several weeks (Sawynok, 2005).

Miscellaneous Agents

Numerous other coanalgesics are available to manage pain in older adult patients with cancer. Corticosteroids can relieve visceral and neuropathic pain, but the side-effect profile that includes hyperglycemia and Cushingoid effects may preclude their use. Clonidine can assist in the management of neuropathic pain. Bisphosphonates and radionuclides may be recommended when cancer has spread to the bone (American Pain Society, 2008). Overall, a tailored approach is necessary to effectively manage pain.

Clinical Practice Recommendations

Older adults are a heterogeneous group, although many seem to have an increased sensitivity to some analgesics (AGS Panel on the Pharmacological Management of Persistent Pain in Older Persons, 2009). Still, the 2009 AGS recommendations describe several general

principles for prescribing analgesics to older adults. The guidelines for the geriatric population can be used in conjunction with cancer-specific guidelines per the Oncology Nursing Society and the National Comprehensive Cancer Network (Aiello-Laws et al., 2009; National Comprehensive Cancer Network, 2010). Healthcare professionals should consider the risks and benefits of NSAIDs, opioids, and adjuvants for each individual before initiating an analgesic trial. Clinicians should choose the least invasive route possible and a long-acting agent that allows for longer intervals between doses; however, the intramuscular route is not recommended because of tissue trauma and variable absorption. Oral or transdermal dosing often is preferred; however, rectal administration can be a good option during end-of-life care. Most oral tablets can be taken rectally, and oral dosing usually is equianalgesic with rectal dosing. However, rectal administration can lead to a faster onset of action because of the area's connections to the portal and systemic circulation. IV and subcutaneous routes can achieve a continuous, steady state of drug, whereas intraspinal routes can be used to deliver a lower dose of medication with fewer systemic side effects. For example, morphine administered via the epidural route uses approximately one-tenth the dose of a drug delivered via IV, whereas intrathecal administration uses only one-tenth that of an epidural dose (American Pain Society, 2008).

For constant pain, clinicians should administer sustained-release formulations to maintain therapeutic analgesic levels and avoid plasma concentration peaks and troughs and end-of-dose failure. One agent should be initiated at a time, starting low (approximately 50% of the adult dose) and increasing slowly until an effective analgesic dose is reached. A longer time interval than typically used with younger populations should be allotted before titrating the dose upward. Ongoing monitoring includes a patient's response to treatment to improve efficacy and limit adverse events, with documentation of all observations. Clinicians should keep in mind any potential pharmacokinetic issues along with the effect of the physiologic processes associated with aging.

When creating and modifying plans of care, clinicians must consider the role and influence of patients' home

and social environments. For example, adherence can be a challenge. Pill boxes (to organize medications and assist with daily dispensing) and journals (to track health status over time) can be helpful tools to recommend to patients. Cost can be an important limiting factor to treatment, and patients should be made aware of financial assistance programs, including Medicare and company-sponsored options.

Conclusion

Unrelieved pain can have important detrimental effects on older adults; conversely, overmedicating can lead to an increased risk of adverse events. With advancing age, physiologic changes alter the pharmacokinetic and pharmacodynamic properties of drugs by reducing their absorption, changing their distribution, and modifying their metabolism and elimination. Also, common comorbidities increase the risk of pharmacologic toxicity and narrow the therapeutic window. In addition, polypharmacy—an issue more common in older adults—increases the complexity of prescribing and risk of adverse events. Consequently, older adults require individualization of their pharmacotherapies to account for such differences. Healthcare professionals should carefully consider the risks and benefits of NSAIDs, opioids, and adjuvants before initiating a trial of an analgesic. AGS guidelines (AGS Panel on the Pharmacological Management of Persistent Pain in Older Persons, 2009) describe several key principles for prescribing analgesics to older adults, as well as specific recommendations and caveats for each drug class.

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