

Pain in Advanced Cancer: Assessment and Management

Case Study and Commentary:

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The pain experienced by patients with cancer is a frequent dilemma confronting physicians during the diagnosis and treatment of the disease. Indeed, pain is among the most prevalent symptoms reported by cancer patients.¹ Adequately addressing this pain, however, is often made more difficult by the paucity of understanding of pain assessment and management among physicians.

The most significant reported barrier to effective pain management has been inadequate pain assessment.² The core-symptom inventory scales discussed in the following case study and developed by various clinical groups have shown promise in arriving at a better understanding of the predominant characteristics of pain in a variety of cancers.³ However, additional work is needed, given the broad array of cancers and their differing presentations and etiology—all of which can affect a patient's individual perception of pain.⁴

Nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and adjuvant drugs are all available to alleviate the pain associated with cancer. Other promising, recently developed therapies include the use of tissue agents such as adrenal medullary allografts; these allografts have been reported to provide pain relief to cancer patients when traditional pharmacologic therapy is no longer effective or feasible.^{5,6} Moreover, nontraditional medications such as ketamine might likewise play a role in diminishing cancer pain; in fact, low-dose ketamine has been reported to be effective in treating intractable cancer pain without causing its well-recognized neurotoxic adverse effects.⁷ The alternative therapies of acupuncture and hypnosis also have shown some promise in relieving the pain related to cancer, as well as the nausea associated with administration of chemotherapeutic agents.^{8,9,10} Other weapons with which the battle against

cancer pain is being fought include surgical innovations,^{11,12,13} antibiotics,¹⁴ corticosteroids,¹⁵ neuroleptic drugs,¹⁶ benzodiazepines,¹⁷ anticonvulsant agents,¹⁸ radiopharmaceuticals,¹⁹ psychiatric techniques,^{20,21} and functional sedation.²²

Physicians themselves might hold beliefs and assumptions that limit their use of appropriate pharmacologic agents in the treatment of pain in cancer patients. A common apprehension is that high levels of opioid analgesics might contribute to an increased mortality in these patients. Although studies have shown that increased opioid dosing does not contribute to any increased mortality of patients, there still seems to be a tremendous inertia to be overcome before changing the prescribing patterns of physicians engaged in treating cancer patients for pain.²³⁻²⁶ In addition, according to reports in the international literature, many pain management drugs might be unused and/or unknown to primary care and specialist physicians because of their high cost to nationalized health care systems.²⁷

In the United States, the Medicare system offers only limited coverage for appropriate end-of-life cancer care—in particular, hospice care—and does not include prescription drug coverage as one of its benefits.²⁸ Such an economically driven insurance structure not only prevents effective access by older patients to appropriate assessment and management of cancer pain but also precludes there being stable loci for

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studying the effectiveness of various pain therapies and other palliative treatments in cancer patients.²⁹

Professional, educational, and administrative reform is needed to provide a better arena for understanding, assessing, and treating cancer pain.^{30,31} Although difficulties exist in obtaining such reform on the national level, some individual hospitals have already established programs to educate physicians and nurses regarding appropriate assessment and management of pain in cancer patients. These preliminary efforts can be a model for future similar efforts, in the absence of broader legislative reform.³²

It is worth noting that decisions made by state boards of medicine regarding discipline of physicians who provide significant pain relief to cancer patients may be protected against arbitrary review. The US Supreme Court has held that patients have a right to palliative care under state statutes that recognize a distinction between palliative care and care that is solely intended to hasten death.^{33,34} As such, physicians should not hesitate to prescribe adequate and appropriate doses of medications to provide cancer patients with relief from the significant pain associated with their disease.

Pain and cancer are inextricably linked. Effective means to address pain in cancer patients requires both adequately assessing that pain and having a complete understanding of the therapeutic armamentarium available for treatment. By encouraging study in this area, using the appropriate tools to alleviate pain, and prescribing significant but appropriate amounts of analgesics, physicians can meaningfully improve the quality of patients' lives.

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Pain is the most common symptom associated with cancer, affecting 70% to 90% of patients with advanced disease.³⁵⁻³⁷ Direct tumor involvement accounts for 70% of the pain.^{37,38} Pain secondary to antineoplastic treatment accounts for 25%³⁷; a small proportion (3% to 10%) of patients experience pain from unassociated causes.³⁵⁻³⁸ Despite knowledge of methods that would allow for adequate cancer pain relief in 80% to 90% of patients, 25% of all cancer patients die with unrelieved pain.³⁷ Unrelieved pain can increase morbidity and impair quality of life.³⁹ It contributes to the severity of other commonly associated symptoms such as weakness, nausea and vomiting, depression, anorexia, and insomnia.^{35,38,40} In addition to its effect on physical well-being, pain also affects patients' psychological, social, and spiritual well-being.^{36,41}

The cost of unrelieved pain is significant and

includes the costs of repeat or prolonged hospitalization.⁴² In a study conducted at the City of Hope Medical Center, the cost of hospitalizations for unrelieved cancer pain was greater than \$5 million over a 12-month period.⁴² Implementation of strategies to improve cancer pain management led to a savings of more than \$2.7 million over 12 months at the same institution.⁴³

Barriers to adequate pain management in patients with advanced cancer include inadequate knowledge of pain management and concerns about patient addiction or tolerance.⁴⁴ Traditionally, health care professionals have had little or no training in pain management,⁴⁵⁻⁴⁷ and knowledge deficits in pain assessment and management have been well-documented.⁴⁸ The potential side effects of analgesics and misconceptions regarding their use in special populations (eg, children and the elderly) are significant factors that prevent health professionals from prescribing analgesics in appropriate doses.^{41,44} Patient barriers include a reluctance to report pain because of fears that pain is synonymous with disease progression and that escalating opioid doses will lead to addiction or tolerance. Institutional barriers include the low priority given cancer pain treatment and inadequate reimbursement.^{41,44}

Recently, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) issued pain management standards in an effort to hold institutions accountable.⁴⁹ In addition, to raise awareness about the importance of pain management, the American Pain Society has recommended that pain be incorporated into patient assessment data as the "fifth vital sign."⁵⁰

CASE STUDY

Initial Presentation

A 57-year-old man with colon cancer is admitted to a hospice program with bilateral leg and foot numbness and pain in the right upper quadrant, radiating to the right shoulder.

History

The patient was diagnosed 1 year ago with colon cancer metastatic to liver and possibly to bone. At that time, he underwent a partial resection of the large and small intestines followed by a 6-month course of chemotherapy. Over the past 2 months, he has experienced escalating severe pain in his shoulder, lower back, and legs in addition to periodic numbness in his lower extremities. There are no aggravating factors or patterns to the pain. He rates his shoulder and back discomfort an 8 on a 0-to-10 scale and describes the pain as intermittent and "sharp and grabbing." On further questioning, he states that a pain intensity of 2 would be

Table 1. Characteristics of Nociceptive and Neuropathic Cancer Pain

	Nociceptive Pain	Neuropathic Pain
Mechanism	Activation of nociceptors in skin, connective tissue, or bone (somatic pain) or viscera (visceral pain)	Peripheral or central neural structure injury caused by direct tumor infiltration or damage caused by treatment
Pathway	Normal pain pathway	Aberrant pain pathway
Quality of pain	Somatic: well-localized; sharp, aching, or throbbing Visceral: poorly localized; cramping, squeezing	Burning, tingling, or shock-like (lancinating) Allodynia, hyperalgesia, hyperesthesia often present
Responsiveness to therapy	Usually responds to opioids and/or adjuvants	Variable response to opioids and/or adjuvants

acceptable. The patient's current management plan does not control the numbness or pain, which interferes with his ability to perform daily activities and wakes him from sleep.

Present medications are transdermal fentanyl 100 µg/h every 3 days, morphine sulfate sustained-release 60 mg orally every 12 hours, and morphine sulfate immediate-release 15 mg orally every 4 hours as needed. The patient has no other significant medical history and no known allergies. He is a nonsmoker and has no history of alcohol or recreational drug use. He is a disabled salesman, married for 4 years, and has 3 daughters from a previous marriage, all of whom live out of state. Current financial difficulties have required his wife to return to work full-time, leaving the patient at home alone during the day.

Physical Examination

Physical examination reveals a cachectic African American man. Cardiopulmonary examination is remarkable for mild pedal edema bilaterally. His abdomen is soft and tender to palpation. Musculoskeletal examination elicits pain on movement of the right shoulder and hips. There is no palpable tenderness over the spine. Results of the neurologic examination are within normal limits, except for decreased pinprick and vibratory sensation in the lower extremities below the knees bilaterally.

QUESTION

- **How is pain defined and classified?**

DISCUSSION

Pain has been defined as an "unpleasant sensory and emotional experience associated with active or potential tissue damage or described in terms of such

damage."⁵¹ The pain experience is multidimensional and subjective; it is "whatever the person says it is, existing whenever the person experiencing it says it does."⁴¹ Pain may be acute or chronic³⁷ and may be classified as nociceptive or neuropathic (**Table 1**). Nociceptive pain occurs when receptors in skin and tissue are activated; it can be somatic or visceral. Somatic pain is typically well-localized and described as sharp, aching, throbbing, or pressure-like. Visceral pain is more diffuse and described as gnawing or cramping. Nociceptive pain usually is responsive to opioid therapy.³⁷

Neuropathic pain occurs in the absence of ongoing peripheral nociception. It is triggered by damage to peripheral and/or central nervous system tissue; this damage is most commonly caused by nerve infiltration or tumor compression. Spontaneous and ectopic firing of neurons produces pain characterized by dysesthesia, hyperalgesia, and allodynia.^{36,37,52} Neuropathic pain usually is less responsive to opioids.^{36,37,52}

The pain of advanced cancer is generally chronic, is usually of moderate or severe intensity, and can be nociceptive and/or neuropathic.³⁶ Frequently, patients with advanced disease experience numerous pains of mixed classification. Distinguishing the type of pain is essential for treatment.

QUESTION

- **What is the approach to pain assessment in patients with cancer?**

DISCUSSION

Pain assessment should be comprehensive and should assess the multidimensional nature of pain (**Table 2**). Various instruments have been validated to address a range of pain characteristics.^{53,54} The Brief Pain Inventory provides information on pain history,

Table 2. Pain Assessment

Assessment of pain intensity and character

Onset and temporal pattern—When did your pain start? How often does it occur? Has its intensity changed?

Location—Where is your pain? Is there more than one site?

Description—What does your pain feel like? What words would you use to describe your pain?

Intensity—On a scale of 0 to 10, with 0 being no pain and 10 being the worst pain you can imagine, how much does it hurt right now? How much does it hurt at its worst? How much does it hurt at its best?

Aggravating and relieving factors—What makes your pain better? What makes your pain worse?

Previous treatment—What types of treatments have you tried to relieve your pain? Were they and are they effective?

Effect—How does the pain affect physical and social function?

Psychosocial assessment

Effect and understanding of the cancer diagnosis and cancer treatment on the patient and the caregiver

The meaning of the pain to the patient and the family

Significant past instances of pain and their effect on the patient

The patient's typical coping responses to stress or pain

The patient's knowledge of, curiosity about, preferences for, and expectations about pain management methods

The patient's concerns about using controlled substances such as opioids, anxiolytics, or stimulants

The economic effect of the pain and its treatment

Changes in mood that have occurred as a result of the pain (eg, depression, anxiety)

Physical and neurologic examination

Examine site of pain and evaluate common referral patterns

Perform pertinent neurologic evaluation

Head and neck pain—cranial nerve and fundoscopic evaluation

Back and neck pain—motor and sensory function in limbs; rectal and urinary sphincter function

Diagnostic evaluation

Evaluate recurrence or progression of disease or tissue injury related to cancer treatment

Tumor markers and other blood tests

Radiologic studies

Neurophysiologic testing (eg, electromyography)

Perform appropriate radiologic studies and correlate normal and abnormal findings with physical and neurologic examination

Recognize limitations of diagnostic studies

Bone scan—false negatives in myeloma, lymphoma, previous radiotherapy sites

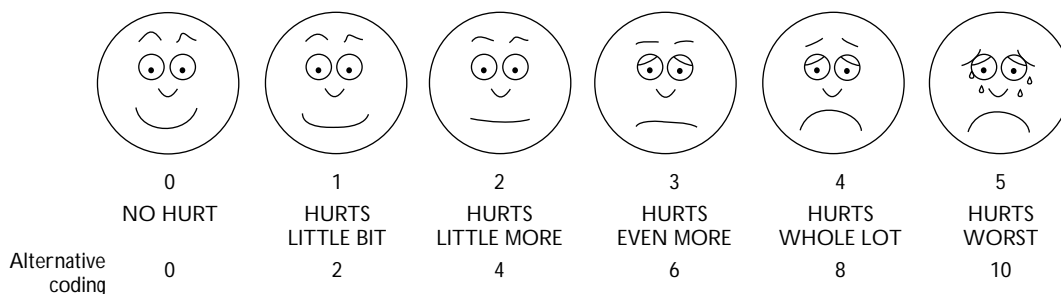
CT scan—good definition of bone and soft tissue but difficulty in imaging entire spine

MRI scan—bone definition not as good as CT; better images of spine and brain

CT = computed tomography; MRI = magnetic resonance imaging. (Adapted from Jacox A, Carr DB, Payne R, et al. Management of cancer pain. Clinical practice guideline No. 9. Rockville [MD]: US Department of Health and Human Services, Agency for Health Care Policy and Research; 1994. AHCPR Pub. No. 94-0592.)

intensity, location, quality, and impact on quality of life (**Figure 1**). Other instruments that measure pain intensity are available as well. The most frequently used scale asks patients to rate their pain from 0 to 10, with 0 being no pain and 10 being the worst pain imaginable. Numeric rating and categorical, facial, and visual ana-

logue scales can be used to quantify pain intensity in diverse patient populations (**Figure 2**). Research has demonstrated that most patients, even those who are elderly and cognitively impaired, can be taught to use some form of rating system.⁵⁵ To evaluate the effectiveness of pain management, a goal level of acceptable



Explain to the person that each face is for a person who feels happy because he has no pain (hurt) or sad because he has some or a lot of pain. Face 0 is very happy because he doesn't hurt at all. Face 1 hurts just a little bit. Face 2 hurts a little more. Face 3 hurts even more. Face 4 hurts a whole lot. Face 5 hurts as much as you can imagine, although you don't have to be crying to feel this bad. Ask the person to choose the face that best describes how he is feeling.

Rating scale is recommended for persons age 3 years and older.

Brief word instructions: Point to each face using the words to describe the pain intensity. Ask the child to choose face that best describes own pain and record the appropriate number.

Figure 2. Wong-Baker FACES Pain Rating Scale. (Reproduced with permission from Wong DL, Hockenberry-Eaton M, Wilson D, et al. Wong's essentials of pediatric nursing. 6th ed. St. Louis: Mosby; 2001:1301. Copyrighted by Mosby, Inc.)

pain intensity should be established by the patient and identified numerically.

QUESTION

- **What are the distinguishing characteristics of this patient's pain ?**

DISCUSSION

The assessment of this patient's pain reveals mixed nociceptive and neuropathic pain. The somatic shoulder, back, and leg pain are intense, continuous, and aggravated by movement—features characteristic of nociceptive pain. Neuropathic pain is evidenced in the intermittent numbness and tingling in the lower extremities. In patients with advanced cancer and bone metastases, spinal cord compression is a major concern. However, the chronic nature of this patient's pain and the lack of focal neurologic weakness make this diagnosis unlikely.

QUESTION

- **What are principles of pharmacologic management of cancer pain?**

DISCUSSION

Analgesic Ladder

In 1986, the World Health Organization (WHO) introduced the "analgesic ladder"⁵⁶ (Figure 3), which presents a progressive approach to the use of analgesic

drugs for pain management. The use of nonopioid agents such as acetaminophen and NSAIDs is recommended for mild pain and as adjuvant medication for moderate to severe pain. As symptoms increase, step 2 opioids such as hydrocodone or low-dose morphine or oxycodone may be used. Patients with moderate pain are commonly treated with a combination product containing acetaminophen or aspirin and an opioid; the doses of these combination products are limited by the maximum recommended dose of the nonopioid. When the maximum dose of the combination product fails to adequately control the patient's pain, the patient should be switched to a pure opioid.^{36,56,57} Step 3 opioids, such as morphine or hydromorphone, are used in the management of persistent or escalating pain.^{36,56-58}

In 1990, WHO published a simple, well-validated method for assuring the rational titration of therapy for cancer patients.⁵⁶ The 5 essential concepts of this method are

- By the mouth
- By the clock
- By the ladder
- For the individual
- With attention to detail

In 1994, the Agency for Health Care Policy and Research (now the Agency for Healthcare Research and Quality) published clinical practice guidelines consistent with the WHO approach, including recommendations for drugs, doses, and routes of administration

as well as titration techniques for opioid and coanalgesic therapies.⁴⁴ These recommendations, based on research and expert opinion, define an approach to care that is effective in providing symptom relief for approximately 80% of patients.^{35,37,44,50}

Nonopioids

The first step in the WHO approach is the use of acetaminophen, aspirin, or another NSAID for mild to moderate pain, particularly pain of a somatic origin.^{56,59} Unlike opioid analgesics, nonopioids have a “ceiling effect” for analgesia (ie, they reach a point at which no therapeutic gain is achieved by increasing doses beyond those recommended). Acetaminophen, while effective and relatively safe, must be taken 4 times per day for continuous effect. Doses greater than 4 g are not recommended because of the risk of hepatotoxicity. Acetaminophen and NSAIDs can be combined safely.

There is a sufficient body of evidence to support the use of NSAIDs for the treatment of pain caused by bony metastasis or soft tissue inflammation.⁵⁹⁻⁶¹ NSAIDs exert analgesic, antipyretic, and anti-inflammatory effects primarily by inhibiting the cyclooxygenase (COX) enzyme, thereby blocking prostaglandin synthesis. In order to maximize efficacy and minimize potential toxicities, NSAID treatment should begin at the lowest recommended dosages. Adverse reactions include gastrointestinal (GI) irritation, hepatic and renal toxicity, bronchospasm, and decreased platelet aggregation. To minimize GI toxicity, H₂ blockers have been recommended; however, only misoprostol or high-dose H₂ blockers are truly cytoprotective.³⁶ When treating cancer pain, it is sensible to choose an NSAID with a short half-life to permit flexible dosing.⁵⁹ Newer NSAID agents with greater specificity for COX-2 inhibition provide analgesia with less GI toxicity.^{62,63} The use of these NSAIDs is indicated in patients at risk for GI hemorrhage and those with known platelet abnormalities. The cost of these agents, however, is considerable.^{62,63}

Opioids

When cancer pain persists or increases, an opioid should be added to the NSAID.^{36,57} Morphine, the first-line agent for moderate to severe cancer pain, is available in a variety of formulations and offers flexibility in routes of administration when the oral route is no longer practical. Extensive first-pass elimination occurs following oral administration, resulting in a bioavailability of 20% to 30%.⁵⁷ As a result, the parenteral-to-oral potency dosing ratio for morphine is 1:3.^{44,57}

For an opioid-naïve patient with severe pain, an acceptable starting dose of morphine is 10 to 20 mg

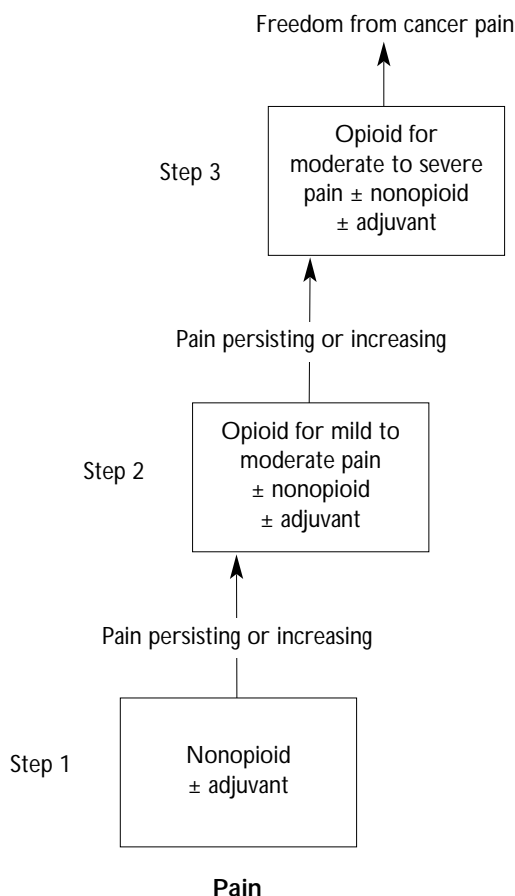


Figure 3. World Health Organization 3-step analgesic ladder. (Adapted with permission from World Health Organization. Cancer pain relief and palliative care. Geneva: The Organization; 1990.)

orally every 4 hours, with rescue doses at 25% of 50% of the regular dose.⁵⁷ The dosage is titrated upward until the patient’s pain level is acceptable or until behavioral indicators in nonverbal patients reflect pain control. Dose adjustments for hepatic and renal impairment may be necessary. Because of the accumulation of morphine-6-glucuronide in renal failure patients, the frequency of administration may require an increase to every 8 hours.³⁶ When pain control is stable for 24 hours, conversion to a sustained-release form may be preferred for the convenience of twice-daily dosing.⁶⁴

Patients vary greatly in opioid dose requirements to manage pain. Concern about tolerance should not influence opioid use early in the disease course, and worsening pain should not be attributed to tolerance but rather to disease progression.⁵⁷ The presence of

opioid tolerance and physical dependence does not equate with addiction.⁴⁴

Other opioids with analgesic properties similar to that of morphine (eg, oxycodone, hydromorphone, fentanyl) can be used should the patient have a morphine intolerance. The use of methadone, a potent long-acting and inexpensive opioid, has demonstrated efficacy in neuropathic pain.⁶⁵ The use of agonist-antagonist opioids as well as meperidine is contraindicated in the cancer patient population. Meperidine's analgesic potency is low, and its active metabolite, normeperidine, can accumulate with the potential to cause seizures.^{35,44,57}

Adverse effects associated with opioids are manageable and should not interfere with the goal of achieving pain control. Common side effects that should be anticipated by the clinician include constipation, sedation, and nausea and vomiting. Occasionally myoclonus, seizures, confusion, and pruritus may occur. Because constipation is a universal complication of opioid use and because tolerance to the constipating effects of opioids does not occur, a prophylactic stimulant laxative should be initiated with the opioid therapy unless otherwise contraindicated.⁴⁴ Transitory sedation is common when an opioid is initiated or when the dosage is increased substantially; however, tolerance to sedation develops rapidly in most patients. Persistent opioid-induced sedation is best managed by decreasing the opioid in each dose and increasing the dosing frequency. In some patients, it may be necessary to change opioids or add a central nervous system stimulant such as methylphenidate.^{44,66} Opioid-induced nausea and vomiting can be managed with antiemetics selected on the basis of their mechanism of action. The most common cause of morphine-induced vomiting is stimulation of the chemoreceptor trigger zone in the brainstem; this is best treated with haloperidol.^{36,64} Vomiting caused by delayed gastric emptying occurs in 5% to 10% of patients and can be managed with a prokinetic agent such as metoclopramide.⁶⁶

Routes of administration. Opioids should be administered by the least invasive, most convenient, and most cost-effective route that will provide adequate analgesia.^{57,64} The oral route is the preferred route. Oral opioids are available in tablet, capsule, and liquid forms and in immediate- and sustained-release formulations.⁴⁴ These agents have a slower onset of action, delayed peak time, and longer duration of effect than opioids given by the parenteral route.⁵⁷ When patients cannot tolerate oral medications, the rectal route provides a noninvasive alternative to parenteral administration. The potency of rectally administered opioids is nearly equal to that of

oral opioids. Fentanyl is available in transdermal and oral transmucosal forms. Although noninvasive, transdermal fentanyl is not suitable for rapid-dose titration and should only be considered for patients with constant stable pain.⁴⁴ Oral transmucosal fentanyl is indicated for breakthrough pain in the opioid-tolerant patient, although this agent is expensive.⁶⁷

The parenteral route should be considered in patients who have impaired swallowing or GI obstruction or who require rapid onset of analgesia. Continuous infusion of opioids produces a more constant plasma level, reduces adverse effects, and is better tolerated by patients than is intermittent infusion.⁶⁴ Using a subcutaneous route for continuous infusion can provide effective analgesia without the discomfort associated with intravenous site access and administration. Intramuscular injection is not recommended. The intraspinal route requires interventional expertise and should be reserved for patients who have not achieved analgesia despite maximum opioid and coanalgesic dosing through less invasive methods.⁶⁸

Equianalgesic dosing. When a patient is switched from one opioid to another or when the route of administration is changed, drug-dependent differences in dosing must be recognized. Dosage conversions using the equianalgesic dose table (**Table 3**) help to prevent both underdosing and overdosing.^{36,57,69} Equianalgesic tables provide a starting point for such conversions, although patients will require individual assessment and titration.

If pain control has been adequate, the dose of a new drug should be 50% to 75% of the equianalgesic dose to account for incomplete cross-tolerance. In the case of inadequate pain control, the starting dose of the new opioid should be 75% to 100% of the equianalgesic dose, depending on pain intensity.⁵⁷ Inadequate pain relief requires an escalation of the opioid dose until analgesia is achieved or until side effects become intolerable.^{36,57,69}

Scheduled dosing. Because patients with persistent cancer pain require continuous relief, it is important to use opioids on a regular "around-the-clock" (ATC) schedule rather than "as needed."^{44,57,69} In addition to an ATC opioid regimen, all patients should have a plan for rescue dosing. Rescue doses are supplements given on an as-needed basis to treat pain that breaks through scheduled medication. The rescue-dose drug should be the same as the scheduled opioid (eg, short-acting morphine for breakthrough with sustained-release morphine) except in the case of transdermal fentanyl, which requires an alternative rescue opioid.⁵⁷ The recommended dose for breakthrough pain is one sixth of

Table 3. Dose Equivalents for Opioid Analgesics

Drug	Approximate Equianalgesic Dose	
	Oral	Parenteral
Opioid agonists		
Morphine	30 mg q 3–4 h (repeat around-the-clock dosing) 60 mg q 3–4 h (single dose or intermittent dosing)	10 mg q 3–4 h
Morphine, controlled-release (MS Contin, Oramorph)	90–120 mg q 12 h	N/A
Hydromorphone (Dilaudid)	7.5 mg q 3–4 h	1.5 mg q 3–4 h
Levorphanol (Levo-Dromoran)	4 mg q 6–8 h	2 mg q 6–8 h
Meperidine (Demerol)	300 mg q 2–3 h	100 mg q 3 h
Methadone (Dolophine, other)	20 mg q 6–8 h	10 mg q 6–8 h
Oxymorphone (Numorphan)	N/A	1 mg q 3–4 h
Combination opioid/NSAID preparations		
Codeine (with aspirin or acetaminophen)*	180–200 mg q 3–4 h	130 mg q 3–4 h
Hydrocodone (in Lorcet, Lortab, Vicodin, others)	30 mg q 3–4 h	N/A
Oxycodone (Roxicodone, also in Percocet, Percodan, Tylox, others)	30 mg q 3–4 h	N/A

Note: Doses given for opioid-naïve adults and children \geq 50 kg. Published tables vary in the suggested doses that are equianalgesic to morphine. Clinical response is the criterion that must be applied for each patient; titration to clinical responses is necessary. N/A = not available; NSAID = nonsteroidal anti-inflammatory drug; q = every. (Adapted from Jacox A, Carr DB, Payne R, et al. Management of cancer pain. Clinical practice guideline No. 9. Rockville (MD): US Department of Health and Human Services, Agency for Health Care Policy and Research; 1994. AHCPR Pub. No. 94-0592.)

*Codeine doses > 65 mg often are not appropriate.

the 24-hour baseline dose. For example, a patient receiving 180 mg of sustained-release morphine twice daily would require a breakthrough dose of 60 mg ($180 \text{ mg} \times 2 = 360 \text{ mg}/24 \text{ hr}$). One sixth of 360 mg/day would be a 60-mg rescue dose. Oral rescue doses are generally offered every 60 to 90 minutes and parenterally every 15 minutes. Rescue dosing beyond 2 to 3 times per day suggests the need to increase the scheduled dose.

Adjuvant Agents

Adjuvant analgesics used for cancer pain include antidepressants, anticonvulsants, local anesthetics, α_2 -adrenergic agonists, and corticosteroids.^{59,60} Commonly used to treat neuropathic pain syndromes, antidepressants have been indicated in the cancer pain population for persistent neuropathic pain unresponsive to opioid therapy and for pain associated with depression or insomnia.⁶⁰ Historically, amitriptyline has been the preferred tricyclic antidepressant because of the abundance of data supporting its analgesic efficacy.⁶¹ Analgesic response usually occurs 4 to 7 days after the effective daily dose is established. Desipramine, a second-generation tricyclic antidepressant, has less sedative and anticholinergic effects than does amitriptyline

but has analgesic effectiveness. Selective serotonin reuptake inhibitors have not been adequately studied for the treatment of neuropathic pain in cancer patients.

Anticonvulsants have been particularly useful for lancinating, shooting, electrical pain and paroxysmal dysesthesias. Although evidence is best for carbamazepine, anecdotal experience suggests phenytoin, clonazepam, and valproate may also be effective.⁶⁰ Of the newer anticonvulsants, gabapentin has been shown effective in neuropathic pain of various types that is unresponsive to amitriptyline or carbamazepine.^{66,70} Analgesic effect appears to be dose dependent. Gabapentin is usually administered 3 times daily, initiated at 100 mg 3 times daily and gradually increased to 3600 mg/day.

Oral and parenteral local anesthetics have been used for continuous dysesthesias associated with peripheral nervous system disorders that are opioid refractory. These drugs block sodium channels and thereby block the generation of an action potential and pain transmission.⁷¹

Corticosteroids have many potential indications for neuropathic pain, diverse types of cancer pain, headache from increased intracranial pressure, and pain caused by obstruction of a hollow viscus. The exact mechanism of

analgesia is unknown, although it is suspected that shrinkage of tumor mass, reduction of peritumoral edema, decreased tissue concentration of some inflammatory mediators, and temperance of aberrant electrical activity from damaged nerves may all be involved.⁶⁰ Administration guidelines recommend high-dose therapy for emergent pain associated with worsening malignant plexopathy and low-dose therapy for advanced cancer pain that is persistent despite optimal opioid dosing. Dexamethasone has the added benefit of improving mood, appetite, and energy and tends to cause less fluid retention than does prednisone.⁶⁶

Adjuvant analgesics are often used in the management of malignant bone pain. Pain associated with bone metastasis may respond to treatment with an opioid, a combination of opioid and NSAID, and corticosteroids.^{59,60} Other adjuvants potentially useful for bone pain include calcitonin, bisphosphonate compounds, gallium nitrate, and selected radiopharmaceuticals.⁶⁰

QUESTION

- **What is the role of nonpharmacologic therapy?**

DISCUSSION

Although analgesics are the mainstay of cancer pain management, there is also a role for nonpharmacologic pain treatment.^{44,58,72} These therapies may diminish the emotional components of pain, strengthen coping abilities, reduce perceived threat, offer patient and family a sense of control, foster hope, provide comfort, and improve quality of life.⁷² Physical modalities such as cutaneous stimulation (massage, hot and cold therapy, and vibration), transcutaneous electrical nerve stimulation, and acupuncture may complement analgesic therapy. Psychosocial interventions such as relaxation and imagery can be used to achieve a state of mental and physical relaxation and can influence the interpretation of pain.^{44,58,72} Art therapy, music therapy, and spiritual counseling may decrease the perception of pain.⁷³

Clinical Course

The patient's escalating pain is managed by maximizing opioid dosing. Over the course of 3 months, his morphine dose increases to 720 mg per day in addition to 300 µg/h of transdermal fentanyl every 3 days.

At the beginning of his fourth month in the hospice program, the patient is admitted to an acute symptom control facility with excruciating uncontrolled pain in his legs and left shoulder, radiating to his left hand. He rates the pain as a 7 usually, but it frequently becomes a

10 intermittently throughout the day. The pain has also been keeping him awake at night.

QUESTION

- **What is the recommended approach to pain not responding to conventional therapy?**

DISCUSSION

Although most patients achieve pain control using oral analgesic regimens, a proportion of patients have pain that is unresponsive to pure opioid agonists and requires rotation to an alternative opioid.⁷⁴ Given the variability of response, it is recommended that all opioid trials should include dose titration until adequate analgesia or intolerable side effects occur.^{36,57} Should an opioid trial fail, a different opioid agonist may be effective.⁷⁴ If adverse effects are intolerable, spinal administration of an opioid should be considered; however, only a small number of patients (< 2%) with cancer pain are candidates for spinal treatment. Indiscriminate use of spinal opioids is not recommended.⁷¹ A major indication for intraspinal opioid delivery is the presence of severe side effects (typically sedation or confusion) from oral opioids.⁷¹ Administration of low opioid doses, local anesthetics, or other agents near sites of activity in the spinal cord may provide relief to these patients.⁷¹

Referral to a palliative medicine or pain specialist should be considered in cases of refractory pain. Palliative medicine provides total care of the body, mind, and spirit, addressing physical pain as well as emotional and spiritual pain that is often unresponsive to pharmacologic intervention. Consultation with a specialist in pain medicine may be warranted when the pain problem is complex or when interventional expertise is required.⁴⁹

Methadone

Neuropathic pain is a frequent problem in patients with advanced cancer. Neuropathic pain resulting from direct tumor infiltration of neural structures or from secondary effects of cancer treatment is present in more than 30% of cancer patients.⁷⁵ The variable response of this kind of pain to opioids and adjuvants makes its management challenging.^{75,76}

Methadone is a synthetic opioid analgesic that can be used as an alternative to morphine for relief of acute or persistent pain.^{75,77,78} Methadone is a useful analgesic in patients with morphine intolerance, morphine allergy, or renal failure.³⁶ In addition to its µ-receptor agonist activity, this agent also has significant effects on the

delta receptor as well as a blocking effect on the *N*-methyl-D-aspartate (NMDA) receptors. Blocking the NMDA receptor may prevent the abnormal pain transmission associated with neuropathic pain. Because of its NMDA-receptor antagonism, methadone is recognized for use in opioid-resistant and neuropathic pain.^{66,79} Improved pain relief may allow for opioid dose reduction and consequentially minimize side effects. The low cost of methadone makes it an inexpensive alternative to the use of multiple adjuvant agents.⁷⁹

Methadone dosing is complex because its long half-life (16 to 80 hours) increases the risk of drug accumulation.^{77,80} Patients usually require frequent doses when the drug is initiated, but the interval between dosing becomes progressively longer. Maintenance therapy for stable pain is usually 2 to 4 doses per day.⁵⁷ Because the time to achieve steady-state levels (5 half-lives) is about 5 days, dosing changes should not be made more frequently than every 3 to 5 days.⁷⁹ Methadone can be given orally, sublingually, or rectally. Bioavailability of rectal administration is 80% of the oral route. Subcutaneous administration is associated with tissue irritation, and intravenous dosing is not recommended because of the drug's long half-life.³⁶ Similar to other opioids, the side effects of methadone can include sedation, nausea, and respiratory depression; however, methadone generally causes less nausea and sedation than does morphine. Also, constipation is usually less problematic than with other opioids.⁸¹ Drug-drug interactions have been reported with several agents.⁷⁸ Caution is advised when methadone is used in elderly patients or in those with dementia or delirium.⁷⁹

Initiation of Methadone

The morphine and fentanyl patches are discontinued, and the patient is started on a scheduled dose of methadone 20 mg every 6 hours, with methadone 10 mg every 6 hours as needed for breakthrough pain. Within 4 days, the pain intensity decreases from a 7 to a 4 and finally to a 2. For the first time in months, the patient is able to raise his left arm above his head without pain.

QUESTION

- **Should adjuvant therapies have been tried in this case before initiating methadone?**

DISCUSSION

The nature of the patient's uncontrolled pain appeared to be neuropathic, possibly radicular. Although adjuvant analgesic agents have been used successfully

in neuropathic pain, they should be initiated after the opioid regimen has been optimized.⁷⁶ In this case, morphine and fentanyl doses were escalated as pain increased. However, there was concern that opioid resistance was limiting pain control. Methadone, with its NMDA activity, is an appropriate analgesic agent for neuropathic, opioid-resistant pain. Using methadone provides relief of both nociceptive and neuropathic pain with a single agent, eliminating potential side effects of the tricyclic antidepressants, and is less costly than gabapentin.

SUMMARY

Achieving adequate pain management in advanced cancer patients is a realistic goal. Comprehensive assessment and classification of the type of pain experienced is essential to determining the appropriate pharmacologic and nonpharmacologic interventions. Patients with severe pain require aggressive management with opioids and adjuvant analgesics. Opioid dosing should be titrated to analgesia or intolerable side effects. Control of neuropathic cancer pain poses an additional challenge to the clinician. Methadone is an inexpensive second-line agent capable of treating both nociceptive and refractory neuropathic pain, particularly when used in combination with adjuvant analgesics. **HP**

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