



*Key steps in assessing and managing pain in patients with cancer are discussed.*

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# Assessment and Management of Pain in Palliative Care Patients

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**Background:** Pain affects more than 70% of cancer patients but is often undertreated.

**Methods:** The authors review and present methodologies to maximize proper palliative approaches to this symptom for the majority of patients.

**Results:** The World Health Organization's stepwise guide to pain control serves as an excellent basis for management. Around-the-clock dosing, using adjuvant treatments, and using noninvasive routes of administration provide good pain control for 80% of patients.

**Conclusions:** Barriers to effective pain control will be reduced as new JCAHO standards regarding pain control are implemented.

## Introduction

The goals of palliative care are to control symptoms in patients with advanced disease and enhance their quality of life. The field of end-of-life care has grown rapidly in the United States since the founding

of the first hospice in Connecticut in 1974. Hospice, which involves providing care to terminally ill patients, has been expanded into most areas of the United States. In 1990, the National Hospice Organization reported that 200,000 patients were cared for by hospice organizations in the country. That number increased to 700,000 patients in 1999.<sup>1</sup>

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Despite the growth of palliative care in this country, the majority of patients die outside of their homes, and many do not receive adequate control of their symptoms. The Robert Wood Johnson Foundation found that although 81% of patients stated that they had a clear preference for dying at home, 56% died in a hospital.<sup>2</sup> Although education and training have

increased for physicians and nurses in the management of pain, many patients do not receive adequate analgesia. More than 70% of cancer patients report pain,<sup>3</sup> and more than 36% of patients with metastatic disease have pain severe enough to impair function.<sup>4</sup> Pain not only adversely affects the quality of life of patients, but also may force otherwise independent individuals to become prematurely institutionalized when they can no longer be managed at home. Pain also can be psychologically devastating because it can be a constant reminder of the incurable and progressive nature of the disease.<sup>5</sup> This article discusses pain management in palliative care and reviews management strategies.

## Assessment

The cornerstone of adequate pain management is a thorough patient assessment and frequent reassessment. A complete history and a physical examination, with emphasis on the patient's symptoms, are obtained, including information regarding the location, intensity, radiation, aggravating factors, timing, quality, and meaning of the pain. Medications and treatments are reviewed, and a psychosocial history is taken.

**Intensity:** The intensity or severity of the pain must first be quantified. Pain rating scales that have been used for more than a decade allow patients to quantify their pain so that health care providers can determine the effectiveness of the therapy. The most commonly used is the numeric rating scale. Pain is rated on a scale of 0-10, with 8-10 being severe pain, 4-7 moderate pain, and 1-3 mild pain.<sup>6</sup> Other scales, including the visual analog scale and the verbal rating scale, are available to quantify the patient's pain. Each of these scales has specific advantages in helping patients to effectively communicate the intensity of their pain. Once the patient is receiving therapy, pain can be tracked by utilizing the pain scale. This approach also allows the patient to objectively evaluate the efficacy of the therapy. The occurrence of severe pain and the frequency in which breakthrough medications are used should be closely monitored. Reliance on breakthrough medication throughout the course of the day should alert the clinician that the patient's therapy needs to be altered. Since most patients have variable tolerances to pain, patients should frequently be asked if the pain is interfering with their daily activities. As some patients are unwilling to admit to having increased pain because this may be associated with progression of their underlying disease, this question often provides insight into the level of pain.

**Location:** Precisely locating the discomfort can also help in determining the type and nature of the

pain. Well-localized pain that does not radiate may be somatic in nature and be indicative of metastatic disease to the bone. Pain that follows a dermatomal distribution may be neuropathic in nature and may represent a radiculopathy. Poorly localized, deep pain may be visceral in nature. Asking the patient to mark on a body outline to demonstrate the location of the pain will help the clinician to determine the type of pain that the patient is experiencing.

**Aggravating/Relieving Factors:** Factors that increase or decrease the intensity of the pain can aid in the management of the patient's symptoms and reveal the efficacy of treatment. Pain that increases with movement, especially if an extremity is involved, often signifies bony involvement of that limb. Pain that intensifies in the recumbent position may mean involvement of the spine, and prompt action should be undertaken. Pain that worsens with a light touch is known as allodynia and may be consistent with neuropathic pain.

**Quality:** Patients should be offered a list of adjectives to describe their pain. Pain that is described as burning, shooting, electrical, "pins and needles," and often constant in nature is typically neuropathic. Somatic pain is often described as sharp, aching, constant, well localized, and worse with movement. Visceral pain can be deep, lancinating, episodic, colicky, and often poorly localized.

**Timing:** Pain that increases or intensifies at certain times of the day generally indicates that the medication dosage is inadequate. More frequent use or changing to longer-acting medications should be considered.

**Radiation:** Pain that radiates over dermatomal or nerve distributions can help in localizing the tumor or provide insight into the type of the pain.

**Meaning of the Pain:** Many patients regard an increase in pain as a sign that their disease is progressing or that uncontrolled pain is inevitable. This can lead to feelings of despair and hopelessness. These patients need reassurance that their pain can be controlled and that their quality of life can be maintained. Table 1 describes a thorough pain assessment in a patient with advanced disease.

All patients should complete a standardized questionnaire or undergo a structured interview. The key to good pain management in patients with advanced disease is thorough and frequent assessment. The entire palliative care team can be useful in monitoring a patient's pain. Palliative care nurses are well trained in evaluating the patient's pain. A recent report revealed

that referring physicians were satisfied with the performances of hospice nurses in pain assessment and the recommendations offered by the nurses for pain control.<sup>7</sup> Frequent reassessment by nurses allows the practitioner to make management decisions quickly, thus resulting in rapid interventions in the management of the patient's pain. Patients are often unable to adequately rate their pain,<sup>7</sup> and it may be necessary to monitor behavior that could be indicative of pain in some

patients.<sup>8</sup> Behavior such as mood swings, agitation, restlessness, and increased fatigue may all signify an increase in the patient's pain. Frequent and thorough reassessment by nurses trained in palliative care who may recognize subtle behavior changes can greatly enhance symptom management. Realistic goals should be set with the patient and family regarding expectations of effective pain management.

**Table 1. — Pain Assessment Questionnaire for a Patient With Advanced Disease**

<p><b>Assessment of Pain Intensity and Character:</b></p> <p><b>Onset and temporal pattern:</b> When did your pain start? How often does it occur? Has its intensity changed? How long does it last? Is it constant?</p> <p><b>Location:</b> Where is your pain? Is there more than one site?</p> <p><b>Description:</b> What does your pain feel like? What words would you use to describe your pain?</p> <p><b>Intensity:</b> On a scale of 0-10, how would you rate your pain? How much does it hurt at its best/worst?</p> <p><b>Aggravating and relieving factors:</b> What makes your pain better/worse?</p> <p><b>Previous treatment:</b> What types of treatments have you tried to relieve your pain? Were they effective?</p> <p><b>Effect:</b> How does the pain affect physical and social function?</p> <p><b>Additional Pain Assessment:</b></p> <ul style="list-style-type: none"> <li>Develop an understanding of the cancer diagnosis and cancer treatment effects on the patient and caregiver.</li> <li>Understand the meaning of pain to the patient and family.</li> <li>Discuss significant past instances of pain and their effect on the patient.</li> <li>Discuss the patient's typical coping responses to stress or pain.</li> <li>Discuss the patient's knowledge of, curiosity about, preferences for, and expectations about pain management methods.</li> <li>Explain the patient's concerns about using controlled substances such as opioids, anxiolytics, or stimulants.</li> <li>Understand the economic effect of the pain and its treatment.</li> <li>Describe changes in mood that have occurred as a result of the pain.</li> </ul> <p><b>Comprehensive History and Physical Examination:</b></p> <p>A complete history and physical examination should be done. Past medical history, medication usage, and a thorough review of systems are required for a proper assessment resulting in good palliative care.</p> <p><b>Close Attention Should Be Given to the Following:</b></p> <ul style="list-style-type: none"> <li>Examine site of pain and evaluate common referral patterns.</li> <li>Perform pertinent neurologic evaluation.</li> <li>Head and neck pain (cranial nerve and fundoscopic evaluation).</li> <li>Back and neck pain (motor and sensory function in limbs; rectal and urinary sphincterfunction).</li> </ul> <p>Adapted from the Department of Health and Human Services, Agency for Health Care Policy and Research, Jacox A, Carr DB, Payne R (co-chairs). <i>Management of Cancer Pain</i>. Clinical Practice Guidelines 9:25, March 1995.</p>
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## Visceral, Somatic, and Neuropathic Pain

Visceral pain arises from direct stimulation of afferent nerves due to tumor infiltration of the soft tissue or viscera.<sup>9</sup> Stretching, distension, or ischemia of the viscera may cause visceral pain. This pain tends to be poorly localized and often ill defined. As already noted, visceral pain can be deep, aching, or colicky pain. In cancer patients, visceral pain may be caused not only by direct tumor infiltration, but also by variable conditions such as constipation, radiation, or chemotherapy.

Somatic pain in cancer patients is generally due to soft tissue inflammation or to metastatic disease to the bone. Bone pain is thought to be due to either direct stimulation of nociceptors in the periosteum, a release in inflammatory mediators, or an increase in interosseal pressure.<sup>10</sup> This type of pain is usually well localized and is described as sharp in nature. The pain is constant and increases with movement. The patient can often point directly to the site of the metastatic lesion.

Neuropathic pain is generally described as burning or electrical in nature. This type of pain is due to neuronal injury either by the effects of treatment or by tumor invasion. For example, cisplatin, vincristine, and procarbazine can be harmful to nerves. Neuropathic pain may not always be responsive to opioid therapy. Patients with neuropathic pain may report discomfort provoked by a stimulus that does not normally cause pain, such as light touch. Neuropathic pain may have a corresponding neurological deficit.

## Etiology of Pain

Pain may arise from different etiologies. It can be due to the direct effects of the cancer or caused by treatment of the disease. Surgery, radiation, and chemotherapy may all result in pain. The patient may also have chronic underlying disease that directly causes or contributes to pain. Diseases such as osteoarthritis, neuropathies, and vascular insufficiency can cause chronic pain or can exacerbate cancer pain. Since different modalities may be required to effectively treat the variable causes of pain, identifying and quantifying

all of the different causes of pain that affect the patient will help to determine the appropriate therapy.

## Pain Management

Symptom control in the home setting may differ from that provided in a more traditional setting such as a hospital or nursing home. In the home setting, the patient or family members provide much or most of the care. The caregivers administer the medications and report changes in the patient's status to the health care team. Although the health care team may visit frequently, the patient is dependent on family members for care, which necessitates good communication between the family and the health care team. Pain management must be responsive to the patient's changing symptoms, and care must be taken to respect the families wishes and limitations. Family members are often reluctant to give injections or administer medicines rectally. Break-through medications are often withheld for fear of getting their loved one "addicted" to opioids. Patients may be faced with either financial problems or the lack of an adequate caregiver. For these reasons, the patient's support system and environment must be evaluated. The members of the health care team must establish good lines of communication and trust with their patients and the patients' families, and they must recognize the limitations that may be present in each home.

In recognizing the need for improved pain management worldwide, the World Health Organization (WHO) instituted a three-step analgesic ladder as a basis for pain management<sup>11</sup>:

**Step 1 - Mild Pain:** acetaminophen or NSAID +/- adjuvant.

**Step 2 - Mild to Moderate:** weaker opioid for mild to moderate pain + acetaminophen or NSAID +/- adjuvant.

**Step 3 - Moderate to Severe Pain:** stronger opioid for moderate to severe pain + acetaminophen or NSAID +/- adjuvant.

The WHO also recommended that in the relief of cancer pain, medication be given according to the following framework:

**By Mouth:** Oral administration of medication is an effective and inexpensive method of medicating patients and should be used when possible. Medicines are easy to titrate using this route and are therefore the preferred method of administration.

**Around the Clock:** Patients should receive their pain medicines throughout the day either by routine administration or by sustained release preparations.

This allows for continuous pain relief and minimizes the episodes of pain the patient may suffer throughout a 24-hour period. The goal is to prevent pain rather than react to pain.

**By the Ladder:** The types of pain medications should be changed according to the severity of the pain, using the WHO stepwise approach as a guide to maximize pain relief.

**On an Individual Basis:** Each patient should be treated individually. Patients may require different dosages and/or interventions in order to attain good symptom relief.

**With Attention to Detail:** Patients need to be closely monitored for the efficacy of the intervention and the appearance of side effects during therapy.<sup>12</sup> The WHO has taken the initiative to advocate aggressive treatment of pain. It has recommended to practitioners that regimens be individualized for each patient and that pain generally can be well controlled by the appropriate use of opioids.

The National Comprehensive Cancer Network recently released practice guidelines for cancer pain.<sup>13</sup> While stressing the importance of a comprehensive pain assessment and ongoing reassessment, these guidelines recommend specific medications and doses dependent on the severity of pain. For both moderate and severe pain, short-acting opioids are recommended for initial titration. Guidelines for the appropriate length of time for follow-up reassessment as well as the recommended dosage changes are also provided. In addition, comprehensive treatment including educational activities and psychosocial support is recommended. The prevention of side effects is also stressed. Although these guidelines have yet to be validated, they appear more medication specific and clearer recommendations at varying pain levels.

## Opioid Use

Although the majority of patients with cancer have pain, proper use of opioids and adjuvant drugs can provide adequate relief in most cases. Jacox et al<sup>14</sup> found that 75%-85% of patients received adequate pain control with oral, rectal, and transdermal drugs. Opioid therapy is initiated when a trial of NSAIDs or acetaminophen is no longer effective. Opioids produce analgesia by binding to specific opioid receptors in the brain and spinal cord. Using the WHO guidelines, a weak opioid is initially used and then titrated to a stronger medication. Important elements in successful opioid use include frequent reassessment of the patient's pain, attention to the prevention of side effects, and effective communication. All

**Table 2. — Opioid Equivalents, Dosing, and Side Effects**

Opioid	Equianalgesic Dose / mg		Initial Dosing	Common Side Effects
	Oral	Parenteral		
Morphine sulfate	30	10	15-30 mg p.o. q4h	Sedation, constipation, nausea
Hydromorphone	4	1.5	2-4 mg p.o. q4h	Sedation, constipation, nausea
Hydrocodone	30	-	5-10 mg p.o. q4h	Sedation, constipation, nausea
Oxycodone	30	-	5-10 mg p.o. q4h	Sedation, constipation, nausea
Codeine	180	-	30-60 mg p.o. q4h	Pruritus, nausea, constipation
Meperidine	300	75	50-100 mg p.o. q4h	Confusion (elderly), convulsions
Methadone*	20	10	5 mg p.o. q6-8h	Prolonged half life, sedation

\* Methadone may be more powerful than indicated in this table.<sup>15</sup>

patients should begin a bowel regimen with a stool softener when opioid therapy is started. Bowel stimulants and suppositories are added if the need arises. Patients are also advised to be aware of possible side effects such as nausea/vomiting or sedation. Although these side effects are generally transient, additional medication may be indicated for relief of the side effects. Any change in the dosage of an opioid should be followed by a reassessment within 24 hours to ensure the effectiveness of the treatment and to preempt any adverse sequelae.

Opioids are the mainstay of pain control in patients with advanced disease, and they are effective in treating most types of pain. “Weak” opioids such as codeine and hydrocodone are used initially. These medications are frequently combined with acetaminophen or aspirin and are prescribed as 1-2 tablets every 4 hours for pain. An awareness of possible side effects is important, especially since many of the patients may be opioid naive. Regimens that include acetaminophen should be used cautiously in patients with compromised hepatic function from cirrhosis or metastatic liver disease.

Once these opioids are no longer effective, consideration must be given to changing to a stronger opioid (morphine sulfate or hydromorphone) or changing to oxycodone that is not compounded with acetaminophen so that higher doses can be used without the possible toxic effects of these agents. Morphine is often referred to as the “gold standard” in palliative care because it is effective, inexpensive, and easy to titrate, and it can administered using many routes including oral, rectal, parenteral, subcutaneous, and spinal. Titration typically begins with a low oral dose at the outset (Table 2). The typical starting dose is 10-30 mg every 4 hours as needed for pain with 10 mg every 2 hours when needed for breakthrough pain. When changing to a stronger opioid, the patient should be reassessed to monitor the efficacy of the new medication.

The goal of good pain management is to minimize both the patient’s pain and the need for breakthrough medication. When comfortable on a given dosing regi-

men, the patient should be converted to a long-acting medication. The patient will then have “around-the-clock” analgesia and will also be provided with breakthrough medication. If 30 mg of morphine every 4 hours provides good pain control, the regimen is changed to sustained-release morphine at 90 mg b.i.d., and breakthrough medication is continued. All patients should have access to breakthrough medication since up to two thirds of patients with well-controlled chronic pain have transitory breakthrough pain.<sup>15</sup> Some have used sustained-relief preparations when moving from step 1 to step 2 on the WHO ladder, although challenges with titration may occur.

Close monitoring of the patient’s symptoms through frequent reassessment dictates the need for titration of the opioid. Titrating the opioid can be accomplished either by adding the total amount of breakthrough medication to the long-acting preparation or by increasing the dose by 25%-50% from the previous day depending on the severity of the patient’s pain.<sup>16</sup> If the patient is taking 90 mg of a long-acting morphine preparation b.i.d. and also requires 20 mg of the short-acting morphine 4 times a day for breakthrough pain, the total daily amount of morphine being used is 260 mg. The long-acting preparation can then be changed to 130 mg of morphine b.i.d. with continued availability of the breakthrough medication at a higher dose.

Transdermal fentanyl patches (Duragesic) are commonplace in cancer pain management as a long-acting opioid. Like morphine, fentanyl is a strong  $\mu$  agonist. These patches are applied once every 3 days and deliver 25, 50, 75, 100  $\mu\text{g/hr}$  of fentanyl. Since this type of delivery system is easy to use and has good efficacy, it is becoming more frequently used by palliative care physicians. Since steady-state plasma concentrations are achieved in 36-48 hours, patients will often need breakthrough medications until the steady state is achieved.<sup>17</sup> Appropriate dosage should be based on the daily dose of supplementary opioid, using the ratio of approximately 50-75 mg/24 hr of oral morphine to a 25- $\mu\text{g/hr}$  increase in the Duragesic dose.<sup>18</sup> Like long-acting oral morphine

preparations, the efficacy of the treatment must be continually assessed. If a patient requires frequent use of the breakthrough medicine, the additional opioid used in a 24-hour period should be added, and the fentanyl dose should be adjusted accordingly.

Methadone is not frequently used in the care of patients with advanced disease. Methadone is a mixed  $\mu$  and  $\delta$  opioid agonist and an NMDA receptor antagonist. Its use is limited due to its long half-life (8-80 hours), which results in an accumulation of methadone. The accumulation makes it difficult to titrate methadone if the patient requires additional analgesia. Methadone had been used by patients with renal disease who were unable to tolerate morphine because of the accumulation of the morphine 6 glucuronide. However, with the development of newer opioids, methadone should be used only by clinicians experienced in its use.

Patients receiving palliative care may have increased pain, but the amount of breakthrough medication they may be using can be difficult to ascertain for several reasons. Patients may choose not to use the breakthrough medication because of uncertainties of addiction or disease progression or because of fears that there may be no effective medications if needed in the future. In these instances, if the patient is having increased pain, it is reasonable to increase the amount of the opioid by 25% to 50% from the previous day's use, depending on the severity of the pain. This will usually provide adequate analgesia.

Patients receiving palliative care often require frequent escalations in opioid dosage to attain good pain control. Foley et al<sup>19</sup> found that 20% of patients required three switches of their medication before finding an effective dose. Reassessment by the health care team is necessary after every medication change. Medications should be titrated with care, but it is important to understand that there is no ceiling for opioids and that the goal is to achieve acceptable pain control. Opioid use in older patients should be monitored closely. Virgano et al<sup>20</sup> showed that older patients may require lower doses of opioids, and therefore these medications should be used cautiously in this patient population.

Opioids should never be discontinued abruptly in patients receiving chronic opioids as this may cause an acute withdrawal reaction. Patients should be advised to never stop their opioid medication use, and they should have access to medications if they are travelling or away from home. If a patient has been taking medication and is no longer able to swallow, other means of administration should be used. Opioids may be administered rectally or transdermally. If

**Table 3. — Guidelines for Appropriate Use of Opioids**

- Frequently assess the patient's pain and response to treatment
- Communicate effectively with the patient and caregiver
- Anticipate side effects and be proactive in their prevention
- Never abruptly stop opioids  
(if the patient is unconscious, use alternate administration routes)
- Determine correct opioid dose by relief of the patient's pain
- Be aware that there is no ceiling in opioid dosing
- Medicate around the clock
- Use adjuvant medication when appropriate

needed, morphine and other opioids may be given via a subcutaneous or intravenous infusion, with dosages adjusted appropriately.

Table 3 lists several key factors to consider in determining the appropriate use of opioids.

## Tolerance and Addiction

Tolerance is defined as the progressive decline of the potency of an opioid with continued use. Patients may also develop a tolerance to the side effects of an opioid. When a physiologic tolerance to a particular opioid has been developed, the patient may have a cross tolerance to other opioids. Patients are often reluctant to increase the dose of their medication because they fear that the tolerance they have developed will lessen the effectiveness of the opioids at a later date. These patients should be assured that tolerance can develop as a normal result of opioid use and that a simple dose escalation is all that is usually required for additional pain control. Physical dependence is a physiologic state characterized by withdrawal manifestations after either an abrupt discontinuation, the administration of a opioid antagonist, or a dose reduction of the opioid in a patient who has been using an opioid for an extended period of time. Typical signs of withdrawal include agitation, tachycardia, diaphoresis, and insomnia.

All patients who have been using an opioid for an extended period of time typically develop physiological dependence. As already noted, opioid use should never be abruptly discontinued. A patient who is no longer able to take an oral opioid should be switched to an alternate route of administration (transdermal or rectal), even if the patient is unconscious. Those who have been using an opioid for an extended period of time and no longer require this type of medication may gradually taper off their opioid use under the supervision of a physician. Addiction is a psychological and behavioral syndrome characterized by drug-seeking behavior. Addiction is rare among patients being treated in palliative care.<sup>21</sup>

## Visceral Pain Management

Visceral pain is one type of nociceptive pain. As previously noted, this type of pain may be caused by a variety of factors such as direct invasion of a tumor, stretching of the hepatic capsule, or damage caused by radiation or chemotherapy. This type of pain is generally opioid responsive, and opioids are the principal line of therapy. Careful assessment of the patient, initiation of opioid therapy, and titration of the medication are all cornerstones of effective therapy.

## Somatic Pain Management

Somatic pain, another type of nociceptive pain, may arise from metastatic disease to the bone in cancer patients.

This pain is generally well localized and constant in nature. Somatic pain is responsive to opioids, but using an additional three-step therapeutic approach enhances treatment. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the mainstay of treatment of somatic pain. NSAIDs inhibit cyclooxygenase, which catalyzes the conversion of arachidonic acid to prostaglandins and leukotrienes. NSAIDs do not activate opioid receptors and thus can be safely used with opioids. The inhibition of prostaglandins is responsible for the properties of this group of medications that reduce inflammation and the release of substance P. NSAIDs are effective in relieving the pain of bony metastasis.<sup>22</sup> Major side effects caused by NSAIDs include gastrointestinal bleeding, renal toxicity, and hepatic dysfunction. Minor side effects include nausea, vomiting, dyspepsia, heartburn, bloating, and constipation.

There has been no conclusive evidence of one NSAID being more effective than another. Nonacetylated salicylates such as choline magnesium trisalicylate have fewer adverse effects on platelet aggregation and fewer gastrointestinal side effects than aspirin. They are favored by some palliative care physicians, as are the new COX-2 inhibitors, celecoxib and rofecoxib, because of their lower side effect profile. However, therapy should begin with a medication that perhaps is less costly. Dosages should be tailored to the individual patient by taking into account the patient's medical history and renal function. If one NSAID is not effective in relieving symptoms brought on by metastasis, switching to another class of NSAIDs may be worthwhile before discontinuing therapy.

If a patient has not had significant relief from somatic pain with NSAIDs, a trial of corticosteroids can be started. The usual starting dose of prednisone is 20 mg b.i.d. in a tapering dose. Corticosteroids can also be

Table 4. — Adjuvant Analgesics

Drug	Approximate Adult Daily Dose Range (ORAL)
<b>Antidepressants</b>	
Amitriptyline	25-150 mg p.o. q.h.s. (monitor levels)
Nortriptyline	25-100 mg p.o. q.h.s. (monitor levels)
Imipramine	25-150 mg p.o. q.h.s.
<b>Anticonvulsants</b>	
Carbamazepine	200-1600 mg p.o. q.d. divided doses (monitor levels)
Phenytoin	300-500 mg p.o. q.d. divided doses (monitor levels)
Gabapentin	100-600 mg p.o. t.i.d.
<b>Corticosteroids</b>	
Dexamethasone	4 mg p.o. q.d. b.i.d.
Prednisone	10-40 mg p.o. q.d.
<b>Local Anesthetics/Antiarrhythmic Drugs*</b>	
Lidocaine	5 mg/kg (also IV/SC)
Tocainide	20 mg/kg

\* Only clinicians who are experienced in the use of local anesthetics and antiarrhythmic agents should prescribe these drugs.

used as adjuvant therapy if the patient has a known hypersensitivity to NSAIDs. Corticosteroid therapy may cause a mild euphoria and increase the patient's appetite. Serious side effects include gastrointestinal bleeding, infections, and diabetes.

A patient with bone metastasis who does not have significant improvement despite the use of opioids, NSAIDs, and/or corticosteroids may be referred to a radiation oncologist for evaluation. Radiation therapy is generally recommended in all patients with bony metastasis, but for frail, homebound patients with advanced disease, it is usually recommended when the other treatment modalities have been shown to be ineffective.

## Neuropathic Pain Management

Managing neuropathic pain in patients with cancer can be challenging and difficult. Neuropathic pain can be caused by compression or infiltration of the nerves by tumor or by nerve trauma from surgery, radiation, or chemotherapy. Unlike visceral or somatic pain, the response to opioids in neuropathic pain may not be optimal. In the outpatient treatment of advanced cancer patients, a stepwise approach for medications is recommended: antidepressants or anticonvulsants followed by steroids or local anesthetics (Table 4).

In the initial assessment of neuropathic pain, nerve injury by compression must be ruled out. If nerve com-

pression is suspected (eg, spinal cord compression or metastatic disease with direct bony extension with nerve impingement), immediate action should be taken. Dexamethasone at 4 mg q.i.d. can be given as an initial step. The overall clinical picture then needs to be discussed with the patient, family, and staff. If the patient has advanced disease and is severely debilitated, invasive therapy may not be indicated. The main focus will be to provide maximum symptom relief; thus, not all patients with suspected disease involving the spine are referred for disease-related therapy. However, a patient who is less functionally impaired and desires more aggressive intervention should be referred for palliative radiation immediately. This decision should be based on the patient's health, functional status, and request for aggressive intervention.

For patients without suspected nerve compression but with typical pain that appears to be neuropathic in origin, the tricyclic antidepressants or antiseizure medications are used initially. The starting dose of the antidepressant medications (amitriptyline, desipramine, and nortriptyline) is usually 25 mg at bedtime. These medications are then titrated until a therapeutic level is reached. The clinical effectiveness as well as the therapeutic levels need to be closely monitored. Common problems with these medications include sedation and anticholinergic side effects. Studies of patients with diabetic neuropathy suggest that 60% of patients have experienced at least 50% relief of pain.<sup>23</sup> Although the mechanism of action is unclear, it is thought that the tricyclic antidepressants exert their effect by potentiation of descending inhibitory pathways.<sup>24</sup>

If the patient does not benefit from the medication once therapeutic levels are achieved, a trial of anticonvulsant medications may be initiated. These agents are thought to work by stabilizing the nerve cell membranes and by potentiating gamma-aminobutyric acid (GABA) inhibitory neurons.<sup>24</sup> Anticonvulsant medications include phenytoin, carbamazepine, valproic acid and, more recently, gabapentin. Like the tricyclics, the seizure medications should be started at a low dose and then gradually increased until either the patient attains sufficient relief or the medications cause intolerable side effects. Side effects include diplopia, headache, nystagmus, and ataxia. Like the tricyclics, plasma levels may need to be monitored frequently. These drugs tend to be more sedating in the elderly and must be used with caution.<sup>25</sup> Since patient response to these medications varies, other medications can be considered if the results do not provide relief within a reasonable time frame.

In homebound patients near the end of life, the tricyclic antidepressants and the antiseizure medications

provide the mainstay for treatment of neuropathic pain. Some centers use local anesthetics such as lidocaine and mexiletine as second-line agents. These agents have demonstrated only variable effectiveness in neuropathic cancer pain.<sup>26</sup> Typical dosing is 1.5 mg/kg IV for lidocaine and 250 mg p.o. b.i.d. for mexiletine. These drugs must be used with caution due to possible side effects including confusion and seizures. The administration of intravenous magnesium, which blocks the N-methyl-D-aspartate receptor for relief of neuropathic pain, has shown promise as a new agent.<sup>27</sup> Its usefulness in homebound patients with life-limiting cancer has yet to be determined.

Patients with a life-limiting illness who are receiving palliative care often have more than one pain syndrome. Grond et al<sup>28</sup> found that 31% of patients receiving treatment for pain related to their cancer had three or more distinct pain syndromes. To reach acceptable levels of symptom relief, patients with neuropathic pain may require both opioid and NSAID therapy in addition to specific neuropathic agents. Again, a thorough initial assessment with frequent follow-up is important. Patients with advanced cancer often need aggressive treatment for multiple pain syndromes and therefore require multiple medications. Each of these agents must be adjusted according to the specific pain syndrome for which it is being used. A patient who is receiving adequate analgesia for nociceptive pain with opioids may require adjustments in the tricyclic antidepressants for neuropathic pain and NSAIDs for somatic pain. Awareness of dosages, plasma levels of medications, side effects, and treatment efficacy or failure must all be monitored and followed closely. Input from the patient and reassessments by the entire health care team are critical for treatment success.

In treating cancer-related pain, clinicians must recognize that the management of patients may vary and that symptoms may change rapidly and often. The entire interdisciplinary team must work together to optimize the management of the patient. Frequent changes in dosage or medications may be necessary. Pain that progresses beyond good control may be more difficult to bring back to acceptable comfort levels. Slow response to changes in the patient's symptoms often results in needless suffering and emergency room visits.

## Infusion Therapy and Spinal Analgesia

Although most patients with advanced disease can usually achieve good pain control using simple routes of administration, some patients require more aggressive therapy for good pain control. The palliative care physician can use alternate routes of administration —

subcutaneous, intravenous, and spinal. If the patient's pain cannot be controlled by escalating doses of medication via the oral, rectal, or transdermal routes, more invasive therapies may be instituted. The subcutaneous route does not require venous access and can be performed in the home environment. Opioids may be given via this route and may be titrated rapidly by patient-controlled analgesia. The subcutaneous route is limited due to variability in absorption of medications in each individual patient depending on the amount of subcutaneous tissue. Since the delivery of the medication is subcutaneous, the amount of fluid and medication that can be effectively administered is limited.

Venous access is a more effective method of delivering larger doses of opioids when rapid escalation is required. Medications are not limited by the concentration, and the variation in absorption is not a factor. However, not all patients have easily obtainable venous access, and central or peripherally inserted central venous catheter (PICC) line placement is often required. The patient may need to have a line inserted in the hospital environment. Like all intravenous access, line infection is a continuous risk, and fastidious care of the insertion site is necessary.

Spinal analgesia should be considered for patients with pain that is poorly responsive to conventional routes. This route should also be considered for patients with poorly controlled pain or for those who cannot tolerate the side effects of oral opioids. Spinal analgesia requires not only a physician skilled in the insertion of the catheter, but also a staff trained in the care of this type of therapy. Its use is generally limited to patients who have not benefited from a more conservative approach and are not homebound.

## Nonpharmacologic Approaches to Pain Control

The mainstay in the treatment of cancer pain is pharmacologic intervention. Nonpharmacologic techniques, however, are also effective in relieving cancer pain.<sup>29</sup> These interventions can be divided into physical and psychosocial modalities. Physical interventions include massage, acupuncture, exercise, stretching, passive range of motion, heat therapy, transcutaneous electrical nerve stimulation, and immobilization. Psychosocial interventions include relaxation techniques, imagery, support groups, family counseling, education, biofeedback, and psychotherapy. These types of nonpharmacologic pain control methods are often offered by hospice organizations or palliative care teams and are available if requested by the patient or family or if recommended by the clinician.

## Case Presentation

A 75-year-old man had adenocarcinoma of the lung with metastasis to the lumbar spine. He initially received chemotherapy and radiation therapy to the spine but elected to forego further treatment. He complained of pain in his chest that he rated as a 9 out of 10. The patient also complained of a constant, burning pain in his sacral area radiating down his left leg. There was a well-localized boring pain midway on the left humerus that worsened with movement. The patient was bedbound and dependent on his daughter and elderly wife for his activities of daily living. He did not wish to go to the hospital and wanted to stay home with his family. His past medical history consisted of chronic obstructive pulmonary disease and hypertension. He smoked two packs of cigarettes per day for 50 years and did not use alcohol. His medication was 1-2 tablets of oxycodone (Percocet) every 6 hours as needed for pain.

Physical examination revealed a cachectic, elderly man in obvious distress due to pain. His blood pressure was 150/88, his pulse rate was 100 beats per minute, and his respiratory rate was 22 per minute. The oral mucosa was dry. He had a tachycardia and markedly diminished breath sounds bilaterally. The abdomen was soft, nontender, and without organomegaly. He had clubbing but no peripheral cyanosis or edema. Movement of his left arm elicited significant discomfort, and an area of extreme point tenderness was noted midway on the lateral humeral shaft. There was allodynia from light touch on the left buttock.

## Discussion

This patient's symptoms were not being well controlled. He had neuropathic pain in his left buttock, most likely caused by tumor infiltration and/or radiation therapy. It would be reasonable to prescribe 25 mg of amitriptyline p.o. per day. This medication could be titrated to a therapeutic level, with monitoring of plasma levels. If the patient does not receive adequate relief with the tricyclic, gabapentin or another anti-seizure medication could be considered. The patient also had pain that appeared to be somatic in nature. He had a well-localized area of pain and tenderness in his left arm that most likely represented a bone metastasis. Because this patient was homebound, radiation therapy was not an option.

An NSAID such as 600 mg of ibuprofen p.o. t.i.d. was a good option for initial treatment. If the NSAID proved to be ineffective, a trial of corticosteroids (eg, 4 mg of dexamethasone p.o. b.i.d.) could be considered. The nociceptive pain that he reported to be a 9 out of

10 needed to be treated promptly, beginning with 15-30 mg of oral morphine every 4 hours as needed for pain. The effectiveness of this regimen needed to be evaluated on a daily basis. Because his opioid regimen was changed, the patient was reassessed in his home the following day.

Over the course of the next few days, the patient attained good symptom control and was comfortable. He began taking 30 mg of morphine 6 times a day. At this time, it would be reasonable to convert the total dose of morphine he requires daily (180 mg) to 90 mg b.i.d. of a long-acting morphine preparation. The immediate-release oral morphine should be given for episodes of breakthrough pain. Serum plasma levels of the tricyclic antidepressant should be obtained and adjusted accordingly. If he starts to use the breakthrough medication frequently, the dose of long-acting morphine should be increased.

## Conclusions

Pharmacologic therapy is the mainstay of pain management in patients with advanced disease. The majority of patients can attain good pain control with the use of opioids and adjuvant medications. Simple means of administration such as oral, transdermal, or rectal can be used in managing the majority of pain syndromes. Principles of good pain management include a thorough initial assessment and frequent reassessment to monitor the efficacy of treatment and the onset of side effects. Physicians need to be knowledgeable of the types of pain syndromes while assessing pain.

Opioids need to be titrated to attain good pain control. Proactive treatment of side effects, appropriate escalation of medication, around-the-clock administration, and frequent assessment are all paramount to good pain control. Patients who do not respond to NSAIDs for control of their somatic pain should undergo a trial of corticosteroids. Neuropathic pain should be treated with tricyclic antidepressants or antiseizure medications. Monitoring of plasma levels is required.

Many cancer patients have more than one pain syndrome, and multiple medications are often indicated. Frequent assessment, rapid intervention, and appropriate use of opioids and their adjuvants are requisites for adequate pain control and an optimal quality of life.

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