Implementing Therapy With Opioids in Patients With Cancer

Oscar de Leon-Casasola, MD

Purpose/Objectives: To review strategies to optimize the management of chronic pain in patients with cancer, with an emphasis on the role of opioid analgesics.

Data Sources: Published research, articles from a literature review, and U.S. statistics.

Data Synthesis: Treatment for cancer pain remains suboptimal. With the therapies currently available, as much as 90% of cancer pain can be controlled. Opioid analgesics are an important component of pain management in patients with cancer.

Conclusions: The management of cancer pain is a challenging endeavor that requires an understanding of the etiologies of cancer and the types of pain they can produce. Opioid analgesics are a mainstay of treatment for cancer pain. New drug formulations, delivery systems, and strategies, particularly opioid rotation, are available to optimize cancer pain management.

Implications for Nursing: Opioid rotation may be useful for opening the therapeutic window and establishing a more advantageous analgesic-to-toxicity ratio in patients with cancer.

Key Points . . .

- Although as much as 90% of cancer pain can be controlled, approximately 42% of patients do not receive adequate palliation.
- A physiologic approach to cancer pain management is required to determine whether pain is visceral, somatic, or neuropathic in nature.
- Approximately 20% of patients rotate through three or more opioid medications before achieving an acceptable balance of efficacy and side effects.
- A therapeutic armamentarium of at least three different opioids should be available for the management of cancer pain.

Pain is one of the most common—and feared—symptoms associated with cancer (National Comprehensive Cancer Network [NCCN], 2007). Often, the chief complaint of patients with advanced cancer is pain. As patients live longer, they have an increased need for effective pain control to improve quality of life (de Leon-Casasola & Lema, 2003). A lack of diagnostic tests makes defining the exact prevalence difficult. However, according to NCCN, pain occurs in approximately 25% of patients with newly diagnosed cancer, 33% of patients undergoing treatment, and 75% of patients with advanced disease. Indeed, an estimated 90% of patients experience at least moderate pain at some point during their illness and 42% do not receive adequate palliation (Oliver, Kravitz, Kaplan, & Meyers, 2001). Undertreated cancer pain is a particular problem in women, minority ethnic groups, and older patients (de Leon-Casasola & Lema). Unrelieved pain denies patients comfort and greatly affects activities, motivation, interactions with families and friends, and overall quality of life (NCCN).

As the area of palliative care grows, efforts to improve pain control will continue to be an essential element of cancer care (Oliver et al., 2001). Yet a number of barriers exist to effective pain relief, including inadequate assessment by practitioners, underreporting of pain by patients and families, practitioners' lack of knowledge regarding current treatment, lack of accountability for effectively treating pain, fear of overregulation by government officials, and inadequate reimbursement for pain treatment or excessive administrative demands on healthcare providers (de Leon-Casasola & Lema, 2003). In fact, in the nearly 70 years since regulatory controls were placed on opioid use, rebuilding confidence in the use of opioids as an effective, safe, and humane treatment for cancer pain has been difficult (Ballantyne, 2003). With the therapies currently available to clinicians, as much as 90% of cancer pain can be controlled with the use of aggressive multimodal pharmacologic therapy and invasive techniques (de Leon-Casasola & Lema). In 2008, there is no reason for most patients with cancer to be in pain.

Classification of Pain

In 1990, the World Health Organization (WHO) established guidelines for cancer pain relief and palliative care. According to the guidelines, potent opioids such as morphine were reserved for treatment of the most severe pain. However, the WHO three-step analgesic stepladder approach is no longer

Oscar de Leon-Casasola, MD, is a professor and the vice chair for clinical affairs in the Department of Anesthesiology at the University of Buffalo and the chief of pain medicine and a professor at Roswell Park Cancer Institute in Buffalo, NY. De Leon-Casasola is on the speakers bureau for King Pharmaceuticals and Endo Pharmaceuticals. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the Oncology Nursing Forum *or the Oncology Nursing Society.* *(Submitted February 2008. Accepted for publication June 14, 2008.)*

Digital Object Identifier: 10.1188/08.ONF.S1.7-12

the most appropriate strategy for pain management because healthcare professionals now know that the management of cancer pain is complex (NCCN, 2007) and that not all pain is the same.

Pain associated with cancer results from tumor infiltration of pain-sensitive structures; from injury to nerves, bone, or soft tissue as a result of chemotherapy, radiotherapy, or surgery; and from tumor- or radiation-induced vascular occlusion (de Leon-Casasola & Lema, 2003; Payne, 1987). Therefore, a pathophysiologic approach to pain management is required in patients with cancer. Such an approach includes a patient history, physical examination, and dedicated testing to determine whether pain is visceral, somatic, or neuropathic in nature (de Leon-Casasola & Lema).

Visceral pain is common in patients with cancer and results from infiltration, compression, distension, or stretching of thoracic and abdominal viscera. Visceral pain usually results from primary or metastatic tumor growth that occurs in patients with liver metastases or pancreatic cancer (de Leon-Casasola & Lema, 2003; Payne, 1987). Patients describe visceral pain as gnawing, cramping, aching, or sharp (NCCN, 2007). Visceral pain is diffuse, and many patients use a whole hand to describe where it hurts. In contrast, somatic pain is well localized (de Leon-Casasola & Lema; Payne, 1987); patients can describe where it hurts with one finger. Somatic pain usually occurs in skin, muscle, or bone (NCCN). Finally, neuropathic pain results from injury to the peripheral or central nervous system as a consequence of tumor compression or infiltration of peripheral nerves or the spinal cord, or as a result of trauma or chemical injury to peripheral nerves from surgery, radiation, or chemotherapy (de Leon-Casasola & Lema; Payne, 1987). Neuropathic pain usually is described as sharp, tingling, burning, or shooting (NCCN). Patients often report the pain as electric shock sensations.

Approaches to Pain Management

Pain relief, or analgesia, is an obvious primary outcome of appropriate pain management, but consider three other important "A's": activities of daily living (e.g., psychological functioning, sleep), adverse effects, and aberrant drug-related behavior (e.g., addiction-related outcomes). In most patients, pain can be adequately relieved initially by pharmacologic or invasive therapies, such as intrathecal analgesia, spinal or peripheral nerve stimulation, and use of radiofrequency to create a lesion in the peripheral nerves. Moreover, adopting a multidisciplinary approach to supportive care is very important. Management strategies should incorporate medical options, physical medicine, procedures such those already mentioned, and psychological considerations, in addition to complementary approaches such as acupuncture (see Figure 1). Pain management must be approached from all fronts. Patients with cancer who are in pain need the support of numerous specialty groups to get the best care available in the 21st century.

Pharmacotherapy remains the most widely used method to control chronic cancer pain. The three categories of analgesic medications most commonly used are nonsteroidal anti-inflammatory drugs, opioids, and adjuvant agents, such as tricyclic antidepressants and corticosteroids (de Leon-Casasola & Lema, 2003). The remainder of this article will focus on the use of opioids.

Medical
- Nonsteroidal anti-inflammatory drugs
- Opioids
- Steroids
- Adjuvants

Psychological
- Stress management
- Biofeedback
- Music

Complementary
- Acupuncture
- Massage
- Herbs

Physical medicine
- Transcutaneous electrical nerve stimulation
- Heat
- Physical therapy
- Ultrasound

Procedural
- Epidural or intrathecal medication
- Neuromodulation
- Nerve blocks
- Trigger points
- Radiation

Figure 1. Approaches to Pain Management

Opioids in Cancer Pain

Opioids are the most effective analgesics for severe pain and the mainstay of therapy for patients with cancer with pain (Ballantyne, 2003). Morphine, hydromorphone, fentanyl, and oxycodone have been the opioids commonly used in the United States (NCCN, 2007). The success of opioid therapy depends on the expertise of the prescriber, who must have knowledge of the nuances of the pharmacologic features of the various opioids and experience in their use to make an appropriate selection for each patient (de Leon-Casasola & Lema, 2003).

The largest group of opioids is the morphine-like agonists. Morphine remains a prototypic opiate analgesic against which all other drugs are compared. Despite morphine's clinical utility, its associated side effects have led to attempts to develop molecules with similar analgesic action without the management challenges (Pasternak, 2001a). In the 20th and 21st centuries, numerous opiate drugs have been synthesized, and the vast majority fall into the mu category (i.e., they target the mu opioid receptor). Initially, all mu opioids were thought to act through a single class of opioid receptors, but subsequent research has identified genetic locations for several mu opioid receptor subtypes. To date, at least 25 variants of the mu receptor have been identified in mice, 8 in rats, and 11 in humans (Pasternak, 2001b). Although mu opioids share many pharmacologic characteristics, differences exist (Pasternak, 2001a).

The concept of multiple mu receptors may help to explain the variability in individual responses to various opioids, the differences in side effects among patients, incomplete cross-tolerance among various mu opioid analgesics, and the clinical utility of opioid rotation (Ballantyne, 2003; Pasternak, 2001a). Opioid rotation now is a widely accepted approach to poorly responsive pain. If side effects with one opioid are significant, an improved balance between analgesia and side effects might be achieved by changing to an equivalent dose of an alternate opioid (NCCN, 2007). Rotation between two or three opioids often is required to obtain satisfactory long-term pain control (McNicol et al., 2003). One survey found that approximately 20% of patients rotate through three or more opioid medications

before achieving an acceptable balance (Cherny et al., 1995). A systematic review of existing literature on opioid rotation (Mercadante & Bruera, 2006) concluded that opioid switching results in clinical improvements in more than 50% of patients with chronic pain who experience a poor response to one opioid.

Expanding the currently limited number of sustained-release oral opioids would provide clinicians with increased treatment options and dosing flexibility (Sloan, Slatkin, & Ahdieh, 2005).

Opioids are used to treat moderate to severe pain (Ballantyne, 2003). Long-acting opioids are indicated for the treatment of chronic pain and offer a number of advantages compared with shorter-acting agents. Sustained-release formulations provide more predictable serum levels, resulting in more predictable pain relief and the avoidance of mini-withdrawals caused by fluctuating opioid levels. In addition, they are easy to use and improve compliance rates. Overall, they result in greater patient satisfaction and less reinforcement of drug-taking behaviors—patients do not need to be taught, for example, to take medications every four hours.

Currently, a number of long-acting agents are available. Controlled-release (CR) oral morphine sulfate (MS Contin®, Purdue Pharma, L.P.) and oxycodone hydrochloride CR (OxyContin®, Purdue Pharma, L.P.) have a duration of action of approximately 8–12 hours (Ballantyne, 2003). The agents are equally effective with similar side-effect profiles. However, the addiction potential is different between morphine and oxycodone. Because of oxycodone's street value, surveillance is warranted in patients who are prescribed the drug (U.S. Drug Enforcement Administration, n.d.). Extended-release (ER) morphine sulfate and oxycodone hydrochloride ER are available.

Morphine also is available as the twice-daily Kadian® (Alpharma Pharmaceuticals LLC) and a once-daily Avinza® (King Pharmaceuticals) capsule formulation that can be broken to release the morphine-containing pellets. The pellets can be sprinkled on applesauce for patients who are unable to swallow a capsule. Importantly, the pellets cannot be chewed, crushed, or dissolved because of the risk of a rapid release and absorption of a potentially fatal dose of morphine.

The fentanyl (Duragesic®, Janssen Pharmaceuticals, Inc.) transdermal patch provides continuous opioid delivery for 72 hours. It also is available in a generic version. When using the fentanyl transdermal system, provide short-acting pain medication for the first 8–12 hours, before effective plasma concentrations are achieved. In 2007, the U.S. Food and Drug Administration (FDA) issued a public health advisory warning healthcare professionals about the safe use of the fentanyl transdermal system. In some cases, deaths and life-threatening side effects occurred after physicians and other healthcare professionals inappropriately prescribed the patch to relieve pain after surgery, headaches, or occasional or mild pain in patients who were not opioid tolerant. In other cases, patients used the patch incorrectly; they replaced it more frequently than directed, applied more patches than prescribed, or applied heat to the patch, all resulting in dangerously high fentanyl levels in the blood (FDA, 2006, 2007a, 2007b).

Oxymorphone hydrochloride (Opana®, ENDO Pharmaceuticals) is one of the newer opioids available. It is a semisynthetic mu opioid agonist that produces a more rapid onset of action and greater analgesic potency compared with its parent compound, morphine (Adams & Ahdieh, 2005). Oxymorphone is available as 5 mg and 10 mg immediate-release tablets and 5, 7.5, 10, 15, 20, 30, and 40 mg ER tablets. It also is supplied as a 1 mg/ml ampule. Studies in healthy men and women have shown that single-dose (see Figure 2) and multiple-dose administration results in a linear and dose-proportional increase in pharmacokinetics for oxymorphone, and peak concentrations are reached within 30 minutes (Adams & Ahdieh). A study in 300 patients with moderate to severe postsurgical pain demonstrated that oxymorphone reached peak clinical effect approximately 45 minutes after administration (Gimbel & Ahdieh, 2004). This attribute of oxymorphone makes the immediate-release formulation a good option for the management of breakthrough pain in patients with cancer.

Two studies directly assessed the efficacy of oxymorphone compared to oxycodone CR and morphine CR in patients with cancer pain. Overall, pain relief was consistent among the opioids tested and the observed adverse effects were typical of opioids. Gabrail, Dvergsten, and Ahdieh (2004) used a 3- to 10-day titration period for 40 patients who completed both a 7- to 10-day double-blind phase and a crossover period of the same length. Oxymorphone ER and oxycodone CR had clinically similar average pain intensity ratings: 2.5 ± 1.3/10 and 2.8 ± 1.3/10, respectively. Also, the amount of rescue medication used by each of the study groups was low and comparable: The oxymorphone patients took an average daily dosage of 16.6 mg morphine immediate release (range = 0–90 mg), whereas the oxycodone group used 12.6 mg (range = 0–75 mg). Once the patients' pain had stabilized, equianalgesic dose ratios were calculated to be 2:1 oxymorphone ER to oxycodone CR.

In the second prospective, open-label pilot study, patients with cancer with moderate to severe pain who were stabilized on either morphine CR or oxycodone CR were safely and rapidly converted to oxymorphone ER at a lower mg dose, with no decrease in analgesic effectiveness or increase in adverse events (Sloan et al., 2005). Long-term follow-up in a small group of patients with cancer for about one year showed little tolerance to oxymorphone based on the mean average pain

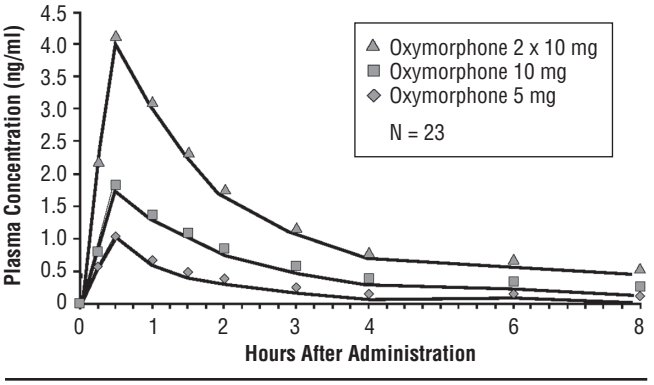


Figure 2. Oxymorphone Plasma Concentrations Following Single Doses in 23 Healthy Men and Women

Note. From "Single- and Multiple-Dose Pharmacokinetic and Dose-Proportionality Study of Oxymorphone Immediate-Release Tablets," by M.P. Adams and H. Ahdieh, 2005, *Drugs in R&D, 6*(2), p. 97. Copyright 2005 by Wolters Kluwer. Adapted with permission.

intensity visual analog scale and a "good to excellent" pain relief rating by 80% of patients based on a categorical scale (data on file, Endo Pharmaceuticals). Based on the results in small numbers of patients, additional trials of oxymorphone ER in chronic cancer pain are warranted.

The Endo Pharmaceuticals data from patients with cancer also showed that, although the incidence of nausea (18%) and vomiting (11%) was similar to that seen with other opioid analgesics, a lower incidence of constipation (11%) than is generally associated with opioid therapy could be achieved by integrating a bowel regimen into the study protocol. The results were duplicated in a 12-week study of low back pain that also used a bowel regimen; 20% of the patients had nausea, whereas only 12% of them experienced constipation and 9% vomiting (Hale, Ahdieh, Ma, & Rauck, 2007).

Understanding the pharmacokinetics and pharmacodynamics of opiates is imperative to providing patients with effective pain relief and avoiding adverse effects, such as sedation, nausea, and vomiting (McNicol et al., 2003; Mercadante, 1999). Efforts are directed at staying within the therapeutic window to avoid side effects that occur when drug concentrations rise above those necessary for pain relief (see Figure 3A) and loss of efficacy when plasma levels are too low (see Figure 3B). Healthcare professionals attempt to open the therapeutic window to improve outcomes for patients (see Figure 3C). This usually can be achieved within two weeks. Use a small dose of a long-acting opioid and allow the patient free access to short-acting opioids. Later, titrate the patient to a higher dose. This approach not only widens the therapeutic window but also avoids side effects.

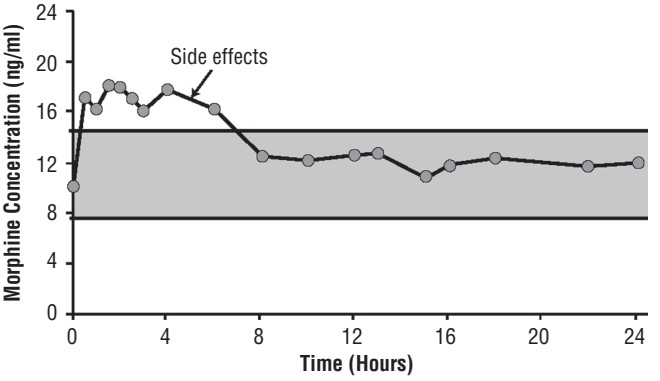
Breakthrough Pain

Breakthrough pain is defined as a transitory increase of more severe pain over relatively well-controlled baseline pain (Caraceni et al., 2004; Payne, 2007). The reported incidence of breakthrough pain ranges from 16%–95% in patients with persistent pain (Payne, 2007). Three types of breakthrough pain exist: end-of-dose failure, incidental pain, and spontaneous or idiopathic pain (Payne, 2007). End-of-dose failure occurs when plasma concentrations fall below the therapeutic window (see Figure 4). To avoid end-of-dose failure, administer a short-acting opioid or decrease the dosing interval. Healthcare professionals should talk to patients about patterns of breakthrough pain.

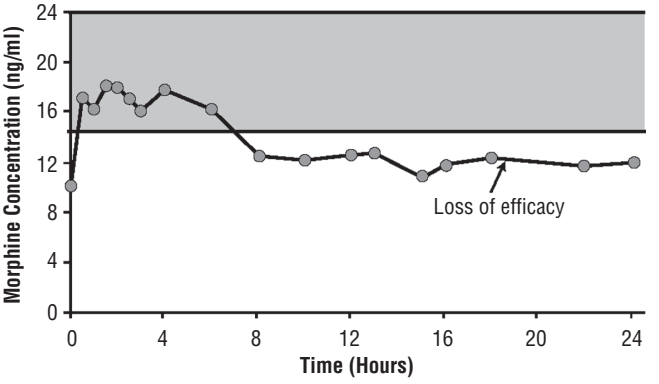
Incidental breakthrough pain and idiopathic breakthrough pain occur despite appropriate plasma levels. Such pain, which rises quickly and is severe, occurs in patients whose pain was well controlled previously. It usually lasts 30–45 minutes before subsiding. A medication with a rapid onset of action such as oral transmucosal fentanyl or a fentanyl buccal tablet is needed to control incidental or idiopathic pain (NCCN, 2007).

Overall, when dealing with breakthrough pain, healthcare professionals should determine whether the pain is end-of-dose failure or incidental, then treat appropriately. Even if a patient is free of pain but has poor quality of life, the pain regimen should be adjusted. Prior to dose titration, pain scores and rescue medications should be monitored along with psychosocial variables, including sleep. Long-acting opioids should be adjusted based on pain scores and the amount of rescue medication used.

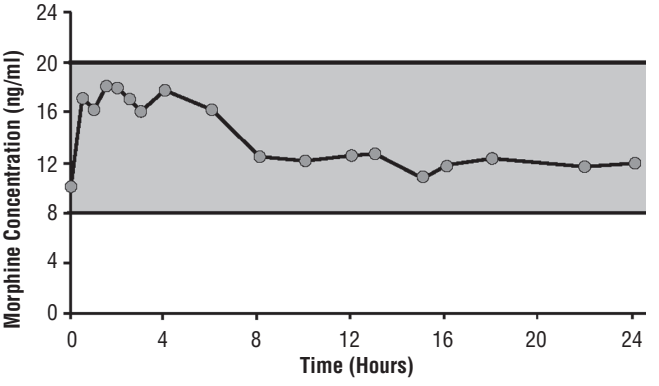
3A. Plasma concentrations rise above the therapeutic window, causing side effects.



3B. Plasma concentrations fall below the therapeutic window, resulting in loss of efficacy.



3C. Therapeutic window is opened to improve patient outcomes.

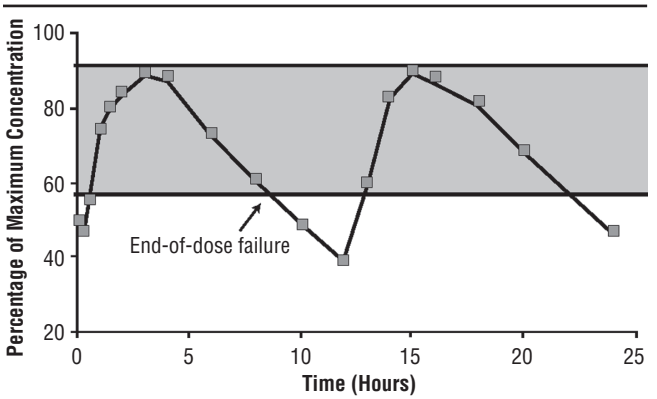


Note. Shaded areas represent the therapeutic window.

Figure 3. Pharmacokinetic and Pharmacodynamic Relationships for Opiates: Illustration of Concepts

Dose Titration

An important problem raised in the opioid literature is conversion rates among various drugs. Most conversion data presented in reference tables are derived from older studies that



Note. Shaded area represents the therapeutic window.

Figure 4. End-of-Dose Failure Concept Resulting in Breakthrough Pain

were not designed to determine relative potencies (Mercadante & Bruera, 2006). Yet an understanding of equianalgesic doses is important when healthcare professionals are titrating long-acting opioids. One practical approach is the "rule of 2" (see Table 1). Assuming a morphine dose of 100 mg every 24 hours and dividing it by two, one arrives at a dose equivalent of 50 mg every 24 hours for oxycodone/hydrocodone. Dividing it by four, one reaches the fentanyl (25 mcg per hour) and oxymorphone (25 mg every 24 hours) dose equivalents. Dividing it by eight, one obtains the equianalgesic dose of 12 mg every 24 hours for hydromorphone. The method allows for relatively quick conversions. Although on the conservative side, the quick conversions should place plasma levels in the therapeutic range. However, patients should be contacted within a day or two to determine whether further titration is required.

Although methadone is a very effective and inexpensive medication, it provides a unique challenge because no good dosing guidelines or easy conversion rates exist (Mercadante, 1999; Mercadante & Bruera, 2006). For patients on a moderate opioid dose, the author usually converts to 10 mg of methadone every six hours for the first week and then decreases the dose to 8 mg every six hours. If a patient is on higher opioid doses, the starting methadone dose is 20 mg for the first week.

Patients on methadone need to be monitored closely. One study found a correlation between the daily dose of methadone and the QTc interval in 17 patients who experienced torsade de pointes (Krantz, Kutinsky, Robertson, & Mehler, 2003). Of note, the relationship persisted after adjustment for the clinical variables known to be associated with QT-segment prolongation (Krantz et al.). In all patients who receive methadone, baseline electrocardiogram (ECG) must be performed. In patients receiving high doses, ECGs should be performed monthly. In addition, electrolyte levels should be monitored, particularly in patients on medications that induce magnesium and potassium loss, including chemotherapeutic agents such as carboplatin and cisplatin. Therefore, in November 2006, the FDA released an alert resulting in the addition of a black box warning to the product labeling for methadone manufactured as Dolophine® Hydrochloride CII (Roxane Laboratories) (FDA, 2006).

Important Considerations in the Use of Opioids

In general, long-term opioid use decreases cortisol levels, which may be why patients experience lassitude and lack of energy. Additionally, opioids decrease prolactin, luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, and estrogen levels, which, in turn, can cause osteoporosis (Ballantyne & Mao, 2003; Daniell, 2002; Mendelson, Mendelson, & Patch, 1975). This problem can be overcome in men easily with testosterone injections or use of a topical gel. However, reduced sex hormones are more problematic in women; consultation with an endocrinologist may be warranted to address the risk of osteoporosis.

Morphine should be administered cautiously and in reduced doses in patients with severe renal or hepatic insufficiency, Addison disease, hypothyroidism, prostatic hypertrophy, or urethral stricture and in older or debilitated patients. Patients with cancer and renal dysfunction sometimes experience myoclonus and hyperanalgesia following morphine administration (Purdue Pharma, L.P., 2006).

Another important consideration in the administration of opioids is their effect on cognitive function (McNicol et al., 2003). Side effects such as sedation, dizziness, and mental clouding interfere with activities that demand alertness, especially driving. Although driving is not advisable at the beginning of treatment, studies have shown that cognitive function, including the ability to drive and operate machinery, often is adequate in patients taking stable, moderate doses of opioids for chronic pain (Bruera, Macmillan, Hanson, & MacDonald, 1989; Vainio, Ollila, Matikainen, Rosenberg, & Kalso, 1995).

Codeine, dihydrocodeine, and hydrocodone must be converted to morphine, the active metabolite, to exert an analgesic effect. The conversion to morphine is driven by enzyme CYP2D6. Without that enzyme, no conversion exists and little pain relief occurs (Supernaw, 2001). Some patients, particularly African Americans, have reduced or absent CYP2D6 function (Supernaw). In addition, other commonly used medications, including fluoxetine, haloperidol, and paroxetine, can inhibit CYP2D6 function, resulting in a lack of pain relief (Supernaw).

Managing Poorly Responsive Patients

When an opioid administered is not providing benefit to a patient, it should be discontinued. Deciding when a patient is more harmed than helped by an opioid is one of the greatest challenges in pain management (Ballantyne, 2003). When evaluating poorly responsive patients, healthcare professionals should consider a number of factors. One of the first

Table 1. Equianalgesic Doses: Rule of Two[a]

Opioid	Equivalent Dose
Oxycodone-hydrocodone/oral	50 mg every 24 hours
Fentanyl	25 mcg every hour
Oxymorphone	25 mg every 24 hours
Hydromorphone/oral	12 mg every 24 hours
Methadone/oral	10–60 mg every 24 hours

[a] Based on a morphine dose of 100 mg every 24 hours

considerations is evidence of abuse or diversion. If the pain has a neuropathic component, the patient may benefit from neuropathic pain medications such as tricyclic antidepressants or anticonvulsants (Ballantyne). If no evidence of abuse, diversion, or neuropathic pain is found, consider increasing the dose of the current opioid or switching to a different opioid. Opioid rotation based on pharmacogenetics is a strategy that clinicians are implementing more frequently. If such maneuvers are ineffective, other interventions should be investigated, including intraspinal administration or alternative treatments, such as biofeedback and other psychological therapies, herbal therapy, and acupuncture.

Summary

The management of cancer pain can be a challenging endeavor, and many patients do not receive adequate palliation. Healthcare professionals' understanding of the various etiologies of cancer and the different types of pain they can produce is essential for appropriate therapeutic intervention (de Leon-Casasola & Lema, 2003).

When strict regulatory controls were placed on opioids in the 1940s, a backlash occurred against their use, and cancer pain was greatly undertreated (Ballantyne & Mao, 2003). Yet opioids are the most effective analgesics and an important component of pain management in patients with cancer. The individual variability in response to different opioids has important implications in clinical practice, and opioid rotation has been shown to be useful for opening the therapeutic window and establishing a more advantageous analgesia-to-toxicity ratio (Mercadante, 1999; Mercadante & Bruera, 2006). A therapeutic repertoire of at least three opioid drugs should be available for the management of chronic pain in patients with cancer (Cherny et al., 1995).

Author Contact: Oscar de Leon-Casasola, MD, can be reached at oscar.deleon@roswellpark.org, with copy to editor at ONFEditor@ons.org.

References

Adams, M.P., & Ahdieh, H. (2005). Single- and multiple-dose pharmacokinetic and dose-proportionality study of oxymorphone immediate-release tablets. *Drugs in R&D, 6*(2), 91–99.

Ballantyne, J.C. (2003). Chronic pain following treatment for cancer: The role of opioids. *Oncologist, 8*(6), 567–575.

Ballantyne, J.C., & Mao, J. (2003). Opioid therapy for chronic pain. *New England Journal of Medicine, 349*(20), 1943–1953.

Bruera, E., Macmillan, K., Hanson, J., & MacDonald, R.N. (1989). The cognitive effects of the administration of narcotic analgesics in patients with cancer pain. *Pain, 39*(1), 13–16.

Caraceni, A., Martini, C., Zecca, E., Portenoy, R.K., Ashby, M.A., Hawson, G., et al. (2004). Breakthrough pain characteristics and syndromes in patients with cancer pain. An international survey. *Palliative Medicine, 18*(3), 177–183.

Cherny, N.J., Chang, V., Frager, G., Ingham, J.M., Tiseo, P.J., Popp, B., et al. (1995). Opioid pharmacotherapy in the management of cancer pain: A survey of strategies used by pain physicians for the selection of analgesic drugs and routes of administration. *Cancer, 76*(7), 1283–1293.

Daniell, H.W. (2002). Hypogonadism in men consuming sustained-action oral opioids. *Journal of Pain, 3*(5), 377–384.

de Leon-Casasola, O.A., & Lema, M.J. (2003). Cancer pain. In T.J. Healy & P.R. Knight (Eds.), *Wylie and Churchill-Davidson's a practice of anesthesia* (7th ed., pp. 1255–1265). London: Arnold Publishers.

Gabrail, N.Y., Dvergsten, C., & Ahdieh, H. (2004). Establishing the dosage equivalency of oxymorphone extended release and oxycodone controlled release in patients with cancer pain: A randomized controlled study. *Current Medical Research Opinion, 20*(6), 911–918.

Gimbel, J., & Ahdieh, H. (2004). The efficacy and safety of oral immediate-release oxymorphone for postsurgical pain. *Anesthesia and Analgesia, 99*(5), 1472–1477.

Hale, M.E., Ahdieh, H., Ma, T., & Rauck, R. (2007). Efficacy and safety of OPANA ER (oxymorphone extended release) for relief of moderate to severe chronic low back pain in opioid-experienced patients: A 12-week, randomized, double-blind, placebo-controlled study. *Journal of Pain, 8*(2), 175–184.

Krantz, M.J., Kutinsky, I.B., Robertson, A.D., & Mehler, P.S. (2003). Dose-related effects of methadone on QT prolongation in a series of patients with torsade de pointes. *Pharmacotherapy, 23*(6), 802–805.

McNicol, E., Horowicz-Mehler, N., Fisk, R.A., Bennett K., Gialeli-Goudas, M., Chew, P.W., et al. (2003). Management of opioid side effects in cancer-related and chronic noncancer pain: A systematic review. *Journal of Pain, 4*(5), 231–256.

Mendelson, J.H., Mendelson, J.E., & Patch, V.D. (1975). Plasma testosterone levels in heroin addiction and during methadone maintenance. *Journal of Pharmacology and Experimental Therapeutics, 192*(1), 211–217.

Mercadante, S. (1999). Opioid rotation for cancer pain: Rationale and clinical aspects. *Cancer, 86*(9), 1856–1866.

Mercadante, S., & Bruera, E. (2006). Opioid switching: A systematic and critical review. *Cancer Treatment Reviews, 32*(4), 304–315.

National Comprehensive Cancer Network. (2007). *Clinical practice guidelines in oncology™: Adult cancer pain* [v.1.2007]. Retrieved August 1, 2007, from http://www.nccn.org/professionals/physician_gls/PDF/pain.pdf

Oliver, J.W., Kravitz, R.L., Kaplan, S.H., & Meyers, F.J. (2001). Individualized patient education and coaching to improve pain control among cancer outpatients. *Journal of Clinical Oncology, 19*(8), 2206–2212.

Pasternak, G.W. (2001a). Insights into mu opioid pharmacology: The role of mu opioid receptor subtypes. *Life Sciences, 68*(19–20), 2213–2219.

Pasternak, G.W. (2001b). The pharmacology of *mu* analgesics: From patients to genes. *Neuroscientist, 7*(3), 220–231.

Payne, R. (1987). Anatomy, physiology, and neuropharmacology of cancer pain. *Medical Clinics of North America, 71*(2), 153–167.

Payne, R. (2007). Recognition and diagnosis of breakthrough pain. *Pain Medicine, 8*(Suppl. 1), S3–S7.

Purdue Pharma, L.P. (2006). MS Contin® [package insert]. Stamford, CT: Author.

Sloan, P., Slatkin, N., & Ahdieh, H. (2005). Effectiveness and safety of oral extended-release oxymorphone for the treatment of cancer pain: A pilot study. *Supportive Care in Cancer, 113*(1), 57–65.

Supernaw, R.B. (2001). CYP2D6 and the efficacy of codeine and codeine-like drugs. *American Journal of Pain Management, 11,* 30–31.

U.S. Drug Enforcement Administration. (n.d.). Narcotics. Retrieved August 1, 2007, from http://www.usdoj.gov/dea/pubs/abuse/4-narc.htm

U.S. Food and Drug Administration. (2006). Death, narcotic overdose, and serious cardiac arrhythmias. Methadone hydrochloride (marketed as Dolophine) information. Retrieved August 1, 2007, from http://www.fda.gov/cder/drug/infopage/methadone/default.htm

U.S. Food and Drug Administration. (2007a). FDA issues second safety warning on fentanyl skin patch. Retrieved September 10, 2008, from http://www.fda.gov/bbs/topics/NEWS/2007/NEW01762.html

U.S. Food and Drug Administration. (2007b). Fentanyl transdermal system (marketed as Duragesic and generics). Retrieved April 22, 2008, from http://www.fda.gov/medwatch/safety/2007/safety07.htm#Fentanyl

Vainio, A., Ollila, J., Matikainen, E., Rosenberg, P., & Kalso, E. (1995). Driving ability in cancer patients receiving long-term morphine analgesia. *Lancet, 346*(8976), 667–670.

World Health Organization. (1990). *Cancer pain relief and palliative care* [Technical report series, No. 804]. Geneva, Switzerland: Author.