

Putting Evidence Into Practice: What Are the Pharmacologic Interventions for Nociceptive and Neuropathic Cancer Pain in Adults?

**Lisa Aiello-Laws, RN, MSN, AOCNS®, APNG, APN-C,
Janice Reynolds, RN, BC, OCN®, CHPN,
Nancy Deizer, MBA, MSN, FNP-BC, AOCN®, ACHPN,
Mary Peterson, RN, ANP-BC, OCN®, Suzanne Ameringer, PhD, RN,
and Marie Bakitas, DNSc, AOCN®, APRN, FAAN**

Cancer pain continues to be undertreated in adults despite the substantial amount of research on pain management. The Oncology Nursing Society coordinated a team for the Putting Evidence Into Practice (PEP) project to develop (and update) a PEP resource summarizing the current evidence for the pharmacologic management of adults with nociceptive and neuropathic cancer pain. The aim of this article is to describe the development process and outcomes of the project. The review established that long-acting opioids in conjunction with immediate-release opioids are recommended for practice; radionuclides and radioisotopes as useful adjuncts for metastatic bone pain are likely to be effective; the effectiveness of tetrodotoxin, a neurotoxin, is not yet established; and spinal opioids, caffeine, or sympatholytic agents have beneficial and harmful effects and should be considered on an individual basis. Pain is a nursing-sensitive patient outcome; that is, pain can be directly affected by nursing interventions. Knowing the current evidence for pharmacologic management of cancer pain is critical to improve patient outcomes.

Despite a plethora of research and publications, pain continues to be undertreated in adults with cancer (American Pain Society [APS], 2005). Pain is the most feared symptom of patients diagnosed with cancer (APS). Successful pain management can relieve pain and improve mobility, healing, and quality of life. Pain is considered a nursing-sensitive patient outcome. Nursing-sensitive outcomes are those that are attained through or are significantly impacted by interventions that are within the scope of nursing practice (Holmes Gobel, Beck, & O'Leary, 2006). In an effort to improve the nursing-sensitive outcome of pain, evidence-based pharmacologic management strategies for adults with nociceptive and neuropathic pain were summarized on an accessible pocket card for bedside nurses. This article describes the process and results of this Oncology Nursing Society (ONS), Putting Evidence into Practice (PEP) initiative.

Methods and Process

ONS convened a project team consisting of two advanced practice nurses (one served as team leader), two staff nurses, and a doctorally-prepared nurse researcher who provided guidance and

At a Glance

- ◆ Pain remains an undertreated symptom of patients with cancer.
- ◆ Cancer pain management is most likely to be effective if it is tailored to pain etiology (i.e., nociceptive or neuropathic).
- ◆ Evidence-based pain interventions are critical in providing expert oncology nursing practice to manage cancer pain.

Lisa Aiello-Laws, RN, MSN, AOCNS®, APNG, APN-C, is a knowledge base manager at ITA Partners in Philadelphia, PA; Janice Reynolds, RN, BC, OCN®, CHPN, is a staff nurse at Mid Coast Hospital in Brunswick, ME; Nancy Deizer, MBA, MSN, FNP-BC, AOCN®, ACHPN, is an associate chief nurse in Tomah Veterans Affairs Medical Center in Wisconsin; Mary Peterson, RN, ANP-BC, OCN®, is a nurse practitioner at the Mayo Clinic in Phoenix, AZ; Suzanne Ameringer, PhD, RN, is an assistant professor in the School of Nursing at Virginia Commonwealth University in Richmond; and Marie Bakitas, DNSc, AOCN®, APRN, FAAN, is a nurse practitioner and clinical researcher at Dartmouth-Hitchcock Medical Center in Lebanon, NH. (Submitted March 2009. Accepted for publication April 23, 2009.)

Digital Object Identifier:10.1188/09.CJON.649-655

oversight. Because of the depth and breadth of literature, another nurse scientist, specializing in pain management, joined the team during the final review process.

The project began with a broad review of guidelines, systematic reviews, and studies that were published between March 2005 and December 2006; ONS had conducted an extensive review of pain research prior to March 2005, so that work was used as a foundation. The team considered a number of possible topics that would be clinically relevant to the bedside nurse, including pain assessment; pharmacologic and nonpharmacologic interventions; specific populations (adult or pediatric); and specific pain syndromes, such as bone pain. The vast amount of research required the team to narrowly define an area of focus. The primary question of the project was "What are the pharmacologic interventions for nociceptive and neuropathic cancer pain in adults?" The team chose to focus on the pharmacologic management of adults with cancer pain as this is one of the most challenging areas for practicing oncology nurses in all patient care settings. Management is divided by the physiologic classification of pain etiology: nociceptive and neuropathic. Nociceptive pain is the result of damage to the somatic and visceral structures by thermal, mechanical, or chemical insult, resulting in transmission of a pain message by activating nociceptors (pain) receptors in skin, viscera, muscles, and connective tissue. In contrast, neuropathic pain results when there is damage to the nerve fibers located in the central and peripheral nervous systems. (National Comprehensive Cancer Center [NCCN], 2008). The pathophysiologic classification and etiology is a key consideration in effective pain management. A focused literature search was then initiated.

With the assistance of the ONS librarian, a search of Medline® and CINAHL® was conducted using the key terms *cancer pain*, *pain* combined with *neoplasms*, *oncologic care*, *pain/drug therapy*, *pharmacology*, *pharmacologic management/treatment*, *neuropathic*, *nociceptive*, *adult*, and *English language*, specifically looking for publication types *research*, *systematic review*, and *clinical trial*. In addition, 16 reviews were located in the Cochrane Pain, Palliative Care, and Supportive Care Group database. Only 4 of 16 reviews were relevant to the topic.

The initial search yielded 128 articles. The project team reviewed titles and abstracts for relevance, eliminating 80 articles. The relevant literature was divided among the team and summarized. Main recommendations from NCCN, APS, and four other guidelines were extracted. Evidence tables were created for each category of literature: systematic reviews (N = 14), guidelines (N = 6), and individual studies (N = 28). The main findings from the literature were synthesized into seven categories: recommended for practice, likely to be effective, benefits balanced with harm, effectiveness not established, effectiveness unlikely, not recommended for practice, and expert opinion. See <http://www.ons.org/Research/PEP/media/ons/docs/research/outcomes/weight-of-evidence-table.pdf> for definitions of the classifications. Data related to nociceptive or neuropathic pain were indicated as a category. A draft card was created and a package containing the card, evidence tables, definitions, and references was sent for field review; suggestions were incorporated into a revised card. Subsequent to completion of the card, the literature review was updated through May 2008. Again, the ONS librarian assisted with the search using Medline, CINAHL, Medscape®, Scopus™, and the

Cochrane Database of Systematic Reviews. The updated search identified 68 articles, of which 38 were considered relevant. New and updated information was added to the card.

Highlights of Reviewed Literature

Recommended for Practice

Nociceptive pain: According to APS (2005) and NCCN (2008) guidelines, acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are beneficial for mild to moderate pain. Acetaminophen works as an analgesic and antipyretic (APS). It can be used alone for mild pain or in combination with opioids to reduce the dose of opioids needed to relieve moderate pain (dose-sparing effect) (APS; NCCN). All NSAIDs have a ceiling dose, whereas analgesic effects are maximized and adverse effects increase. Although well-tolerated, acetaminophen use is limited by a ceiling of 4,000 mg maximum in a 24-hour period (3,000 mg in frail older adults) (NCCN). APS and NCCN guidelines advise using selective and nonselective NSAIDs for mild to moderate acute and persistent cancer pain unless contraindicated. In addition to analgesic and antipyretic properties, NSAIDs have anti-inflammatory properties and cause decreased platelet aggregation. Unfortunately, their side-effect profile can limit their use. Several of the more severe side effects include gastrointestinal (GI) bleeding and discomfort, bleeding from other sources, and renal and cardiac toxicity (APS; NCCN). Nonspecific (Cox-1) NSAIDs include ibuprofen, naproxen, fenoprofen, ketoprofen, oxaprozin, indomethacin, sulindac, etodolac, ketorolac (the only NSAID available in IV formulation), tolmetin, mefenamic acid, diclofenac potassium, meloxicam, piroxicam, and nabumetone (APS; NCCN).

APS (2005), NCCN (2008), and American Geriatric Society ([AGS], 2002) guidelines as well as findings from five meta-analyses and systematic reviews recommend opioids for moderate to severe cancer-related pain (Nicholson, 2007; Reid, Martin, Sterne, Davies, & Hanks, 2006; Tassinari et al., 2008; Wiffen & McQuay, 2007; Wootten, 2004). Opioids include morphine, hydromorphone, oxycodone, hydrocodone, codeine, fentanyl, levorphanol, methadone, and oxymorphone (Nicholson; Reid et al.; Zeppetella & Ribeiro, 2006). The drugs attach to the mu (μ) opioid receptor, are considered central acting, and have the important advantage of no ceiling effect (APS). The oral route is preferred as it is the easiest, safest, and least invasive. Seven studies (Centeno & Vara, 2005; Colella et al., 2006; Elsner, Radbruch, Loick, Gartner, & Sabatowski, 2005; Koshy, Kuriakose, Sebastian, & Koshy, 2005; Mercadante, Arcuri, Fusco, et al., 2005; Smith & Coyne, 2005; Weinbroum, 2005) and the 2005 APS guidelines indicated that IV, subcutaneous (SC), oral transmucosal (OT), transdermal (TD), or rectal (PR) routes should be used in some cases. The intraspinal (IS) route also may be appropriate (Centeno & Vara; Colella et al., 2006; Elsner, Radbruch, Loick, Gartner, & Sabatowski, 2005; Koshy et al., 2005; Weinbroum, 2005). Patients should always be monitored closely, particularly if drug, route, or dose changes.

Two studies (Carrow, Plummer, Conney, Gorman, & Glare, 2007; Wallace et al., 2008) and the NCCN (2008) guidelines stressed the importance of using a long-acting (LA) opioid around the clock (ATC) for persistent pain (i.e., pain present for at least 12 of 24 hours). To calculate the dose for the LA medication, add the total amount of short-acting (immediate release [IR]) medication

used in the previous 24 hours and then use an equianalgesic chart to convert to the LA dose. For breakthrough pain, 10%–15% of the 24 hour total opioid dose should be available in an IR analgesic dosed at regular intervals. If breakthrough doses are required frequently or an end-of-dose failure occurs, the LA and breakthrough dose should be increased. The right dose is the one that provides the best relief and causes the fewest side effects (APS, 2005; Grosset et al., 2005; Maltoni et al., 2005; Mercadante, Villari, Ferrera, & Casuccio, 2006; NCCN, 2008).

TD fentanyl is the only available opioid that can be administered topically and absorbed systemically. It is useful for patients who have difficulty swallowing or who cannot take oral medications (Pergolizzi et al., 2006; Wootten, 2004). One recent study showed wide individual variability with absorption via the TD route (Solassol et al., 2005). Another study identified two factors that can affect dosing: age and type of pain (Hagen, Fisher, Victorino & Farrar, 2007). Older patients may require a lower dose, whereas patients with neuropathic pain may require a higher dose. OT and buccal fentanyl formulations (absorbed through the mucosa) peak in 5–10 minutes and have been found to be effective for breakthrough pain (Zeppetella & Ribeiro, 2006). Of note, mucositis does not appear to affect buccal fentanyl absorption (Darwish, Kirby, Robertson, Tracewell, & Jiang, 2007).

Methadone is an opioid with a number of unique qualities and is the least costly opioid. Dosing can be difficult and potentially dangerous because of its complex pharmacodynamics and pharmacokinetics. Therefore, it should only be prescribed by experienced clinicians with skill in methadone conversions and dosing. Methadone has several disadvantages. It may cause QT prolongation and *torsades de pointes*, a form of ventricular tachycardia that can cause sudden death, has a number of drug-drug interactions, and has the stigma of use as a treatment for opioid addiction within “methadone maintenance” programs (APS, 2005; Auret et al., 2006; Centeno & Vara, 2005; Moryl, Kogan, Comfort, & Obbens, 2005; Nicholson, 2007).

The management of opioid-related side effects is of primary importance for patient adherence. Constipation, nausea, and sedation are common side effects (APS, 2005; Komurcu et al., 2007; Pan et al., 2007). Whereas nausea and sedation improve with continued use, tolerance to the side effect of constipation does not occur. Therefore, a bowel regimen should be initiated concurrently with opioids to prevent constipation (e.g., stool softener, laxative) (APS; Maltoni et al., 2005; NCCN, 2008; Reid et al., 2006; Wiffen & McQuay 2007; Zeppetella & Ribeiro, 2006). Additional suggestions are recommended in the ONS PEP resource on constipation (Woolery et al., 2008). Nausea may be controlled with prophylactic antiemetics until tolerance occurs (NCCN). Sedation usually resolves with tolerance. If it persists, the best approach is to reduce the opioid dose and increase the frequency (APS). Respiratory depression is a rare side effect that is more likely to be seen in the opioid naïve patient, particularly when a central nervous system (CNS) depressant such as a benzodiazepine is given concurrently. Naloxone is used to reverse opioid-induced respiratory depression but is rarely needed. If naloxone is necessary, administer incremental doses until respiratory function is improved but analgesia is not reversed (APS).

Corticosteroids are effective in managing acute and persistent cancer pain by inhibiting prostaglandins, decreasing inflammation, directly lysing tumor cells, and reducing edema (NCCN,

2008). Unfortunately, the side effects of chronic, long-term use can be significant and can include weight gain, osteoporosis, Cushing syndrome, proximal myopathy, euphoria, increased appetite, and psychosis. Corticosteroids may increase the risk of GI bleeding, particularly when used with NSAIDs or anticoagulants. Therefore, the drugs should not be used routinely in conjunction with corticosteroids. Dexamethasone produces the least mineralocorticoid effect (APS). Benefits can outweigh risks in patients with life-limiting, progressive disease. Doses should be tapered to prevent a rapid withdrawal, which can exacerbate pain and adrenal insufficiency (APS). Because corticosteroids may inhibit prostaglandins, directly lyse tumor cells, decrease edema surrounding neural tissue, and ameliorate painful nerve and spinal cord compression, they are considered the standard emergency treatment for suspected malignant spinal cord compression (NCCN). Corticosteroids also are considered useful for cancer plexopathies, liver capsule expansion because of tumor involvement, and bone pain. The use of systemic glucocorticoids is effective for nausea and CNS effects from increased intracranial pressure because of primary brain cancer and metastasis to the brain. The symptoms often can potentiate pain complaints (APS).

Anesthetics may be indicated for cancer pain. Topical or injectable local anesthetics are effective in reducing the pain associated with procedures, including lumbar puncture, bone marrow aspirate, and port-a-cath access (APS, 2005).

Neuropathic pain: Neuropathic pain, a common issue for patients with cancer, results from damage to the peripheral nervous system or CNS (Challallapi, Tremont-Lukats, McNicol, Lau, & Carr, 2005). Pharmacologic management of neuropathic pain should be guided by the following general principles.

As with nociceptive pain, the effectiveness of analgesics is variable, so drugs and doses must be individualized. Coanalgesics are effective for certain neuropathic pain conditions. Coanalgesics, previously referred to as adjuvants, are medications whose initial use was not necessarily indicated for pain management. Individual categories of coanalgesics include anticonvulsants, antidepressants, and topical anesthetics. With many coanalgesics, the onset of pain relief is delayed and analgesia may take weeks. Short-acting opioids may be considered to provide pain relief until the coanalgesic is effective.

When managing neuropathic pain, coanalgesics initially should be administered as a single agent, though some patients may require combinations from different coanalgesic categories. Even though a drug class may be considered part of first- or second-line treatment, not all members of the class are recommended for neuropathic pain. First-line treatments include certain antidepressants (i.e., tricyclic antidepressants [TCA] and dual reuptake inhibitors of serotonin and norepinephrine [SSNRI]), calcium channel α 2- δ ligands (i.e., gabapentin and pregabalin), topical lidocaine, opioid analgesics, and tramadol (the latter in patients with moderate to severe pain or in patients who are refractory to other first-line medications). Second-line treatments include other anticonvulsant and antidepressant medications, cannabinoids, mexiletine, N-methyl-D-aspartate receptor antagonists, and topical capsaicin (Dworkin et al., 2007). One should consider referral to a pain specialist if neuropathic pain persists at a level that affects quality of life.

Anticonvulsants used in neuropathic pain include gabapentin, pregabalin, carbamazepine, oxycarbazepine, topiramate, sodium valproate, tiagabine, levetiracetam, and zonisimide (Duntzman, 2005; Dworkin et al., 2007). These drugs decrease firing of central motor neurons that contribute to neuropathic pain. Anticonvulsants are effective for the treatment of trigeminal neuralgia, postherpetic neuralgia, glossopharyngeal neuralgia, and posttraumatic neuralgia. Gabapentin is the best studied and the best tolerated (APS, 2005; NCCN, 2008; Ross et al., 2005). However, not all anticonvulsants are recommended. For example, phenytoin has been found to be effective against neuropathic pain but has many side effects (e.g., confusion, ataxia) and requires that serum drug levels be monitored closely (APS). TCAs and SSNRs also are considered first-line treatment for neuropathic pain (Dworkin et al.). Two SSNRI's in particular that are recommended are duloxetine and venlafaxine.

TCAs relieve pain independent of their antidepressant effect. They are useful for neuropathic pain related to surgical trauma, post-herpetic neuralgia, radiation therapy, chemotherapy, and malignant nerve infiltration. The dose for analgesic effect often is much lower than the antidepressant dose. The drugs typically are started at a low dose and then slowly titrated up until the desired pain relief is achieved (APS, 2005). TCAs are contraindicated in patients with coronary disease and can worsen ventricular arrhythmia. A baseline electrocardiogram is recommended to rule out conduction abnormalities, particularly in patients receiving anthracycline antitumor agents. TCAs include amitriptyline, doxepin, desipramine, imipramine, and nortriptyline. Amitriptyline is the most effective but the least tolerated; its side effects include potent anticholinergic effects, sedation, and hypotension. Amitriptyline should be given at bedtime to promote sleep and decrease daytime sedation. Desipramine has the best pharmacokinetic and side-effect profile. Desipramine and nortriptyline should be given during the daytime because they can cause insomnia (APS).

When considering anesthetics, the topical lidocaine patch may be effective for peripheral neuropathies, complex regional pain syndromes, mononeuropathy, and stump pain (APS, 2005). Systemic lidocaine was as effective as morphine for post-herpetic neuralgias. Evidence suggests that epidural and IV administration of anesthetics are effective but only for short-term use (APS; Challapalli et al., 2005).

For many years, opioids were not considered effective with neuropathic pain. Opioids in combination with antidepressants and anticonvulsants are considered first-line treatment for neuropathic pain, particularly in patients who have severe acute neuropathic pain (Keskinbora, Pekel, & Aydinli, 2007). Again, the combination is recommended because coanalgesics will have a delayed onset of pain relief (Dworkin et al., 2007).

Tramadol, a weak μ opioid agonist and a norepinephrine and serotonin reuptake inhibitor, has been shown to be effective as a second-line medication. Tolerance and physical and psychological dependence are rare with tramadol (Mercadante, Arcuri, Fusco, et al., 2005); however, because it has a maximum dose of 400 mg per day, its usefulness for severe pain is limited. Dosing should be titrated gradually over weeks to months. In renal or hepatic insufficiency, dosing must be decreased. Side effects are most pronounced when started at full dose and include dizziness, nausea, constipation, and somnolence. The respiratory effects are not fully reversible with naloxone. Tramadol must be

used with caution, if at all, with TCAs because of increased risk of CNS depression, psychomotor impairment, seizures, and serotonin syndrome. In addition, the concurrent use of tramadol and transdermal fentanyl has not been thoroughly investigated and studies suggest a synergistic effect (Marinangeli et al., 2007).

Likely to Be Effective

Bisphosphonates, radionuclides, and radioisotopes have been studied and shown to be effective, but the studies were not strong. Bisphosphonates have been proven to provide some relief from bone metastasis; however, not enough evidence exists to recommend them as first-line treatment. Therefore, bisphosphonates are recommended when analgesics and/or radiotherapy are inadequate (Auret et al., 2006; Glare, Walsh, & Sheehan, 2006; Wong & Wiffen, 2002; Yuen, Shelley, Sze, Wilt, & Mason, 2006). Bisphosphonates may cause a rare but serious toxicity, osteonecrosis of the jaw (Challapalli et al., 2005; Novartis Pharmaceuticals, 2008).

Radionuclides and radioisotopes have been useful in small trials as adjuncts for metastatic bone pain (Baczyk et al., 2007; Liepe & Kotzerke, 2007; Sartor, Reid, Bushnell, Quick, & Ell, 2007). However, response can take two to three weeks, requiring continuation of analgesic treatment (APS, 2005). The major adverse effects are leukocytopenia and thrombocytopenia (Baczyk et al.; Dworkin et al., 2007; Roque et al., 2003; Sartor et al.).

Benefits Balanced With Harm

Potential benefits of interventions such as IS opioids, caffeine, and sympatholytic agents should be weighed against the harmful effects. Although IS may improve pain relief in certain patients, long-term use of the route can be complicated by catheter problems and can be costly (Ross et al., 2005). In addition, the use of epidural clonidine (sympatholytic agent) may be effective in relieving neuropathic pain but can cause bradycardia and hypotension (APS, 2005).

An optimal dose for the use of caffeine to increase analgesia when given with aspirin-like drugs for uterine cramping, headaches, and other pain symptoms has not been established. Rebound pain and headache may occur when stopped abruptly (APS, 2005).

Effectiveness Not Established

Many coanalgesics for nociceptive pain fall into the category of effectiveness not established, including antihistamines, dextroamphetamine, ketamine, skeletal muscle relaxants, and topical agents. This group of interventions has insufficient or conflicting data or data of inadequate quality but has no clear indication of harm.

Antihistamines (e.g., hydroxyzine, diphenhydramine) can be used concurrently with analgesics to improve sleep and reduce itching. As mild CNS depressants, they may increase analgesic effect, but data are lacking (APS, 2005).

When dextroamphetamine is used in combination with opioids in the postoperative period, this drug may produce additive analgesia (APS, 2005). Ketamine has been studied in two forms, IV and sublingual (SL). APS determined that insufficient evidence existed that supported the use of IV ketamine, particularly because of the intolerable side effects. A case series of three patients reported pain relief with SL administration (Mercadante, Arcuri, Ferrera, et al., 2005).

The use of skeletal muscle relaxants has mixed evidence for use in acute muscle injury. They should be used for only a few days as needed (APS, 2005). Topical agents penetrate the skin and act locally in the peripheral tissues when applied directly on the painful body area. Medications from “compounding pharmacies” should be used cautiously, as the vehicle that allows for skin penetration in the drug formulation is as important as the pharmacologically active agent and can result in systemic activity or lack of penetration (APS).

Tetrodotoxin is a neurotoxin that has been studied in the treatment of nociceptive and neuropathic pain and can be administered SC and intramuscular (IM) (Hagen et al., 2008; Hagen, Fisher, Lapointe, et al., 2007). The few studies on tetrodotoxin use in patients with cancer report inconsistent findings, and a minimal efficacious dose has not been established.

Effectiveness Unlikely

Interventions considered not likely to be effective were chosen based on evidence from a single, rigorously conducted, controlled trial; consistent negative evidence from well-designed controlled trials using small samples; or guidelines developed from evidence and supported by expert opinion. Antidepressants, other than those already discussed (APS, 2005), antiarrhythmics (APS), calcitonin (Martinez-Zapata, Roque, Alonso-Coello, & Catala, 2006), dextromethorphan (APS; Dudgeon et al., 2007) and topical capsaicin (APS) are not recommended for controlling neuropathic pain.

Studies in the use of antiarrhythmics in neuropathic pain have yielded mixed results (APS, 2005; Challapalli et al., 2006; Roque et al., 2003). Specifically, mexiletine and tocainimide have shown disappointing results with respect to their efficacy (APS; Challapalli et al.). They are contraindicated in patients with second- and third-degree heart block, congestive heart failure, and abnormal liver function tests. No evidence supports the use of calcitonin or dextromethorphan in neuropathic pain (APS; Roque et al.). Although topical capsaicin is effective for surgical neuropathic pain, its effectiveness in post-herpetic neuralgia and polyneuropathy is inconclusive. As capsaicin causes initial local burning, it may not be well tolerated. Its use in the clinical setting in cancer pain has been disappointing (APS).

Not Recommended for Practice

Interventions for which the lack of effectiveness or harmfulness has been demonstrated by strong evidence from rigorously conducted studies, meta-analyses, or systematic reviews, or interventions for which the costs, burdens, or harms associated with the intervention exceed anticipated benefit include mixed agonists-antagonists (APS, 2005), meperidine (APS; Mercadante et al., 2007), propoxyphene (APS; NCCN, 2008) codeine (Maltoni et al., 2005), IM route (APS), placebos (APS; Pfizer Inc., 2007), phenothiazines (APS), and carbamazepine (APS).

Expert Opinion

Interventions recommended by expert opinion generally are low-risk, are consistent with sound clinical practice, are suggested by an expert in a peer-reviewed publication, and have limited evidence. Experts recommend consulting an equianalgesic dosing chart when switching opioids or their routes (APS, 2005). For a good example of an equianalgesic dosing chart, see www.residentandstaff.com/issues/articles/2007-04_06.asp, Table 3 (Yuen et al., 2006). Opioid rotation, using an equianalgesic chart, is recommended when the opioid regimen has become ineffective or when side effects become intolerable (Ballantyne & Carwood, 2005; Bell, Eccleston, & Kalso, 2003; Mercadante, Arcuri, Ferrera, et al., 2005; Mercadante et al., 2006; Stearns et al., 2005).

Implications for Nursing Research

Pharmacologic treatment of pain from cancer has been studied for centuries and much evidence is available to guide effective treatment. However, additional research is needed to determine the role of some coanalgesics (i.e., bisphosphonates, radioisotopes, antihistamines, and ketamine) and opioids in combination with coanalgesics in the treatment of cancer pain. Adequate evidence may be available to produce PEP resources on other clinically important cancer pain-related topics such as pediatric cancer pain, alternative treatments (i.e., herbal therapies, music therapy, cognitive therapies, and other nonpharmacologic approaches), patient education, clinician education, and specific pain syndromes or sites (i.e., bone pain, radicular pain, and organ encapsulation pain).

Conclusion

Opioids, nonopioids, and coanalgesics are proven to be effective in treating neuropathic and nociceptive pain. Other pharmacologic agents whose primary use is not analgesia (i.e., bisphosphonates, caffeine, and antihistamines) need further research. A preponderance of evidence-based recommendations are available for pain relief; evidence summaries, such as PEP resources, may be an effective way to educate clinicians in the intricacies of pain management, resulting in improving the nursing-sensitive outcome of pain.

The authors take full responsibility for the content of the article. The authors did not receive honoraria for this work. The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the authors, planners, independent peer reviewers, or editorial staff.

Author Contact: Lisa Aiello-Laws, RN, MSN, AOCNS®, APNG, APN-C, can be reached at llaws@itapartners.com, with copy to editor at CJONEditor@ons.org.

References

- American Geriatrics Society. (2002). Clinical practice guidelines: The management of persistent pain in older persons. *Journal of the American Geriatrics Society*, 50(6, Suppl.), S205-S224.
- American Pain Society. (2005). *Guideline for the management of cancer pain in adults and children*. Glenview, IL: Author.
- Auret, K., Roger Goucke, C., Ilett, K.F., Page-Sharp, M., Boyd, F., & Oh, T.E. (2006). Pharmacokinetics and pharmacodynamics of methadone enantiomers in hospice patients with cancer pain. *Therapeutic Drug Monitoring*, 28(3), 359-366.

- Baczyk, M., Czepczynski, R., Milecki, P., Pisarek, M., Oleksa, R., & Sowinski, J. (2007). 89Sr versus 153Sm-EDTMP: Comparison of treatment efficacy of painful bone metastases in prostate and breast carcinoma. *Nuclear Medicine Communications*, 28(4), 245–250.
- Ballantyne, J.C., & Carwood, C.M. (2005). Comparative efficacy of epidural, subarachnoid, and intracerebroventricular opioids in patients with pain due to cancer. *Cochrane Database of Systematic Reviews*, 1, CD005178.
- Bell, R., Eccleston, C., & Kalso, E. (2003). Ketamine as an adjuvant to opioids for cancer pain. *Cochrane Database of Systematic Reviews*, 1, CD003351.
- Centeno, C., & Vara, F. (2005). Intermittent subcutaneous methadone administration in the management of cancer pain. *Journal of Pain and Palliative Care Pharmacotherapy*, 19(2), 7–12.
- Challapalli, V., Tremont-Lukats, I.W., McNicol, E.D., Lau, J., & Carr, D.B. (2005). Systemic administration of local anesthetic agents to relieve neuropathic pain. *Cochrane Database of Systematic Reviews*, 4, CD003345.
- Colella, J., Scrofine, S., Galli, B., Knorr-Mulder, C., Gejerman, G., Scheuch, J., et al. (2006). Prostate HDR radiation therapy: A comparative study evaluating the effectiveness of pain management with peripheral PCA vs. PCEA. *Urologic Nursing*, 26(1), 57–61.
- Currow, D.C., Plummer, J.L., Conney, N.J., Gorman, D., & Glare, P.A. (2007). A randomized, double-blind, multi-site, crossover, placebo-controlled equivalence study of morning versus evening once-daily sustained-release morphine sulfate in people with pain from advanced cancer. *Journal of Pain and Symptom Management*, 34(1), 17–23.
- Darwish, M., Kirby, M., Robertson, P., Tracewell, W., & Jiang, J.G. (2007). Absorption of fentanyl from fentanyl buccal tablet in cancer patients with or without oral mucositis: A pilot study. *Clinical Drug Investigation*, 27(9), 605–611.
- Dudgeon, D.J., Bruera, E., Gagnon, B., Watanabe, S.M., Allan, S.J., Warr, D.G., et al. (2007). A phase III randomized, double-blind, placebo-controlled study evaluating dextromethorphan plus slow-release morphine for chronic cancer pain relief in terminally ill patients. *Journal of Pain and Symptom Management*, 33(4), 365–371.
- Dunteman, E.D. (2005). Levetiracetam as an adjunctive analgesic in neoplastic plexopathies: Case series and commentary. *Journal of Pain and Palliative Care Pharmacotherapy*, 19(1), 35–43.
- Dworkin, R.H., O'Connor, A.B., Backonja, M., Farrar, J.T., Finnerup, N.B., Jensen, T.S., et al. (2007). Pharmacologic management of neuropathic pain: Evidence-based recommendations. *Pain*, 132(3), 237–251.
- Elsner, F., Radbruch, L., Loick, G., Gartner, J., & Sabatowski, R. (2005). Intravenous versus subcutaneous morphine titration in patients with persisting exacerbation of cancer pain. *Journal of Palliative Medicine*, 8(4), 743–750.
- Glare, P., Walsh, D., & Sheehan, D. (2006). The adverse effects of morphine: A prospective survey of common symptoms during repeated dosing for chronic cancer pain. *American Journal of Hospice and Palliative Medicine*, 23(3), 229–235.
- Grosset, A.B., Roberts, M.S., Woodson, M.E., Shi, M., Swanton, R.E., Reder, R.F., et al. (2005). Comparative efficacy of oral extended-release hydromorphone and immediate-release hydromorphone in patients with persistent moderate to severe pain: Two randomized controlled trials. *Journal of Pain and Symptom Management*, 29(6), 584–594.
- Hagen, N.A., du Souich, P., Lapointe, B., Ong-Lam, M., Dubuc, B., Walde, D., et al. (2008). Tetrodotoxin for moderate to severe cancer pain: a randomized, double blind, parallel design multicenter study. *Journal of Pain and Symptom Management*, 35(4), 420–429.
- Hagen, N.A., Fisher, K., Victorino, C., & Farrar, J.T. (2007). A titration strategy is needed to manage breakthrough cancer pain effectively: Observations from data pooled from three clinical trials. *Journal of Palliative Medicine*, 10(1), 47–55.
- Hagen, N.A., Fisher, K.M., Lapointe, B., du Souich, P., Chary, S., Moulin, D., et al. (2007). An open-label, multi-dose efficacy and safety study of intramuscular tetrodotoxin in patients with severe cancer-related pain. *Journal of Pain and Symptom Management*, 34(2), 171–182.
- Holmes Gobel, B., Beck, S., & O'Leary, C. (2006). Nursing-sensitive patient outcomes: The development of the Putting Evidence Into Practice resources for nursing practice. *Clinical Journal of Oncology Nursing*, 10(5), 621–624.
- Keskinbora, K., Pekel, A.F., & Aydinli, I. (2007). Gabapentin and an opioid combination versus opioid alone for the management of neuropathic cancer pain: A randomized open trial. *Journal of Pain and Symptom Management*, 34(2), 183–189.
- Komurcu, S., Turhal, S., Altundag, K., Atahan, L., Turna, H.S., Manavoglu, O., et al. (2007). Safety and efficacy of transdermal fentanyl in patients with cancer pain: Phase IV, Turkish oncology group trial. *European Journal of Cancer Care*, 16(1), 67–73.
- Koshy, R.C., Kuriakose, R., Sebastian, P., & Koshy, C. (2005). Continuous morphine infusions for cancer pain in resource-scarce environments: Comparison of the subcutaneous and intravenous routes of administration. *Journal of Pain and Palliative Care Pharmacotherapy*, 19(1), 27–33.
- Liepe, K., & Kotzerke, J. (2007). A comparative study of 188Re-HEDP, 186Re-HEDP, 153Sm-EDTMP and 89Sr in the treatment of painful skeletal metastases. *Nuclear Medicine Communications*, 28(8), 623–630.
- Maltoni, M., Scarpi, E., Modonesi, C., Passardi, A., Calpona, S., Turriziani, A., et al. (2005). A validation study of the WHO analgesic ladder: A two-step vs. three-step strategy. *Supportive Care in Cancer*, 13(11), 888–894.
- Marinangeli, F., Ciccozzi, A., Aloisio, L., Colangeli, A., Paladini, A., Bajocco, C., et al. (2007). Improved cancer pain treatment using combined fentanyl-TTS and tramadol. *Pain Practice*, 7(4), 307–312.
- Martinez-Zapata, M.J., Roque, M., Alonso-Coello, P., & Catala, E. (2006). Calcitonin for metastatic bone pain. *Cochrane Database of Systematic Reviews*, 3, CD003223.
- Mercadante, S., Arcuri, E., Ferrera, P., Villari, P., & Mangione, S. (2005). Alternative treatments of breakthrough pain in patients receiving spinal analgesics for cancer pain. *Journal of Pain and Symptom Management*, 30(5), 485–491.
- Mercadante, S., Arcuri, E., Fusco, F., Tirelli, W., Villari, P., Bussolino, C., et al. (2005). Randomized double-blind, double-dummy crossover clinical trial of oral tramadol versus rectal tramadol administration in opioid-naive cancer patients with pain. *Supportive Care in Cancer*, 13(9), 702–707.
- Mercadante, S., Villari, P., Ferrera, P., & Casuccio, A. (2006). Opioid-induced or pain relief-reduced symptoms in advanced cancer patients? *European Journal of Pain*, 10(2), 153–159.
- Mercadante, S., Villari, P., Ferrera, P., Casuccio, A., Mangione, S., & Intraiva, G. (2007). Transmucosal fentanyl versus intravenous morphine in doses proportional to basal opioid regimen for episodic-breakthrough pain. *British Journal of Cancer*, 96(12), 1828–1833.
- Moryl, N., Kogan, M., Comfort, C., & Obbens, E. (2005). Methadone in the treatment of pain and terminal delirium in advanced cancer patients. *Palliative and Supportive Care*, 3(4), 311–317.
- National Comprehensive Cancer Network. (2008). *NCCN Clinical Practice Guidelines in Oncology™: Adult cancer pain* [v.1.2008]. Retrieved October 29, 2008, from http://www.nccn.org/professionals/physician_gls/PDF/pain.pdf
- Nicholson, A.B. (2007). Methadone for cancer pain. *Cochrane Database of Systematic Reviews*, 3, CD003971.

- Novartis Pharmaceuticals. (2008). *Aredia® (pamidronate disodium for injection)* [Package insert]. Retrieved October 29, 2009, from <http://www.pharma.us.novartis.com/product/pi/pdf/aredia.pdf>
- Pan, H., Zhang, Z., Zhang, Y., Xu, N., Lu, L., Dou, C., et al. (2007). Efficacy and tolerability of oxycodone hydrochloride controlled-release tablets in moderate to severe cancer pain. *Clinical Drug Investigations*, 27(4), 259-267.
- Pergolizzi, S., Iati, G., Santacaterina, A., Palazzolo, C., Di Pietro, A., Garufi, G., et al. (2006). Treatment planning in patients with bone metastases. Final results of a prospective study using pre-medication with fentanyl to improve irradiation reproducibility. *Supportive and Palliative Cancer Care*, 2(2), 71-75.
- Pfizer Inc. (2009). *Celebrex® (celecoxib)* [Package insert]. Retrieved October 29, 2009, from http://pfizer.com/pfizer/download/uspi_celebrex.pdf
- Reid, C.M., Martin, R.M., Sterne, J.A., Davies, A.N., & Hanks, G.W. (2006). Oxycodone for cancer-related pain: Meta-analysis of randomized controlled trials. *Archives of Internal Medicine*, 166(8), 837-843.
- Roque, M., Martinez-Zapata, M.J., Alonso, P., Catala, E., Garcia, J.L., & Ferrandiz, M. (2003). Radioisotopes for metastatic bone pain. *Cochrane Database of Systematic Reviews*, 4, CD003347.
- Ross, J.R., Goller, K., Hardy, J., Riley, J., Broadley, K., A'hern, R., et al. (2005). Gabapentin is effective in the treatment of cancer-related neuropathic pain: A prospective, open-label study. *Journal of Palliative Medicine*, 8(6), 1118-1126.
- Sartor, O., Reid, R.H., Bushnell, D.L., Quick, D.P., & Ell, P.J. (2007). Safety and efficacy of repeat administration of samarium Sm-153 lexidronam to patients with metastatic bone pain. *Cancer*, 109(3), 637-643.
- Smith, T.J., & Coyne, P.J. (2005). Implantable drug delivery systems (IDDS) after failure of comprehensive medical management (CMM) can palliate symptoms in the most refractory cancer pain patients. *Journal of Palliative Medicine*, 8(4), 736-742.
- Solassol, I., Caumette, L., Bressolle, F., Garcia, F., Thezenas, S., Astre, C., et al. (2005). Inter- and intra-individual variability in transdermal fentanyl absorption in cancer pain patients. *Oncology Reports*, 14(4), 1029-1036.
- Stearns, L., Boortz-Marx, R., Du Pen, S., Friehs, G., Gordon, M., Halyard, M., et al. (2005). Intrathecal drug delivery for the management of cancer pain: A multidisciplinary consensus of best clinical practices. *Journal of Supportive Oncology*, 3(6), 399-408.
- Tassinari, D., Sartori, S., Tamburini, E., Scarpi, E., Raffaelli, W., Tombesi, P., et al. (2008). Adverse effects of transdermal opiates treating moderate-severe cancer pain in comparison to long-acting morphine: A meta-analysis and systematic review of the literature. *Journal of Palliative Medicine*, 11(3), 492-501.
- Wallace, M., Rauck, R.L., Moulin, D., Thippawong, J., Khanna, S., & Tudor, I.C. (2008). Conversion from standard opioid therapy to once-daily oral extended-release hydromorphone in patients with chronic cancer pain. *Journal of International Medical Research*, 36(2), 343-352.
- Weinbroum, A.A. (2005). Superiority of postoperative epidural over intravenous patient-controlled analgesia in orthopedic oncologic patients. *Surgery*, 138(5), 869-876.
- Wiffen, P.J., McQuay, H.J. (2007). Oral morphine for cancer pain. *Cochrane Database of Systematic Reviews*, 4, CD003868.
- Wong, R., & Wiffen, P.J. (2002). Bisphosphonates for the relief of pain secondary to bone metastases. *Cochrane Database of Systematic Reviews*, 2, CD002068.
- Woolery, M., Bisanz, A., Lyons, H.F., Gaido, L., Yenulevich, M., Fulton, S., et al. (2008). Putting Evidence Into Practice: Evidence-based interventions for the prevention of management of constipation in patients with cancer. *Clinical Journal of Oncology Nursing*, 12(2), 317-337.
- Wooten, M. (2004). Morphine is not the only analgesic in palliative care: Literature review. *Journal of Advanced Nursing*, 45(5), 527-532.
- Yuen, K.K., Shelley, M., Sze, W.M., Wilt, T., & Mason, M.D. (2006). Bisphosphonates for advanced prostate cancer. *Cochrane Database of Systematic Reviews*, 4, CD006250.
- Zeppetella, G., & Ribeiro, M.D. (2006). Opioids for the management of breakthrough (episodic) pain in cancer patients. *Cochrane Database of Systematic Reviews*, 1, CD004311.

Receive free continuing nursing education credit for reading this article and taking a brief quiz online. To access the test for this and other articles, visit <http://evaluationcenter.ons.org>. After entering your Oncology Nursing Society profile username and password, select CNE Listing from the left-hand tabs. Scroll down to *Clinical Journal of Oncology Nursing* and choose the test(s) you would like to take.

Journal Club Discussion Questions

This article has been identified as appropriate for a journal club. When you read this article, think about how you would change your current practice regarding nociceptive and neuropathic cancer pain in your patients. See the Evidence-Based Practice column in the February 2009 *Clinical Journal of Oncology Nursing* (Vol. 13, No. 1, pp. 109-112) on how to implement and participate in journal clubs. Photocopying of this article for discussion purposes is permitted.

1. What is the clinical practice question the authors are trying to address?
2. Is the purpose of the article described clearly?
3. Is the literature review comprehensive, and are major concepts identified and defined?
4. What are the medications recommended for nociceptive and neuropathic pain management?
5. How do the clinical recommendations compare to your current practice?
6. What practice change recommendations will you make based on the evidence presented in this article?
7. What patient education materials are available on this topic?