

CANCER PAIN GOALS AND OBJECTIVES

Course Description

“Cancer Pain” is a home study continuing education course for rehabilitation professionals. This course presents updated information about cancer pain including sections on assessment, physical examination, outcome measures, pharmacological management, physical and psychosocial interventions, cognitive-behavioral interventions, anti-neoplastic interventions, and invasive interventions.

Course Rationale

The purpose of this course is to present current information about cancer pain. Both therapists and therapy assistants will find this information pertinent and useful when creating and implementing rehabilitation programs that address the challenges and needs specific to individuals who experience pain secondary to cancer.

Course Goals and Objectives

Upon completion of this course, the therapist or assistant will be able to:

1. identify barriers to effective pain management of patients with cancer
2. recognize common cancer pain syndromes
3. Identify the key components of an initial pain assessment
4. understand the principles of Step I analgesic administration including types of medications, dosages, routes of administration, contraindications, and side effects
5. understand the principles of opioid administration including types of medications, dosages, switching, routes of administration, contraindications, and side effects
6. recognize the common adjuvant drugs used for cancer pain management
7. identify and understand the physical interventions utilized to manage cancer pain
8. identify and understand cognitive-behavioral techniques used to manage cancer pain
9. identify antineoplastic interventions used to manage cancer pain
10. identify invasive interventions used to manage cancer pain
11. recognize special considerations for assessing and treating cancer pain in geriatric individuals

Course Instructor

Michael Niss, DPT

Target Audience

Physical therapists, physical therapist assistants, occupational therapists, and occupational therapist assistants

Course Educational Level

This course is applicable for introductory learners.

Course Prerequisites

None

Criteria for issuance of Continuing Education Credits

A documented score of 70% or greater on the written post-test.

Continuing Education Credits

Four (4) hours of continuing education credit (4 NBCOT PDUs/4 contact hours)
AOTA - .4 AOTA CEU, Category 1: Domain of OT – Client Factors, Context

Determination of Continuing Education Contact Hours

“Cancer Pain” has been established to be a 4 hour continuing education program. This determination is based on an accepted standard for home-based self-study courses of 10-12 pages of text (12 pt font) per hour. The complete instructional text for this course is 48 pages (excluding References and Post-Test).

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CANCER PAIN Course Outline

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Overview

The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Cancer pain can be managed effectively through relatively simple means in up to 90% of the 8 million Americans who have cancer or a history of cancer. Unfortunately, pain associated with cancer is frequently undertreated.¹

Cancer pain or associated symptoms cannot always be entirely eliminated; however, appropriate use of available therapies can effectively relieve pain in most patients. Pain management improves the patient's quality of life throughout all stages of the disease. Patients with advanced cancer experience multiple concurrent symptoms with pain; therefore, optimal pain management necessitates a systematic symptom assessment and appropriate management for optimal quality of life.² Despite the wide range of available pain management therapies, data are insufficient to guide their use in children, adolescents, older adults, and special populations.³

State and local laws often restrict the medical use of opioids to relieve cancer pain, and third-party payers may not reimburse for noninvasive pain control treatments. Thus, clinicians should work with regulators, state cancer pain initiatives, or other groups to eliminate these health care system barriers to effective pain management. Changes in health care delivery may create additional disincentives for clinicians to practice effective pain management.

Barriers to Effective Pain Management

- Problems related to health care professionals:
 - Inadequate knowledge of pain management.
 - Poor assessment of pain.⁴
 - Concern about regulation of controlled substances.
 - Fear of patient addiction.
 - Concern about side effects of analgesics.
 - Concern about patients becoming tolerant to analgesics.
- Problems related to patients:
 - Reluctance to report pain.
 - Concern about distracting physicians from treatment of underlying disease.
 - Fear that pain means disease is worse.
 - Concern about not being a “good” patient.
 - Reluctance to take pain medications.
 - Fear of addiction or of being thought of as an addict (this fear may be more pronounced in minority patients).⁵
 - Worries about unmanageable side effects.

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- Concern about becoming tolerant to pain medications.
- Poor adherence with the prescribed analgesic regimen.⁶
- Problems related to the health care system:
 - Low priority given to cancer pain treatment.
 - Inadequate reimbursement.
 - The most appropriate treatment may not be reimbursed or may be too costly for patients and families.
 - Restrictive regulation of controlled substances.
 - Problems of availability of treatment or access to it.
 - Opioids unavailable in the patient's pharmacy.

Patient Management

Flexibility is the key to managing cancer pain. As patients vary in diagnosis, stage of disease, responses to pain and interventions, and personal preferences, so must pain management. The recommended clinical approach outlined below emphasizes a focus on patient involvement.

1. Ask about pain regularly. Assess pain and associated symptoms systematically using brief assessment tools. Assessment should include discussion about common symptoms experienced by cancer patients and how each symptom will be treated.^{2,3}
2. Believe patient and family reports of pain and what relieves the pain.^{7,8}
3. Choose pain-control options appropriate for the patient, family, and setting.
4. Deliver interventions in a timely, logical, coordinated fashion.
5. Empower patients and their families. Enable patients to control their course as much as possible.

Effective pain management is best achieved by a team approach involving patients, their families, and health care providers. The clinician should:

- Discuss pain and its management with patients and their families.
- Encourage patients to be active participants in their care.
- Reassure patients who are reluctant to report pain that there are many safe and effective ways to relieve pain.
- Consider the cost of proposed drugs and technologies.
- Share documented pain assessment and management with other clinicians treating the patient.
- Know state/local regulations for controlled substances.

Pain Assessment

Failure to assess pain is a critical factor leading to undertreatment. Assessment involves both the clinician and the patient. Assessment should occur:

- At regular intervals after initiation of treatment.
- At each new report of pain.
- At a suitable interval after pharmacologic or nonpharmacologic intervention, e.g., 15 to 30 minutes after parenteral drug therapy and 1 hour after oral administration.

Identifying the etiology of pain is important to its management. Clinicians treating patients with cancer should recognize the common cancer pain syndromes. Prompt diagnosis and treatment of these syndromes can reduce morbidity associated with unrelieved pain. Distinct cultural components may need to be incorporated into a multidimensional assessment of pain.⁹ A comprehensive review of cancer pain with a focus on neuropathic pain provides an overview of pain pathophysiologies and an extensive review of available and investigational pharmacotherapies.¹⁰

Common Cancer Pain Syndromes

Pain Syndrome	Associated signs and symptoms	Affected nerves
Tumor infiltration of a peripheral nerve	Constant burning pain with dysesthesia in an area of sensory loss.	Peripheral nerves
	Pain is radicular and often unilateral.	
Postradical neck dissection	Tight burning sensation in the area of sensory loss.	Lower cranial nerves
	Dysesthesias and shock like pain may be present.	
	Musculoskeletal pain may be caused by a drooped-shoulder syndrome.	Cervical plexus
Postmastectomy pain	Tight, constricting, burning pain in the posterior arm, axilla, and anterior chest wall.	Intercostobrachial
	Pain exacerbated by arm movement, possibly caused by musculoskeletal dysfunction or	

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Pain Syndrome	Associated signs and symptoms	Affected nerves
	edema.	
Postthoracotomy pain	Aching sensation in the distribution of the incision with sensory loss with or without autonomic changes.	Intercostal
	Often exquisite point tenderness at the most medial and apical points of the scar with a specific trigger point in the muscle.	
Postnephrectomy pain	Numbness, fullness, or heaviness in the flank, anterior abdomen, and groin.	Superficial cutaneous nerves
	Dysesthesias are common.	
Postamputation pain	Persistent, severe phantom limb pain in a minority of patients.	Peripheral nerves and their central projections
	Stump pain generally resolves with wound healing, although pain associated with scar sensitivity may emerge after months or years.	
Chemotherapy-induced peripheral neuropathy	Painful paresthesias and dysesthesias.	Peripheral nerves (e.g., polyneuropathy)
	Hyporeflexia.	
	Less frequently: motor and sensory loss; rarely: autonomic dysfunction.	
	Commonly associated with the vinca alkaloids (e.g., vincristine, vinblastine), cisplatin, and paclitaxel.	
Peripheral nerve tumors	Radiation therapy may promote malignant fibrosarcoma.	Peripheral nerves
	Painful, enlarging mass in a previously irradiated area.	

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Pain Syndrome	Associated signs and symptoms	Affected nerves
	Patients with neurofibromatosis more susceptible.	
Cranial neuropathies	Severe head pain with cranial nerve dysfunction.	Cranial nerves V, VII, IX, X, XI, XII are most common.
	Leptomeningeal disease.	
	Base of skull metastasis.	
Acute and postherpetic neuralgia	Painful paresthesia and dysesthesia.	Thoracic and cranial nerve V are most common.
	Constant burning and aching pain.	
	Shocklike paroxysmal pain.	
	Immunosuppression from disease or treatment is a risk factor; postherpetic neuropathy incidence increases with age.	

Initial Assessment

The goal of the initial assessment of pain is to characterize the pathophysiology of the pain and to determine the intensity of the pain and its impact on the patient's ability to function. Factors that may influence analgesic response and result in persistent pain include changing nociception due to disease progression, intractable side effects, tolerance, neuropathic pain, and opioid metabolites.¹¹ The following are essential to the initial assessment:

- Detailed history.
- Physical examination.
- Psychosocial assessment.
- Diagnostic evaluation.

The experience of cancer pain is complex and includes physical, psychosocial, and spiritual dimensions. There is no universally accepted pain classification measure that would assist with predicting the complexity of pain management, particularly for cancer pain patients, who may be more difficult to treat. Clinicians and researchers lack a common language to discuss and compare outcomes of cancer pain assessment and management. Oncologists use the tumor, nodes,

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metastases (TNM) system to provide a universal language to describe a variety of cancers. The need for a similar classification system for cancer pain resulted in the development of the Edmonton Staging System.¹²

Edmonton Staging System for Cancer Pain

A Mechanism of Pain

- A1 Visceral Pain
- A2 Bone-soft Tissue
- A3 Neuropathic Pain
- A4 Mixed
- A5 Unknown

B Pain Characteristics

- B1 Non-incidental Pain
- B2 Incidental Pain

C Previous Narcotic Exposure

- C1 Less than 60 mg of equivalent oral morphine/day
- C2 60 - 300 mg of equivalent oral morphine/day
- C3 More than 300 mg of equivalent oral morphine/day

D Cognitive Function

- D1 Normal cognitive function
- D2 Impaired cognitive function

E Psychological Distress

- E1 Patients without major psychological distress
- E2 Major psychological distress

F Tolerance

- F1 Increase of <5% of initial dose/day
- F2 Increase of >5% of initial dose/day

G Past History

- G1 Negative history for alcoholism or drug addiction
- G2 Positive history for alcoholism or drug addiction

Stage 1: good prognosis

A1, A2, B1, C1, C2, D1, E1, F1, G1

Stage 2: intermediate prognosis

A4 (if not stage 3), A5, C3 (if not stage 3); D2 (if not stage 3)

Stage 3: poor prognosis

A3, B2, E2, F2, G2

(A patient has a poor prognosis if they score positive for any of these, regardless of scoring in any other category)

This system has been further refined in two reports that have gathered construct validity evidence using an international panel of content experts¹³ and a multicenter study to determine interrater reliability and predictive value.¹⁴ The development of an internationally recognized classification system for cancer pain could play a significant role in improving the assessment of cancer pain, allow a more meaningful assessment of clinical prognosis and treatment, and better enable researchers to compare results with regard to cancer pain management.

Patient Self-Report

The mainstay of pain assessment is the patient self-report; however, family caregivers are often used as proxies for patient reports, especially in situations in which communication barriers exist, such as cognitive impairment or language difficulties. Family members who act as proxies typically, as a group, report higher levels of pain than patient self-reports, but there is individual variation.¹⁵ Differences in clinician assessment of pain intensity are also significant. A retrospective review of 41 patient charts using pain ratings of palliative care consultants as the gold standard found high agreement with assessments performed by bedside nurses (registered nurses [RNs] and clinical nurse assistants [CNAs]) when pain was not present or was mild but poor agreement for moderate or severe pain (sensitivity: RNs, 45%; CNAs, 30%).¹⁶

Pain assessment tools may be unidimensional or multidimensional. Multiple assessment tools exist. Among the more commonly used bedside tools are numeric rating scales, verbal rating scales, visual analog scales, and picture scales.¹⁷ To enhance pain management across all settings, clinicians should teach families to use pain assessment tools in their homes. The clinician should help the patient to describe:

Pain

Listen to the patient's descriptive words about the quality of the pain; these provide valuable clues to its etiology. Elicit the temporal features including onset, duration, and diurnal variation. Ask about breakthrough or episodic pain (a transitory increase in pain that occurs in addition to persistent pain). Some patients may have episodic pain without persistent pain.¹⁸

Location

Ask the patient to indicate the exact location of the pain on his or her body, or on a body diagram, and whether the pain radiates.

Intensity

Encourage the patient to keep a log of pain-intensity scores to report during follow-up visits or by telephone. Examples of simple self-report pain-intensity scales include the simple, descriptive, numeric, and visual analog scales.

Aggravating and Relieving Factors

Ask the patient to identify factors that cause the most pain and also what relieves the pain.

Cognitive Response to Pain

Cognitive appraisals of pain can be based on a range of psychological variables such as perceived control, meaning attributed to pain experience, fear of death, and hopelessness. All these variables appear to contribute to the experience of cancer pain and suffering. A study of women with metastatic breast cancer found that although the site of metastasis did not predict the intensity of pain report, greater depression and the belief that pain represented the spread of disease significantly predicted the degree of pain experienced.¹⁹ It was also reported that patients who thought that their pain represented disease progression reported more pain-related interference with function.²⁰

Cognitive Impairment

Note behavior that suggests pain in patients who are cognitively impaired or who have communication problems relating to education, language, ethnicity, or culture. Cognitive impairment itself and the degree of cognitive impairment may impact patient self-report of pain. Preliminary data suggest that mild degrees of cognitive impairment are associated with increased intensity of pain-report in older patients with cancer who are receiving hospice care.¹⁵ In contrast, cognitively impaired nursing home residents are less likely to report pain.

Goals for Pain Control

Document the patient's preferred pain assessment tool and the goals for pain control (such as scores on a pain scale).

Pain Diary

The daily pain diary is a well-established tool in symptom management research and in clinical practice. Benefits of using a pain diary include heightened awareness of pain, guidance for pain management behaviors, enhanced sense of control, and a tool for communication.²¹ It is difficult to get good pain-diary compliance with adolescents who are experiencing intense chronic pain.

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0	1	2	3	4	5	6	7	8	9	10
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No pain

Worst pain imaginable

Date	Time	Pain rating (0-10) see scale	Pain medication (name, dose, how often taken)	Other pain-relief methods tried	Side effects from pain medicine
<i>June 6 (example)</i>	<i>8 am</i>	<i>6</i>	<i>Morphine 30 mg every 4 hrs</i>	<i>massage</i>	<i>constipation</i>

Doctor's Name:
Address:
Phone:
Nurse's Name:
Address:
Phone:
Pharmacist's Name:
Address:
Phone:
Social Worker/Therapist:
Address:
Phone:
Questions To Ask:

Physical Examination

A thorough physical examination is required to determine the pathophysiology of pain. Specific features of the neurologic examination such as altered sensation (hypoesthesia, hyperesthesia, hyperpathia, allodynia) in a painful area are suggestive of neuropathic pain. Physical findings of tumor growth and metastasis are also important to identify.

Changes in pain pattern or the development of new pain should trigger diagnostic evaluation and modification of the treatment plan. Persistent pain indicates the need to consider other etiologies (e.g., related to disease progression or treatment) and alternative (perhaps more invasive) treatments.

Assessment of the Outcomes of Pain Management

Pain-related outcomes

Clinicians should document and be aware of outcomes of pain therapy. It is helpful to think of pain-related outcomes as primarily measured in two ways: decreased pain intensity and improvement in psychosocial functioning. Using rating scales of pain intensity at its worst and on average and using pain interference scales can help clinicians monitor outcomes. Measurement of the percentage of pain relief is also useful, though measuring patient satisfaction is less useful because of the low expectations patients sometimes hold for pain control.²²

Drug-taking outcomes

Clinicians treating patients taking chronic opioids should also monitor and document patients' drug-taking behaviors. Outcomes related to addiction in cancer patients are rare but nonetheless should be periodically assessed; these assessments can be reassuring to patients. Tolerance and dependence are not addiction related. Documentation of patients' compliance with regard to changes in dosing and duration of prescriptions is essential in all pain practice.

The clinical assessment of drug-taking behaviors in medically ill patients with pain is complex. Aberrant drug-taking behavior from cancer pain management is related to premonitory history of drug addiction and the likelihood of other pain treatment. A pilot questionnaire was used to characterize drug-related behaviors and attitudes in cancer and AIDS patients. Despite limitations, this study highlights wide potential variation among different palliative care populations in patterns of past and present aberrant drug-taking behaviors and the need for a clinically useful screening approach. The implications for psychosocial and pharmacological management of symptoms such as pain, as well as any aberrant behavior, remains unclear.²⁴

Previous drug abuse is likely to lead to specific needs for appropriate dosing during cancer pain therapy. A prospective open-label study compared morphine dosage and effectiveness in AIDS patients with and without previous substance abuse. Results demonstrated that both groups benefited, but patients with a history of drug use require and will tolerate substantially higher morphine doses to achieve stable pain control.²⁵ This study should increase confidence in providing appropriate pain management to patients who have a history of drug use.

Pharmacologic Management

Basic Principles of Cancer Pain Management

The World Health Organization (WHO) has described a three-step analgesic ladder as a framework for pain management.²⁶ It involves a stepped approach based on the severity of the pain. If the pain is mild, one may begin by prescribing a Step 1 analgesic such as acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). Potential adverse effects should be noted, particularly the renal and gastrointestinal adverse effects of the NSAIDs. If pain persists or worsens despite appropriate dose increases, a change to a Step 2 (mild opioid) or Step 3 (strong opioid) analgesic is indicated. Most patients with cancer pain will require a Step 2 or Step 3 analgesic. Step 1 can be skipped in those patients presenting at the onset with moderate-to-severe pain in favor of Step 2 or Step 3. At each step, an adjuvant drug or modality such as radiation therapy may be considered in selected patients.

Analgesics should be given “by mouth, by the clock, by the ladder, and for the individual.”²⁶ This requires regular scheduling of the analgesic, not just as needed. In addition, rescue-doses for breakthrough pain need to be added. The oral route is preferred as long as a patient is able to swallow. Each analgesic regimen should be adjusted for each patient’s individual circumstances and physical condition.

Acetaminophen and Nonsteroidal Anti-inflammatory Drugs

NSAIDs are effective for relief of mild pain and may have an opioid dose-sparing effect that helps reduce side effects when given with opioids for moderate-to-severe pain. Acetaminophen is included with aspirin and other NSAIDs because it has similar analgesic potency, though it lacks peripheral anti-inflammatory activity. Side effects can occur at any time, and patients who take acetaminophen or NSAIDs, especially elderly patients, should be followed carefully. There is growing debate about whether NSAIDs are useful and have significant opioid-sparing effects. One meta-analysis²⁷ suggests that the usefulness of NSAIDs is limited and that they do not significantly spare opioid doses. Another study suggests that NSAIDs are useful and reduce the need for

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opioid dose increases; however, only patients with pain progression after 1 week of opioid stabilization were selected for the study.²⁸

The coxibs are a subclass of NSAIDs designed to selectively inhibit cyclooxygenase-2 (COX-2). Development of these drugs was based on the hypothesis that COX-2 was the source of prostaglandins E₂ and I₂, which mediate inflammation, and COX-1 was the source of the same prostaglandins in gastric epithelium, with the potential advantage over traditional NSAIDs of less gastrointestinal ulceration and bleeding and the absence of platelet inhibition. Direct comparisons between COX-2 inhibitors are few. A systematic meta-analysis of COX-2 inhibitors compared with traditional NSAIDs or different COX-2 inhibitors for postoperative pain suggests that rofecoxib, 50 mg, and parecoxib, 40 mg, are equipotent to traditional NSAIDs for postoperative pain after minor and major surgical procedures and have a longer duration of action after dental surgery. Rofecoxib was found to provide superior analgesic effect compared with celecoxib, 200 mg. There were insufficient data to comment on toxicity.

There are 3 coxibs that were approved by the U.S. Food and Drug Administration (FDA): celecoxib, rofecoxib, and valdecoxib. On September 30, 2004, rofecoxib was withdrawn from the market after a study demonstrated that subjects in a colon cancer prevention trial taking the drug at higher-than-typical doses on a long-term basis had a significant increase in the incidence of serious thromboembolic complications. The question that remains unanswered is whether the increased risk applies to all COX-2 inhibitors, with the caution that the burden of proof rests with those who might claim that this is a problem for rofecoxib alone and does not extend to other coxibs. On April 7, 2005, valdecoxib was withdrawn from the market. FDA is also asking manufacturers of all marketed prescription NSAIDs, including celecoxib (Celebrex) to revise the labeling (package insert) for their products to include a boxed warning, highlighting the potential for increased risk of cardiovascular events and/or the serious, potentially life-threatening gastrointestinal bleeding associated with use of these drugs.

Dosage

Use patient response to determine the effective dosing interval for aspirin, acetaminophen, and other NSAIDs. When pain relief is not attained with the maximum dosage of one NSAID, try other drugs within this category before abandoning NSAID therapy.

Route of administration

Use readily available oral tablets, capsules, or liquid. During intervals of nausea and vomiting, use suppositories. Ketorolac tromethamine is the only NSAID available for parenteral use.

Contraindications

Patients taking NSAIDs are at risk for platelet dysfunction that may impair blood clotting. The table below lists NSAIDs with minimal antiplatelet activity.

Other side effects

Follow patients carefully for adverse effects, which range from mild gastrointestinal discomfort to more serious problems including the following:

- Gastric ulceration.
- Hepatic dysfunction.
- Myocardial infarction.
- Renal failure.

Because both NSAIDs and other drugs (e.g., warfarin, methotrexate, digoxin, cyclosporine, oral antidiabetic agents, and sulfonamide-containing drugs) are highly protein-bound, there is potential for altered efficacy or toxicity when they are given simultaneously.

Dosing Recommendations for Acetaminophen and NSAIDS

Drug	Usual dose for adults and children ≥50 kg body weight	Usual dose for adults and children ¹ <50 kg body weight
Orally administered acetaminophen and over-the-counter NSAIDs		
acetaminophen	650 mg q 4 h	10–15 mg/kg q 4 h
	975 mg q 6 h	15–20 mg/kg q 4 h (rectal)
aspirin	650 mg q 4 h	10–15 mg/kg q 4 h
	975 mg q 6 h	15–20 mg/kg q 4 h (rectal)
ibuprofen (Motrin, Advil)	400–600 mg q 6 h	5–10 mg/kg q 4–6 h
magnesium salicylate (Doan's, Magan, Mobidin, others)	650 mg q 4 h	
naproxen (Naprosyn, Aleve)	250–275 mg q 6–8 h	5 mg/kg q 8 h
naproxen sodium (Anaprox)	275 mg q 6–8 h	

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Drug	Usual dose for adults and children ≥ 50 kg body weight	Usual dose for adults and children ¹ < 50 kg body weight
Prescription NSAIDs		
carprofen (Rimadyl)	100 mg tid	
choline magnesium trisalicylate (Trilisate)	1,000–1,500 mg q 6–8 h	25 mg/kg q 6–8 h
choline salicylate (Arthropan)	870 mg q 3–4 h	
diflunisal (Dolobid)	500 mg q 12 h	
etodolac (Lodine)	200–400 mg q 6–8 h	
fenoprofen calcium (Nalfon)	300–600 mg q 6 h	
ketoprofen (Orudis)	25–60 mg q 6–8 h	
ketorolac tromethamine (Toradol)	10 mg q 4–6 h to a maximum of 40 mg/day	
	IV administration should not exceed 5 days	
meclofenamate sodium (Meclomen)	50–100 mg q 6 h	
mefenamic acid (Ponstel)	250 mg q 6 h	
sodium salicylate (Anacin, Bufferin)	325–650 mg q 3–4 h	
Parenteral NSAIDs		
ketorolac tromethamine (Toradol)	60 mg initially, then 30 mg q 6 h	
	IV administration should not exceed 5 days	

Opioids

Opioids, the major class of analgesics used in management of moderate-to-severe pain, are effective, are easily titrated, and have a favorable benefit-to-risk ratio.

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The predictable consequences of long-term opioid administration—tolerance and physical dependence—are often confused with psychological dependence (addiction) that manifests as drug abuse. This misunderstanding can lead to ineffective prescribing, administering, or dispensing of opioids for cancer pain. The result is undertreatment of pain.

Clinicians may be reluctant to give high doses of opioids to patients with advanced disease because of a fear of respiratory depression. Many patients with cancer pain become opioid tolerant during long-term opioid therapy. Therefore, the clinician's fear of shortening life by increasing opioid doses is usually unfounded.

Opioid Types

Opioids are classified as full morphine-like agonists, partial agonists, or mixed agonist-antagonists, depending on the specific receptors to which they bind and their activity at these receptors. The benefits of using opioids and the risks associated with their use vary among individuals.

Morphine is the most commonly used opioid in cancer pain management, largely for reasons of availability and familiarity; however, it is useful to be familiar with more than one type of opioid. Wide interindividual variability in response to both the analgesic and adverse effects of opioids is recognized.²⁹ Some patients may not experience adequate pain control despite appropriate dose adjustments, while others may develop intolerable adverse effects to one particular opioid (see below). Alternative opioids include hydromorphone, oxycodone, methadone, and fentanyl. Knowledge of several medications and formulations give the caregiver much more flexibility in tailoring a regime to a particular patient's needs.

Short-acting opioids are generally recommended when opioid therapy is being initiated for the first time or when patients are medically unstable or the pain intensity is highly variable. Once stable, patients can be switched to a controlled-release or slow-release formulation. This is more convenient and promotes compliance.

Full agonists - Morphine, hydromorphone, codeine, oxycodone, hydrocodone, methadone, levorphanol, and fentanyl are classified as full agonists because their effectiveness with increasing doses is not limited by a ceiling. Full agonists will not reverse or antagonize the effects of other full agonists given simultaneously.

Morphine - The most commonly used opioid, morphine, is readily available in several forms, including sustained-release (8–24 hours duration of effectiveness) formulations for oral administration.

Other agonists - For the patient who experiences dose-limiting side effects with one oral opioid (e.g., hallucinations, nightmares, dysphoria, nausea, or

mental clouding), other oral opioids should be tried before abandoning one route in favor of another.

Methadone - Methadone has had a revival in interest for the management of cancer pain. Success has been reported with oral, intravenous (IV), and suppository methadone use. Subcutaneous methadone has been reported to cause tissue irritation at the injection site but has been used effectively in some patients without clinically significant local toxicity.³⁰

Methadone is a synthetic opioid agonist that has been reported to have a number of unique characteristics. These include excellent oral and rectal absorption, no known active metabolites, prolonged duration of action resulting in longer administration intervals, and lower cost than other opioids. Methadone is available as a pill, an elixir, and for parenteral use. Methadone has an average oral bioavailability of approximately 80% (range, 41%–99%).³¹

Morphine is the international gold standard for first-line treatment of cancer pain. Methadone, however, can be considerably less expensive than existing rapid-release or sustained-release morphine or other opioid options. A randomized trial of 103 patients compared the effectiveness and side effects of morphine and methadone as first-line treatments for cancer pain. The outcome of successful pain management was similar for both groups; however, there were significantly more opioid-related dropouts in the methadone group. This study did not demonstrate superior analgesic effectiveness or overall tolerability of methadone over morphine as a first-line treatment for cancer pain. Despite this finding, the authors of this report suggested that study limitations did not allow definitive conclusions that methadone could not be a useful first-line opioid. Further research exploring other doses and schedules of methadone should still be explored.

Meperidine (Demerol) - Useful for brief courses (a few days) to treat acute pain, meperidine is not recommended in treating persistent cancer pain because of its short duration of action (2.5–3.5 hours) and its neurotoxic metabolite, normeperidine. Accumulation of this metabolite, particularly when renal function is impaired, causes central nervous system (CNS) stimulation that may lead to delirium or seizures. Seizures are typically preceded by development of multifocal myoclonus, which can be used as a warning sign.

Partial agonists - Partial agonists such as buprenorphine have less effect than full agonists at opioid receptors. They are subject to a ceiling effect and thus are less effective analgesics.

Mixed agonist-antagonists - Mixed agonist-antagonists block or are neutral at one type of opioid receptor while activating a different opioid receptor. Mixed agonist-antagonists are contraindicated for use in the patient receiving an opioid

agonist because they may precipitate a withdrawal syndrome and increase pain. Mixed agonist-antagonists include pentazocine (Talwin), butorphanol tartrate (Stadol), dezocine (Dalgan), and nalbuphine hydrochloride (Nubain). Their analgesic effectiveness is limited by a dose-related ceiling effect.

Principles of Opioid Administration

Most patients with cancer pain require fixed-schedule dosing to manage the constant pain and prevent the pain from worsening. An Italian study of patients whose baseline pain was well controlled on morphine when admitted to a palliative care unit found that most episodes of breakthrough pain were rapidly controlled with IV morphine equivalent to 20% of the calculated equianalgesic total daily dose. Adverse effects were uncommon. An as-needed rescue dose (breakthrough dose) should be combined with the regular fixed-schedule opioid to control the episodic exacerbation of pain, often referred to as breakthrough pain. When this pain is elicited by an action such as weight-bearing, breathing, or defecation, it is termed incident pain. Rescue or breakthrough doses can be given hourly or more frequently as needed, depending on route of administration, pharmacokinetic properties of the drug, and presence or absence of side effects. The breakthrough dose is generally calculated to be 10% to 20% of the total dose of the fixed schedule. Adherence rates are improved when patients are prescribed around-the-clock opioids compared with as-needed prescribing.³⁵ Preliminary data suggest that the intensity of incident pain related to bone metastases may be diminished by increasing the dose of the scheduled opioid above that needed for control of baseline pain, while maintaining it below that associated with the development of limiting side effects.³⁶

Dosage - The appropriate dosing interval is determined by the opioid and formulation used. The analgesic effects of short-acting oral opioids such as morphine, hydromorphone, codeine, and oxycodone begin within a half hour after administration and last for approximately 4 hours. The dosing interval of these drugs is usually 4 hours.

In patients given controlled-release formulations of morphine or oxycodone, relief should begin in 1 hour, peak in 2 to 3 hours, and last for 12 hours; these formulations are usually prescribed in 12-hour intervals. A small group of patients, however (10%–20% of those on 12-hour controlled-release formulations), may require administration every 8 hours. The analgesic effect of transdermal fentanyl begins approximately 12 hours after the application of the patch, peaks in 24 to 48 hours, and lasts for approximately 72 hours. Patches are therefore changed every 72 hours. In a select group of patients who consistently experience end-of-dose failure despite increases in the patch doses, the dosing interval can be increased to every 48 hours (<10% of patients on fentanyl patches). Transdermal fentanyl is not recommended for control of acute pain or poorly controlled pain because there is a delayed onset of action until reaching steady-state either with new use or with a change in the dose. Patients receiving

transdermal fentanyl may be switched to a continuous IV or subcutaneous infusion of fentanyl using a conversion ratio of 1:1 to facilitate more rapid titration.

Types of opioids - The debate regarding whether any individual opioid causes fewer side effects or is more effective is characterized by much speculation but little clinical evidence. These inconclusive findings have prompted expert working groups of the European Association of Palliative Care to recommend that there is currently little evidence of the clinical superiority of one opioid over another regarding the side-effect profile and/or analgesia. Even constipation and other side effects may be positively affected by a switch. Compared with morphine, fentanyl may cause less constipation.³⁹ Studies suggesting that oxycodone and hydromorphone may cause less nausea and hallucinations than morphine⁴⁰ are juxtaposed with other studies that found no significant differences between them.^{41,42} One study found that transdermal fentanyl was better tolerated than sustained-release oral morphine and equally effective.⁴³

Tolerance - Assume that patients actively abusing heroin or prescription opioids (including methadone) have some pharmacologic tolerance that will require higher starting doses and shorter dosing intervals.

Opioid switching

A series of case reports have demonstrated the clinical problem of inadequate pain control with escalating opioid doses in the presence of dose-limiting toxic effects, including hallucinations, confusion, hyperalgesia, myoclonus, sedation, and nausea.⁴⁴⁻⁴⁶ It was suggested that these problems could be managed by switching to an alternative opioid, with the result being improved pain management and decreased toxic effects. The improvement with opioid switching, although predominantly demonstrated initially with morphine, has also been reported with other opioids. A retrospective review over a 1-year period in a pediatric oncology center supports efficacy of this technique in children, with resolution of adverse opioid effects, largely pruritus, achieved in 90% of patients, while maintaining pain control.⁴⁷

Guidelines for opioid switching are intended to reduce the risk of relative overdosing or underdosing as one opioid is replaced by another. These guidelines require a working knowledge of an equianalgesic-dose table. The equianalgesic-dose table provides only a broad guide for dose selection when switching from one opioid to another. Wide ranges in interindividual responses to the various opioids have been noted.⁴⁸ Therefore, because of incomplete cross-tolerance in most cases, the calculated dose-equivalent of a new drug must be reduced by 25% to 50% to ensure safety. These figures are based on clinical experience rather than empiric data. The selection of an alternative opioid is largely empirical. There is little clinical evidence to indicate that one opioid has therapeutic superiority over another opioid. A patient, for example, who requires a switch from morphine to another opioid can be switched to hydromorphone, oxycodone, fentanyl, or methadone. In one prospective study of 186 cancer

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patients being treated with morphine, 25% did not respond and required switching to another opioid (oxycodone). The primary reasons for switching included pain, confusion, drowsiness, nightmares, and nausea. Of the 47 patients who required switching to an alternative opioid, 37 (79%) obtained good relief. This result provides beginning evidence for the prevalence of the need to switch, as well as determining the success rate once switching occurs.⁴⁹ Patients should be followed closely after a switch and should be reassessed, and the new opioid dose should be adjusted according to the intensity of pain and lack or presence of adverse effects.

It has been suggested that a less complicated approach than opioid switching would be reassessment of the clinical situation and use of adjuvant analgesics, decreasing the opioid dose if possible, use of medical management for opioid-related side effects, and correction of any contributing metabolic abnormalities. Nevertheless, there does appear to be an emerging consensus that opioid switching does have a useful role when pain control remains inadequate with escalating opioid doses and opioid use results in unacceptable opioid-related side effects.^{50,51}

Morphine, as the strong opioid of choice for the management of cancer pain, was used increasingly during the 1970s and 1980s. Associated with this increasing experience was the clinical observation of the risk of accumulation of morphine metabolites, particularly in the presence of renal impairment. Morphine-6-glucuronide, an analgesic metabolite, was recognized as having a useful role in enhancing analgesia. A number of reports, however, have described seizures, cognitive impairment, nausea, and problems of myoclonus that were associated with accumulation of morphine-6-glucuronide.⁵²⁻⁵⁴

The potential role of morphine metabolites, in particular the ratio of 3-glucuronide to 6-glucuronide in the development of opioid-related toxicity, has been reported. The literature on this issue has been somewhat controversial. There is no disagreement that morphine metabolites increase in the presence of deteriorating renal function; however, there has been conflicting evidence regarding the role and ratios of the metabolites in patients exhibiting both a poor response to increasing morphine doses and associated toxicity.⁵⁵

Switching from one opioid to another requires familiarity with a range of opioids and the use of opioid dose-conversion tables. When using these ratios, it must be understood that the guidelines should be reviewed and the patients should be monitored more closely during the switching phase. Wide ranges in ratios are noted. In the case of methadone, it is much more potent than previously thought (on average 10 times more potent), and its equianalgesic dose-ratio compared to other opioids changes according to the dose of the previous opioid; the higher the dose, the higher the ratio. (Note that potency does not denote more effectiveness but denotes the equivalent dose required to obtain the same effect.)

Approximate Dose Equivalents for Opioid Analgesics

Drug	Oral dose (mg)	Parenteral dose
Morphine	30	10 mg
Codeine	200	100 mg
Fentanyl	NA	100 µg
Hydrocodone (Vicodin)	30–45	NA
Hydromorphone (Dilaudid)	8	2 mg
Levorphanol (Levo-Dromoran)	4	2 mg
Methadone	The conversion ratio of methadone is variable.	
Oxycodone (OxyContin)	20–30	10–15 mg
Oxymorphone		
(Numorphan)	NA	1 mg
(Opana and Opana ER)	10	1 mg

Route of Administration

Oral - Oral administration is preferred in patients with intact gastrointestinal tracts because it is convenient and usually inexpensive. When patients cannot take oral medications, other less invasive routes (e.g., rectal or transdermal) should be offered. Parenteral methods should be used only when simpler, less demanding, and less costly methods are inappropriate, ineffective, or unacceptable to the patient. In general, assessing the patient's response to several different oral opioids is advisable before abandoning the oral route in favor of anesthetic, neurosurgical, or other invasive approaches.

Rectal - Use this safe, inexpensive, effective route for delivery of opioids as well as nonopioids when patients have nausea or vomiting. Rectal administration is inappropriate for the patient who has diarrhea, anal/rectal lesions, mucositis, thrombocytopenia, or neutropenia. The use of suppositories is not always culturally acceptable and may not be practical for patients who are obese, have fractures, are physically unable to place the suppository in the rectum, or prefer other routes. When changing from the oral to the rectal route, begin with the same dosage as had been given orally, then titrate as needed.

Transdermal (fentanyl) - Patches currently available are formulated to provide analgesia lasting up to 72 hours. This preparation is not suitable for rapid dose titration and should be used for relatively stable analgesic requirements when rapid increases or decreases in dosage are not likely to be needed. In the chronic setting, considerable inter- and intraindividual variability may exist in the rate of absorption of fentanyl from transdermal patches in patients receiving a stable dose of transdermal fentanyl. Based on a case series, it has been proposed that conversion from transdermal to IV fentanyl using a 1:1 conversion ratio can be safe and effective during acute exacerbations of cancer pain. Although other opioids are sometimes compounded into gel form for transdermal application, there is insufficient evidence to support this practice.

Transmucosal (fentanyl) - Oral transmucosal fentanyl citrate is used for the relief of breakthrough pain. The lipid solubility of fentanyl allows rapid onset of pain relief. In open-label studies, 72% to 92% of patients found a dose that provided relief from breakthrough pain. Side effects in these studies were consistent with other opioid therapies, including sedation, constipation, stomatitis, and nausea.⁵⁶ There is growing interest in the use of rapidly acting, highly lipophilic opioids such as fentanyl for the management of difficult breakthrough pain syndromes. An oral transmucosal fentanyl citrate compound for buccal administration has become available for this purpose. Other opioids such as morphine, hydromorphone, and oxycodone are not very lipophilic and therefore not suited for buccal or sublingual administration. In the home setting, opioids are sometimes administered buccally or sublingually with erratic absorption that is likely via the lower gastrointestinal tract.

Parenteral: IV and subcutaneous - IV administration provides a rapid onset of analgesia within 2 to 10 minutes. The duration of action after a bolus dose may be shorter than with other routes. This route may be useful if a patient cannot swallow and IV access is established.

The subcutaneous route is as effective as the IV route.⁵⁷ In some situations, it may even be more convenient, especially if patients are being cared for at home or in a hospice. To facilitate administration via this route, a 25- or 27-gauge butterfly needle can be inserted subcutaneously and left in place for up to 7 days at a time. The anterior thighs, abdomen, upper arms, subclavicular area, and upper back are possible areas for needle insertion. The site should be monitored for signs of infection or irritation and should be changed if these are noted.

The bioavailability of parenterally administered opioids (morphine, hydromorphone, oxycodone, and codeine) is generally 2 to 3 times that of the oral route. The dose therefore needs to be halved or decreased by a third when switching from the oral to the subcutaneous and IV routes, respectively. Opioids administered parenterally may be given either intermittently (usually every 4 hours) or by a continuous infusion. With some exceptions, these two methods appear to be similarly effective.

Intraspinal - The intraspinal administration of opioids (epidural or intrathecal), especially when combined with a local anesthetic, can be helpful in a very small select group of patients with intractable pain. Use of the epidural or intrathecal route requires skill and expertise that may not be available in all settings. The table below presents the advantages and disadvantages of intraspinal administration. Although intrathecal opioid therapy has been FDA approved since 1991, the utility of an implantable drug delivery system (IDDS) to deliver spinal opioids was only recently compared with comprehensive medical management (CMM) in a randomized trial. There were 202 patients enrolled in this unblinded study. Of the 101 patients randomized to the IDDS, 51 actually received this therapy. Sixteen of these patients (31%) had serious adverse effects. Patients using the IDDS experienced more than 20% reduction in both pain and opioid toxicity more often than the CMM group ($P = .02$). These data and further analysis in follow-up reports^{58,59} suggest that the use of an IDDS delivery system may offer benefit for some cancer patients. More research is needed to determine which subsets of patients will benefit the most from this device, and what the proper timing should be for a trial of intrathecal opioids. An open-label study demonstrated that patients with refractory cancer pain experienced better pain relief, fewer opioid-associated side effects, and decreased systemic opioid use when managed with patient-activated intrathecal delivery of morphine via an implanted delivery system. The device was implanted in 119 patients. There were 7 serious adverse events related to the device and 55 serious adverse events related to the implant and delivery-system refill procedures. The FDA denied the application for market approval of this system.

Advantages and Disadvantages of Intraspinal Drug Administration

System	Advantages	Disadvantages
Percutaneous temporary catheter	Used extensively both intraoperatively and postoperatively.	Mechanical problems include catheter dislodgment, kinking, or migration.
	Useful when prognosis is limited (<1 month).	Increased risk of infection.
Permanent silicone-rubber epidural	Catheter implantation is a minor procedure.	
	Dislodgment and infection less common than with temporary catheters.	
	Can deliver bolus injections, continuous infusions, or PCA (with or without continuous	

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System	Advantages	Disadvantages
	delivery).	
Subcutaneous implanted injection port	Increased stability, less risk of dislodgment.	Implantation more invasive than external catheters.
	Can deliver bolus injections or continuous infusions (with or without PCA).	Approved only for epidural catheter in United States. Potential for infection increases with frequent injections.
Subcutaneous reservoir	Potentially reduced infection in comparison with external system.	Difficult to access, and fibrosis may occur after repeated injection.
Implanted pumps (continuous and programmable)	Potentially decreased risk of infection.	Need for more extensive operative procedure.
		Need for specialized equipment with programmable systems.

Other routes - Some studies suggest that the use of inhaled opioids for the management of pain and cancer-related shortness of breath are, with some exceptions, not more effective than systemic administration. Their absorption via this route is unpredictable.

The intramuscular administration of opioids is not recommended.

Patient-Controlled Analgesia - Patient-controlled analgesia (PCA) may be used to determine the opioid dose needs when initiating opioid therapy. Once the pain is well controlled, a regular opioid dose can be instituted on the basis of the PCA doses required. This method is contraindicated in patients with cognitive impairment or patients with significant psychological undercurrents to their pain experience.

Drugs and Routes To Be Avoided

The following two tables present data on drugs and routes of administration not recommended for the management of cancer pain.

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Class	Drug	Rationale for NOT Recommending
Opioids	meperidine (Demerol)	Short (2-3 hour) duration of analgesia.
		Repeated administration may lead to CNS toxicity (tremor, confusion, or seizures).
Opioid agonist-antagonists	pentazocine (Talwin), butorphanol (Stadol), nalbuphine (Nubain)	Risk of precipitating withdrawal in opioid-dependent patients.
		Analgesic ceiling.
		Possible production of unpleasant psychotomimetic effects (e.g., dysphoria, delusions, hallucinations).
Partial agonist	buprenorphine (Buprenex)	Analgesic ceiling.
		May precipitate withdrawal.
Antagonists	naloxone (Narcan), naltrexone (ReVia)	May precipitate withdrawal.
		Limit use to treatment of life-threatening respiratory depression. Give in diluted form to opioid-tolerant patients.
Combination preparations	Brompton's cocktail	No evidence of analgesic benefit to using Brompton's cocktail over single-opioid analgesics.
	DPT (meperidine, promethazine, and chlorpromazine)	Efficacy is poor compared with that of other analgesics.
		High incidence of adverse effects.
Anxiolytics alone	benzodiazepine (e.g., alprazolam, Xanax; diazepam, Valium; lorazepam, Ativan)	Analgesic properties not demonstrated except for some instances of neuropathic pain.
		Added sedation from anxiolytics may compromise neurologic assessment in patients receiving opioids.

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Class	Drug	Rationale for NOT Recommending
Sedative/hypnotic drugs alone	barbiturates, benzodiazepine	Analgesic properties not demonstrated.
		Added sedation from sedative/hypnotic drugs limits opioid dosing.

Routes of Administration	Rationale for Not Recommending
Intramuscular	Painful.
	Absorption unreliable.
	Should not be used in children or patients prone to develop dependent edema or patients with thrombocytopenia.
Transnasal	The only drug approved by the FDA for transnasal administration is butorphanol, an agonist-antagonist drug that generally is not recommended. (See opioid agonist-antagonists above.)

Side Effects of Opioids

Clinicians should anticipate and monitor for side effects. The more common adverse effects include nausea, somnolence, and constipation. These should be discussed with patients before starting opioids. Somnolence and nausea are more often encountered with initiation of opioid treatment but tend to resolve within a few days. Clinicians who follow patients during long-term opioid treatment should watch for potential side effects and manage them as the need arises.

Constipation - Anticipate the constipating effects of analgesics. Opioids compromise gastrointestinal tract peristaltic function (a nearly universal side effect). Consequently, stool within the gut lumen becomes excessively dehydrated. The cornerstone of effective prophylaxis, therefore, is measurement aimed at keeping the patient well hydrated to maintain well-hydrated stool. All patients using opioid medications should be prescribed a scheduled regimen of stool-softening agents (e.g., docusate sodium) at the commencement of opioid treatment. Patients who do not adequately respond to an aggressive regimen with stool softeners may benefit from the addition of mild osmotic agents (e.g., 70% sorbitol solution, lactulose, milk of magnesia), lubricants (e.g., mineral oil), bulk-forming laxatives (e.g., psyllium) with appropriate orally administered

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hydration, or mild cathartic laxatives (e.g., senna). Stimulant cathartics (e.g., senna, bisacodyl) may be useful in severely constipated patients; however, they may be relatively ineffective in situations in which stool has become desiccated. Opioid-induced constipation is a frequent cause of chronic nausea and is observed in 40% to 70% of patients receiving opioids. It appears to be dose-related, is characterized by large variability in individuals, and is opioid-receptor mediated via both central and peripheral mechanisms. Opioids extend the gastrointestinal transit time and desiccate the intraluminal content. Unlike nausea, complete tolerance to this effect does not generally develop, and most patients require laxative/stool-softener therapy for as long as they take opioids. A plain x-ray of the abdomen may be helpful in assessing the extent of fecal load.

Initiating a regular laxative regimen emphasizes prevention of opioid-induced constipation. Recommendations regarding laxative treatment have been largely based on clinical experiences and observations. Combinations of a sennoside and a stool softener such as docusate are generally suggested. Reports that fentanyl causes less constipation than oral morphine are interesting but need to be confirmed in further prospective studies. A recent study demonstrated decreased laxative use in patients on transdermal fentanyl as compared with patients receiving oral morphine treatment. Whether this decrease in laxative usage is clinically significant, however, and whether the decrease relates to the route of administration instead of the opioid type need to be demonstrated. In a single small series, opioid switching of morphine to methadone resulted in a reduction in constipation.⁶⁰ Severe opioid-induced constipation may occur. At an extreme it may be present as a severe ileus and pseudo bowel obstruction. As is the case with opioid-induced nausea and constipation, management relies on the use of gastrointestinal prokinetic agents. The use of orally administered opioid-antagonists such as naloxone is being studied. Although the oral bioavailability of these medications is very limited, opioid withdrawal syndromes have been noted when higher doses have been used. Methylnaltrexone, a quaternary derivative of naltrexone, is an opioid antagonist that does not cross the blood-brain barrier. Preliminary studies suggest that it may be effective in the management of opioid-associated constipation without causing opioid withdrawal.⁶¹

Nausea and vomiting - Nausea and vomiting occurs in approximately one third to two thirds of patients taking opioids. It is a common complication of early exposure to opioids and usually disappears within the first week of treatment. Appropriate antiemetic coverage during the opioid-initiation phase is usually effective in limiting this adverse effect. Nausea alone does not represent an allergic reaction to the opioid. Occasionally, nausea may be experienced when an opioid dose is significantly increased. An antiemetic should be available on an as-needed basis to address this situation.

Three main mechanisms underlie this opioid-related adverse effect. The predominant mechanism appears to be stimulation of the chemoreceptor trigger zone, where dopamine is the main neurotransmitter. Another is reduced

gastrointestinal motility, including delayed gastric emptying. Nausea via increased vestibular sensitivity is uncommon.

Multiple antiemetic regimens have been proposed for the management of opioid-induced emesis, but prospective studies comparing one regimen over another are lacking. Metoclopramide or domperidone are generally recommended as first-line agents because they improve gastrointestinal motility and are antidopaminergic. Metoclopramide can be administered orally or subcutaneously at doses of 10 mg 4 times a day or every 4 hours, depending on the severity of the nausea. Rescue doses should also be ordered on an as-needed basis. Extrapyramidal-related adverse effects are a potential complication of these medications. The incidence of extrapyramidal reactions is low with domperidone, but this drug is not available in a parenteral formulation. The antihistamines act on the histamine receptors in the vomiting center and on vestibular afferents. They are generally reserved for cases in which vestibular sensitivity, often manifesting as motion-induced nausea, is suspected or for cases in which bowel obstruction precludes the use of gastrointestinal prokinetic agents. Haloperidol may also be used under the latter circumstances. The phenothiazines are an alternative group of antiemetics, but extrapyramidal and anticholinergic adverse effects may be dose-limiting. Chlorpromazine has modest antiemetic activity but a high incidence of sedation, postural hypotension, and anticholinergic adverse effects, whereas piperazine derivatives such as prochlorperazine are stronger antiemetics but cause more extrapyramidal side effects. Anticholinergic side effects also limit the use of anticholinergic agents such as hyoscine hydrobromide (scopolamine) in opioid-induced nausea, particularly in patients with advanced cancer. These patients seem to be more vulnerable to these adverse effects. The role of 5-HT₃-receptor antagonists such as ondansetron in ameliorating opioid-induced nausea is not clear.

There appear to be differences between individual patients in the extent to which different opioids cause nausea. These differences form the basis for the strategy of switching from one opioid to another when a particular opioid produces persistent nausea. Switching the route, specifically from the oral to the parenteral, has also been suggested, but the study supporting this strategy is small.⁶²

Nausea and vomiting can sometimes persist beyond the opioid-initiation phase or occur de novo in patients on long-term opioid treatment. It may become chronic in nature. The multicausal nature of the problem needs to be recognized since management is directed at identifying and addressing the various causes. Chronic nausea has been associated with the accumulation of active opioid metabolites. A number of strategies are suggested to manage chronic nausea, including switching the opioid or decreasing the dose when pain is well controlled.

Cognitive and other neurotoxic side effects of opioids - Opioid-related neurotoxicity may manifest as cognitive impairment, hallucinations, delirium, generalized myoclonus, hyperalgesia and/or allodynia. Patients who have renal impairment or who are taking higher doses of opioids are at greater risk of developing these side effects. The mechanisms underlying these side effects are unclear, but the opioid metabolites are implicated. When patients present with generalized pain of an unknown source and the opioid dose has been recently increased, hyperalgesia should be considered as a possible diagnosis. The etiological contribution of opioids to cognitive impairment and delirium in the cancer patient is often difficult to determine. This is the case particularly in patients with advanced disease in which the baseline vulnerability is associated with multisystem impairment, and the concurrent administration of other psychotropic agents can complicate the assessment of etiology. Nonetheless, opioid-induced cognitive problems have been reported with increasing frequency in the last decade.^{63,64} In addition to cognitive impairment within the context of delirium, other effects include myoclonus, hyperalgesia, perceptual disturbance, and seizures. Although the remarkable characteristics, potential severity, and impact of delirium contribute to its dominance in the spectrum of opioid-related cognitive dysfunction, more subtle psychomotor and cognitive opioid effects have been described. Neuropsychological testing has been used to study these more-subtle effects in less-advanced cancer disease, chronic nonmalignant pain, and in healthy volunteers. Collectively, studies of neuropsychological testing have demonstrated somewhat mixed findings,⁶⁵ with some detecting opioid-associated impairment in certain aspects of psychomotor or cognitive function and others detecting minimal or no impairment. Clinical experience and some studies suggest that patients become tolerant of the sedating effects that accompany either the initiation of opioid therapy or dose increases,⁶⁶ thereby allowing patients who are otherwise physically able, and on stable opioid doses, to safely engage in activities such as driving.

Decreased brain cholinergic activity is recognized as one of the potential underlying pathophysiological mechanisms of delirium. In the case of meperidine, the anticholinergic activity associated with its active metabolite normeperidine is suspected to be the basis of the cognitive impairment and delirium occurring in association with this opioid.⁶⁷ Other opioid metabolites have been studied in relation to the generation of neuroexcitatory states in animal laboratory models and delirium in human subjects. A series of animal studies have demonstrated neuroexcitatory states in association with morphine metabolites, morphine-3-glucuronide (M-3-G) and normorphine-3-glucuronide, and the hydromorphone metabolite, hydromorphone-3-glucuronide.⁶⁸ In a hospice study of 36 patients with advanced cancer receiving morphine, both M-3-G and morphine-6-glucuronide (M-6-G) levels were studied in relation to the development of side effects, which included nausea and vomiting in 10 patients and cognitive impairment in 9 patients.⁶⁹ Creatinine levels, and plasma levels of M-3-G, M-6-G, and dose-corrected M-3-G and M-6-G, were higher in the 19 patients with side effects, suggesting that the elevation of morphine metabolites in association with

renal impairment was associated with opioid toxicity, including cognitive impairment. Evidence is extensive demonstrating elevation of opioid-metabolite levels in the setting of renal impairment,^{70,71} and some studies have noted an association with features of neurotoxicity, including cognitive impairment.⁶⁹ Switching to another opioid is one strategy for abating the side effects in cases in which accumulation of active metabolites is considered responsible for side effects such as generalized myoclonus, sedation, confusion, or chronic nausea.

The general management approach to opioid-induced delirium requires a multidimensional assessment to determine the presence of other potentially treatable contributory factors such as dehydration, other centrally acting medications, sepsis, and hypercalcemia. Clinical experience suggests that the presence of tactile hallucinations and myoclonus, although not exclusively associated with opioid toxicity, raise the suspicion of this cause. A careful assessment can also identify prognostic factors associated with greater difficulty in achieving pain control, the need for higher opioid doses, and consequently greater risk of opioid-induced delirium. These factors include neuropathic pain, incidental pain, tolerance, somatization of psychological distress, and a positive history of drug or alcohol abuse.⁷²

In addition to searching for underlying reversible causes of delirium, the symptomatic management of delirium requires the addition of a neuroleptic agent to control agitation and perceptual or delusional disturbance. Haloperidol is regarded as the drug of choice in this context, and methotrimeprazine and chlorpromazine are considered useful alternatives, especially when a greater level of sedation is required. Midazolam, a sedating and short-acting benzodiazepine given by continuous infusion, is sometimes necessary, especially in the case of nonreversible delirium. Typical anxiolytics, including lorazepam, can be used to manage comorbid anxiety. Early data suggest that some atypical antipsychotics may be beneficial in improving pain control and decreasing opioid requirements in the cancer patient with mild cognitive impairment and/or anxiety. It is unclear whether this benefit is due to a primary effect or to its secondary impact on cognitive impairment and/or anxiety.⁷³

The specific management approach to opioid-induced cognitive and other neurotoxic side effects involves either a dose reduction, a change in route, or an opioid switch. If the pain is well controlled, and the cognitive and neurotoxic side effects are not severe, modest opioid dose reduction may be effective. The rationale for switching opioids is that a more favorable balance between analgesia and side effects can be achieved, often with a lower dose than that predicted by the conventional analgesic table. This can reflect incomplete cross-tolerance among opioids in relation to analgesic and other effects. It is also possible that switching to a new opioid could allow for the elimination of potentially toxic opioid metabolites. Reduction in opioid dose in the context of an opioid-induced delirium has not been systematically evaluated but is also likely to have beneficial results. Although there is growing evidence to suggest a

beneficial role for opioid switching,⁷⁴ controversy persists over the relative value of opioid switching versus dose reduction.

Cognitive benefit has been reported with the use of methylphenidate in patients receiving a continuous infusion of opioids for cancer pain.⁷⁵ The psychostimulant benefit is likely to relate to mitigation of sedation associated with upward dose titration of opioid. Although psychostimulants have been advocated for hypoactive delirium, any evidence of perceptual or delusional disturbance is considered a contraindication. An open-label study of donepezil, a long-acting selective acetylcholinesterase inhibitor, suggests that it relieves opioid-associated fatigue and sedation in patients who are receiving opioids for cancer pain.⁷⁶

Respiratory depression - Patients receiving long-term opioid therapy generally develop tolerance to the respiratory-depressant effects of these agents. When indicated for reversal of opioid-induced respiratory depression, naloxone titrated in small increments or as an infusion should be administered to improve respiratory function without reversing analgesia. Monitor the patient carefully until the episode of respiratory depression resolves. Note that the opioid antagonists have a short half-life and may have to be given repeatedly until the agonist drug is sufficiently cleared.

Subacute overdose - Perhaps more common than acute respiratory depression, subacute overdose may manifest as slowly progressive (hours to days) somnolence and respiratory depression. Before analgesic doses are reduced, advancing disease must be considered, especially in the dying patient. Generally, withholding one or two doses of an opioid analgesic is adequate to assess whether mental and respiratory depression are opioid related. If symptoms resolve after temporary opioid withdrawal, reduce the scheduled opioid dosage by 25%. If symptoms do not abate, but the patient complains of or exhibits signs of increased pain, or if symptoms referable to opioid withdrawal occur, consider alternative causes for CNS depression and reinstate analgesic treatment. Ongoing assessment is essential to maintain adequate pain relief.

Sexual Side Effects - Reduced libido is a well-known phenomenon for those using heroin or those in a methadone maintenance program; however, clinicians prescribing opioids for pain poorly understand this effect. Early case studies of persons using heroin or methadone described diminished libido, sexual dysfunction, reduced testosterone levels in men, and amenorrhea in women.⁷⁷ These effects resolve after the opioid has been discontinued. More recent case reports of patients receiving opioids for relief of chronic pain suggest these same findings.⁷⁸ The long-term effects of reduced testosterone and amenorrhea are not well known. Sexuality is an essential component of quality of life in many patients, including patients with advanced disease. Patients should be assessed for changes in libido and sexual dysfunction. If these changes are distressing to the patient, serum testosterone levels may be obtained. Should the patient seek

improvement in libido and performance, treatment is often empirical, keeping in mind that there are many potential causes of changes in sexual function. Treatment includes using nonopioids for pain, adding adjuvant analgesics in the hope the opioid dose may be reduced, or replacing testosterone through injections or a patch (if not contraindicated). More research is needed to understand the relationship between opioids and sexual function, as well as the most effective treatment strategies.

Other opioid side effects - Dry mouth, urinary retention, pruritus, dysphoria, euphoria, sleep disturbances, and inappropriate secretion of antidiuretic hormone are less common.

Adjuvant Drugs

Adjuvant drugs are valuable during all phases of pain management to enhance analgesic efficacy, treat concurrent symptoms, and provide independent analgesia for specific types of pain. Adverse drug reactions are common, however, and there are wide interindividual and ethnic differences in drug metabolism. A survey on symptom severity and management in 593 cancer patients treated for an average of 51 days reported that during this time, anticonvulsants were used in 11.8% of patients, antidepressants in 16%, corticosteroids in 28%, and bisphosphonates in 7.3%.⁷⁹ Patients with advanced cancer on palliative medicine services are reported to receive on average 5 medications for symptom relief, and as a result are at high risk of drug interactions. Nevertheless, adjuvant analgesics have been extensively studied and reviewed in noncancer settings and are generally endorsed as an important intervention in the provision of adequate pain management.⁸⁰ Few trials compare adjuvant analgesics in the cancer setting.

Antidepressants

The analgesic benefits of tricyclic antidepressants have been well established and are generally considered first-line therapy for many neuropathic pain syndromes.⁸² Supporting evidence is strong for amitriptyline and desipramine, and there is endorsement of other newer antidepressants such as maprotiline and paroxetine. Patients with neuropathic pain characterized by continuous dysesthesias are generally believed to be the most likely to benefit from antidepressant management; however, a randomized placebo-controlled study of amitriptyline for neuropathic pain in cancer patients found only slight analgesic benefit with significantly worse adverse effects.⁸¹

The most common side effects of tricyclic antidepressants are constipation, dry mouth, blurred vision, cognitive changes, tachycardia, and urinary retention.

Caution has also been advised in treating patients with cardiac disease, and an electrocardiogram is sometimes recommended as a prudent measure. A slow upward titration is suggested as a good way to avoid side effects.

Anticonvulsants

The group of commonly used anticonvulsants as adjuvant analgesics for neuropathic pain includes carbamazepine, valproate, phenytoin, and clonazepam.

Clinical experience with carbamazepine is extensive, but use of this drug is limited in the cancer population because of concern that it causes bone marrow suppression, in particular leukopenia. Other common adverse effects include nystagmus, dizziness, diplopia, cognitive impairment, and mood and sleep disturbance.

Dosing guidelines for phenytoin are similar to those for the treatment for seizures. This drug can be administered using a loading dose, which may be particularly useful in patients with severe pain.

Gabapentin is increasingly reported as useful for the management of neuropathic pain associated with cancer and its treatment.⁸³ Commonly reported side effects include somnolence, dizziness, ataxia, and fatigue.⁸³

Clonazepam is an anticonvulsant from the benzodiazepine class and is commonly used for treating lancinating or paroxysmal neuropathic pain. The patient must be monitored carefully for drowsiness and cognitive impairment.

Local anesthetics

The use of mexiletine has been described for chronic neuropathic pain. Side effects are reported as common and include gastrointestinal toxicity, in particular nausea, and CNS side effects such as dizziness. Patients with a history of cardiac disease and those on higher doses are at increased risk of adverse effects, and it is recommended that they receive appropriate cardiac evaluation, including an electrocardiogram.

Corticosteroids

These drugs have achieved wide acceptance in the management of patients with cancer pain. They are indicated as adjuvant analgesics for cancer pain of bone, visceral, and neuropathic origin. Adverse effects include neuropsychiatric syndromes, gastrointestinal disturbances, proximal myopathy, hyperglycemia, aseptic necrosis, capillary fragility, and immunosuppression. The risk of adverse effects increases with the duration of use. As a result, use is often restricted to patients with a limited life expectancy; in addition, once effective pain control is obtained, it is commonly recommended that the dose be tapered as much as possible. Dosage recommendations vary from a trial of low-dose therapy such as dexamethasone 1 to 2 mg or prednisone 5 to 10 mg once or twice daily, to a starting dose of dexamethasone 10 mg twice daily with subsequent tapering to the minimal effective dose.⁸⁴

Another suggested use of corticosteroids is in high doses for short periods in patients with severe pain. This empirical approach recommends a regime of a single bolus of dexamethasone 100 mg IV followed by a small amount given 4 times per day and then tapered over the next few weeks.

Although there is widespread acceptance of steroid therapy, mostly via the oral route but also subcutaneously and intravenously, data remain inadequate for definitive conclusions regarding efficacy and dosing guidelines.

Bisphosphonates

These drugs have been recommended for the management of bone pain as well as the prevention of skeletal complications in patients with metastatic bone disease.⁸⁵ Their use in a study of breast cancer patients resulted in improved quality of life compared with that of patients not using bisphosphonates.⁸⁶ The bisphosphonates most frequently used are clodronate, pamidronate, and zoledronic acid.

Clodronate can be given orally or intravenously. Dosage recommendations are oral clodronate, 1,600 mg per day; or IV clodronate, 600 to 1,500 mg every 2 to 3 weeks. Clodronate is not available in the United States.

Pamidronate has been recommended in the dose range of 60 to 90 mg IV over 2 hours every 3 to 4 weeks; however, pooled results from 2 multicenter, double-blind, randomized, placebo-controlled trials (n = 350) using pamidronate (90 mg every 3 weeks) failed to demonstrate a benefit for bone pain.⁸⁷

Zoledronic acid is a potent bisphosphonate that can be given as an IV bolus over 15 to 30 minutes in the dose range of 4 to 8 mg; however, the 8-mg dose has been associated with deterioration of renal function.⁸⁸

Ibandronate can be given orally or intravenously. Dosing recommendations are 50 mg orally daily or 6 mg intravenously every 3 to 4 weeks.

Despite the potential benefits, a caution was released by the FDA regarding reports of osteonecrosis of the jaw in patients who received pamidronate disodium or zoledronic acid. Osteonecrosis occurred in patients who did not have malignancy in the head and neck region and who had not received radiation therapy to the jaw. Most of the cases were associated with dental procedures such as tooth extraction. While receiving these drugs, patients should avoid invasive dental procedures if possible.

Other Medications

Baclofen - This drug is generally used for spasticity but may also be used for the treatment of neuropathic pain.⁸⁰ Side effects include drowsiness, dizziness, ataxia, confusion, and nausea and vomiting.

Calcitonin - Although the mechanism by which calcitonin produces analgesia is unknown, historically it has been recommended for the treatment of both bone and neuropathic pain.⁸⁰ However, a systematic review of randomized double-blind clinical trials assessing the efficacy of calcitonin for control of metastatic bone pain does not support its use.⁸⁹ Because only two of these studies were evaluated as well designed, further research is necessary. The utility of calcitonin for bone pain is unclear.

Clonidine - This traditional antihypertensive can be given via the oral, epidural, or transdermal route and has been recommended as a trial for the management of neuropathic pain. Reported side effects include dry mouth, dizziness and hypotension, sedation, and constipation. The maximum recommended dose is 2.4 mg per day.

Psychostimulants - Psychostimulants such as dextroamphetamine, methylphenidate, and modafinil may enhance the analgesic effects of opioids. They may also be used to diminish opioid-induced sedation when reducing the dose is not possible.

NMDA Receptor Antagonists - There is increasing evidence for the importance of NMDA receptors and the possibility that NMDA antagonists may have a role in refractory cancer pain management.⁹⁰ Ketamine in subanesthetic doses has been used in this setting. The severe psychomimetic adverse effects associated with this treatment, including vivid hallucinations, limit widespread use of ketamine. Coadministration of a neuroleptic or benzodiazepine is recommended to limit the emergence of these effects. Ketamine is generally given subcutaneously at a low starting dose such as 0.1 mg per kg of body weight per hour, with a gradual escalation. Oral ketamine may be a more potent analgesic and have a more favorable side-effect profile than parenteral ketamine. One study suggests short-duration therapy of a continuous subcutaneous infusion of ketamine over 3 to 5 days. The initial dose is 100 mg per day, and if pain control is inadequate, the dose is escalated to 300 mg per day and then to a maximum dose of 500 mg per day. Treatment is continued for 3 days at either the lowest effective dose or 500 mg per day and then discontinued. A systematic review of the benefits and harms of ketamine in managing cancer pain revealed a general lack of studies and small subject numbers,⁹¹ precluding a definitive conclusion on benefits and harms.

Methadone, particularly the racemic mixture, appears to have significant NMDA-antagonist properties. The d-isomer blocks the NMDA receptor and as a result may yield independent analgesic effects and perhaps reverse some analgesic tolerance to the opioid. This may explain the often-unanticipated high potency of methadone.

Dextromethorphan, a commonly prescribed antitussive, may also have NMDA-blocking properties. The clinical significance of this effect, however, is unclear

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and studies have not been able to determine at what dose these effects may manifest. Oral dextromethorphan in doses of 60 or 90 mg given preoperatively and postoperatively has been shown to reduce pain intensity and opioid use after orthopedic oncology surgery.⁹² Additional studies are warranted in nonoperative oncology pain syndromes.

Adjuvant Medications Daily Dose Range

Class	Drug	Daily Dose Range
Antidepressants	amitriptyline (Elavil)	10–25 mg every day
	desipramine (Norpramin)	10–150 mg every day
	maprotiline (Ludiomil)	25 mg bid–50 mg tid
	duloxetine (Cymbalta)	20 mg bid–30 mg bid
	nortriptyline (Pamelor, Aventyl)	10–100 mg every day
	venlafaxine (Effexor)	37.5–225 mg every day
Anticonvulsants	carbamazepine (Tegretol)	100 mg tid–400 mg tid
	valproate (Depacon)	500 mg tid–1,000 mg tid
	gabapentin (Neurontin)	100 mg tid–1,000 mg tid
	clonazepam (Klonopin)	0.5 mg bid–4 mg bid
	lamotrigine (Lamictal)	25 mg bid–100 mg bid
	pregabalin (Lyrica)	150 mg divided into 2 or 3 doses; increase to 300 mg starting at day 3–7; if needed, increase to 600 mg 7 days later
Local anesthetics	mexiletine (Mexitil)	100 mg bid–300 mg tid
	lidocaine patch (Lidoderm)	5% patch contains 700 mg; one patch, 12 hours on, 12 hours off
Miscellaneous	baclofen (Lioresal)	5 mg tid–20 mg tid
	calcitonin (Calcimar)	100–200 IU (subcutaneous or intranasal)
	clonidine (Catapres)	0.1 mg bid–0.3 mg bid
	methylphenidate (Ritalin)	2.5 mg bid–20 mg bid

Physical and Psychosocial Interventions

Patients should be encouraged to remain active and participate in self-care when possible. Noninvasive physical and psychosocial modalities can be used concurrently with drugs and other interventions to manage pain during all phases of treatment. The effectiveness of these modalities depends on the patient's participation and communication of which methods best alleviate pain.

Physical Stimulation Techniques

Physical stimulation techniques have direct mechanical effects on tissues and enhance relaxation when applied gently. In this series of techniques, the skin is stimulated so that pressure, warmth, or cold is felt, but the feeling of pain is lessened or blocked. Massage, pressure, vibration, heat, cold, and menthol preparations are used to stimulate the skin. These techniques also change the flow of blood to the area that is stimulated. Sometimes skin stimulation will get rid of pain or lessen pain during the stimulation and for hours after it is finished.

Skin stimulation is done either on or near the area of pain. You can also use skin stimulation on the side of the body opposite the pain. For example, you might stimulate the left knee to decrease the pain in the right knee. Stimulating the skin in areas away from the pain can be used to increase relaxation and may relieve pain.

Heat

The use of heat on recently irradiated tissue is contraindicated, and diathermy and ultrasound are not recommended for use over tumor sites.

Cold

Cold treatment reduces swelling and may provide longer-lasting relief than heat but should be used cautiously in patients with peripheral vascular disease and on tissue damaged by radiation therapy.

Menthol

Many menthol preparations are available for pain relief. There are creams, lotions, liniments, or gels that contain menthol. When they are rubbed into the skin, they increase blood circulation to the affected area and produce a warm (sometimes cool) soothing feeling that lasts for several hours.

To use menthol preparations, test the skin by rubbing a small amount of the substance in a circle about the size of a quarter in the area of the pain (or the area to be stimulated). If the menthol does not create a problem, rub some more into the area. The feeling from the menthol gradually increases and remains up to several hours. To increase the strength and length of the feeling, the skin pores can be opened with heat (e.g., shower, sun). A heating pad should not be used because it may cause a burn).

Massage

Using a slow, steady, circular motion, massage over or near the area of pain. Some people find brushing or stroking lightly more comforting than deep massage.^{93,94,95}

Pressure

To use pressure, press on various areas over and near the pain with either the entire hand, heel of the hand, fingertip, or knuckle; or use one or both hands to encircle an entire arm or leg. Apply pressure for about 10 seconds. Pressure usually works best if it is applied as firmly as possible without causing more pain. Pressure may be used for up to 1 minute. This often will relieve pain for several minutes to several hours after the pressure is released.

Vibration

Vibration over and near the area of the pain may bring temporary relief. For example, the scalp attachment of a hand-held vibrator often relieves a headache. For low back pain, a long, slender battery-operated vibrator placed at the small of the back may be helpful. Vibrating devices such as a small battery-operated vibrator, a hand-held electric vibrator, a large heat-massage electric pad, or a bed vibrator may all be used. Do not use a vibrator on the stomach. Avoid vibration over red, raw, tender, or swollen areas.

Exercise

Exercises are recommended to strengthen weak muscles, mobilize stiff joints, restore coordination and balance, and promote cardiovascular conditioning.^{96,97,98} Therapists should instruct family members and other caregivers on techniques to help preserve strength and joint function. During acute pain, exercise should be limited to self-administered range-of-motion. Weight-bearing exercise should be avoided when bone fracture is likely.

Repositioning

Reposition the immobilized patient frequently to maintain correct body alignment, to prevent or alleviate pain, and to prevent pressure ulcers.

Immobilization

Use restriction of movement to manage acute pain or to stabilize fractures or otherwise compromised limbs or joints. Use adjustable elastic or thermoplastic braces to help maintain correct body alignment. Keep joints in positions of maximal function rather than maximal range. Avoid prolonged immobilization.

Transcutaneous Electrical Nerve Stimulation (TENS)

Controlled low-voltage electrical stimulation applied to large myelinated peripheral nerve fibers via cutaneous electrodes to inhibit pain transmission. Patients with mild-to-moderate pain may benefit from a trial of TENS to see if it is effective in reducing the pain. TENS is a low-risk intervention.⁹⁹

Acupuncture

Pain is treated by inserting small, solid needles into the skin, with or without the application of electrical current. Needle placement follows the Eastern theory of vital energy flow. It is noteworthy that almost all reported clinical studies on the effects of acupuncture on cancer or cancer therapy–related symptoms focus on symptom management rather than the disease itself. Investigations into the effects of acupuncture on chemotherapy-induced nausea and vomiting, many of which were randomized and well-controlled, produced the most convincing findings. Although a considerable number of favorable clinical acupuncture studies have been reported, most were case studies, clinical observations, or nonrandomized and poorly controlled clinical trials. In many studies, methodologic flaws in clinical study design hampered rigorous scientific efforts to evaluate the effects of acupuncture. Although pain relief is the most clinically common use of acupuncture, only a few studies on cancer pain are well-controlled or have sample sizes large enough to support their findings.^{100,101,102}

Cognitive-Behavioral Interventions

Cognitive-behavioral interventions are an important part of a multimodal approach to pain management. They help the patient obtain a sense of control and develop coping skills to deal with the disease and its symptoms. Guidelines by a National Institutes of Health assessment panel suggest integration of pharmacologic and behavioral approaches for treatment of pain and insomnia.¹⁰³ Recent studies suggest that behavioral interventions targeted to specific symptoms, such as pain and fatigue, can significantly reduce symptom burden and improve the quality of life for patients with cancer.¹⁰⁴ Realistic expectations are needed for delivery of cognitive-behavioral interventions. One study¹⁰⁵ of cognitive-behavioral interventions for pain management randomly assigned 57 patients (most of whom were women with metastatic breast cancer who were maintained on daily opioid use for pain) to three 20-minute interventions delivered by audiotape (progressive muscle relaxation [PMR], positive mood induction, or a distraction condition) or to a no-intervention control. The patients were provided the audiotapes by a research nurse, given brief instructions, and asked to use the tapes at least five times a week for 2 weeks; more than half of the patients reported complying with these instructions. The relaxation condition and the “distraction” condition produced significant immediate effects on pain, but the positive mood induction tapes showed no effects. The effects, however,

neither carried over to general symptom management nor affected pain management at other times. One conclusion of this study is that ideally, interventions should be matched to patient preferences; for more extended effects, additional instruction and support may be needed, as suggested by other studies.

Interventions introduced early in the course of illness are more likely to succeed because they can be learned and practiced by patients while they have sufficient strength and energy. Patients and their families should be given information about and encouraged to try several strategies, and to select one or more of these cognitive-behavioral techniques to use regularly:

Relaxation

Simple relaxation techniques should be used for episodes of brief pain (e.g., during procedures). Brief, simple techniques are preferred when the patient's ability to concentrate is compromised by severe pain, a high level of anxiety, or fatigue.¹⁰⁶

Relaxation relieves pain or keeps it from getting worse by reducing tension in the muscles. It can help promote sleep, provide more energy, reduce anxiety, and help other pain relief methods work better. Some people, for instance, find that taking pain medicine or using a cold or hot pack works faster and better when they relax at the same time.¹⁰⁷

There are many methods. Here are some examples:

Visual concentration and rhythmic massage:

- Open eyes and stare at an object, or close eyes and think of a peaceful, calm scene.
- With the palm of the hand, firmly massage near the area of pain in a circular pattern.

Inhale/tense, exhale/relax:

- Inhale deeply while contracting a muscle or a group of muscles. (For example, squeeze eyes shut, frown, clench teeth, make a fist, stiffen arms and legs, or draw up arms and legs.)
- Hold breath and keep muscles tense for a second or two.
- Relax. Exhale and let body go limp.

Slow rhythmic breathing:

- Stare at an object or close eyes and concentrate on breathing or on a peaceful scene.
- Take a slow, deep breath and, while breathing in, tense muscles.
- Breathe out and relax muscles.

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- Remain relaxed and breath slowly and comfortably, concentrating on breathing, taking about 9 to 12 breaths a minute.
- Continue slow, rhythmic breathing for a few seconds up to 10 minutes.
- To end slow rhythmic breathing, have the patient count silently and slowly from one to three
- Open eyes

Other methods that can be added to slow rhythmic breathing:

- Imagery.
- Listening to slow, familiar music through an earphone or headset.
- Progressive relaxation of body parts.

Precautions:

Some people who have used relaxation for pain relief have reported the following problems and have suggested the following solutions:

- Relaxation may be difficult to use with severe pain. Solution: Use quick and easy relaxation methods such as visual concentration with rhythmic massage or breathe in/tense, breathe out/relax.
- Sometimes breathing too deeply for a while can cause shortness of breath. Solution: take shallow breaths and/or breathe more slowly.
- Falling asleep. Solution: Sit in a hard chair while doing the relaxation exercise or set a timer or alarm.

Imagery

Imagery is the use of imagination to create mental pictures or situations. The way imagery relieves pain is not completely understood.¹⁰⁸ Imagery can be thought of as a deliberate daydream that uses all of the senses — sight, touch, hearing, smell, and taste. Some people believe that imagery is a form of self-hypnosis.

Imagery usually works best with eyes closed. It is sometimes helpful to use a relaxation technique before using imagery. The image can be something like a ball of healing energy or a picture drawn in the mind of a person without pain. Or have the patient think of a pleasant, safe, relaxing place or activity that has made them happy. Exploring this place or activity in their mind in great detail can help them feel calm.

Here is an exercise with the ball of energy.

- Close eyes. Breathe slowly and feel relaxed.
- Concentrate on breathing. Breathe slowly and comfortably from the abdomen. While breathing in, say silently and slowly, "In, one, two." While breathing out, say, "Out, one, two." Breathe in this slow rhythm for a few minutes.

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- Imagine a ball of healing energy forming in the lungs or on the chest. It may be like a white light. It can be vague. It does not have to be vivid. Imagine this ball forming, taking shape.
- When ready, imagine that the air breathed in blows this healing ball of energy to the area of pain. Once there, the ball heals and relaxes.
- When breathing out, imagine the air blows the ball away from the body. As it goes, the ball takes the pain with it.
- Repeat the last two steps with each inhalation and exhalation.
- Imagine that the ball gets bigger and bigger as it takes more and more discomfort away from the body.
- To end the imagery, have the patient count slowly to three, breathe in deeply, open their eyes, and say silently, "I feel alert and relaxed."

Problems that may occur with imagery are similar to the ones that occur with the relaxation techniques.

Hypnosis

Hypnotic techniques may be used to induce relaxation and may be combined with other cognitive-behavioral strategies. Hypnosis is a trance-like state of high concentration between sleeping and waking. In this relaxed state, a person becomes more receptive or open to suggestion. Hypnosis can be used to block the awareness of pain, to substitute another feeling for the pain, and to change the sensation to one that is not painful.¹⁰⁸ People can easily be taught, by a hypnotherapist, to place themselves in a hypnotic state, make positive suggestions to themselves, and to leave the hypnotic state. Hypnosis is effective in relieving pain in individuals who can concentrate well, can use imagery, and are motivated to practice.

Cognitive Distraction

Focusing attention on stimuli other than pain or negative emotions accompanying pain may involve distractions that are internal (e.g., counting, praying, or making self-statements such as "I can cope") or external (e.g., listening to music, watching television, talking, listening to someone read, or using a visual focal point). Distraction focuses on turning attention to something other than the pain. People use this method without realizing it when they watch television or listen to the radio to "take their minds off" a worry or their pain.

Distraction may be used alone to manage mild pain or used with medicine to manage brief episodes of severe pain, such as pain related to procedures. Distraction is useful when the patient is waiting for pain medicine to start working. Distraction can be a powerful way of relieving even the most intense pain for awhile.

Patient/Family Education

Both oral and written information and instructions should be provided about pain, pain assessment, and the use of drugs and other methods of pain relief. Patient education should emphasize that almost all pain can be effectively managed. Major barriers to effective pain management should be discussed to correct patient and family misconceptions. Health care providers need to take into consideration family members' interpretation of patient pain when providing pain management education services, as some caregivers overestimate patient pain.⁶ Educational intervention programs to help patients who have cancer and their families manage pain have been described and may improve clinical outcomes. These programs are based on adult learning principles and incorporate key strategies, including provision of information using academic detailing, skill building with ongoing nurse-coaching, and interactive nursing support. Training partners to participate in management of cancer pain increases partner self-efficacy for controlling their loved one's pain and other symptoms.¹⁰⁹

Psychotherapy and Structured Support

Some patients benefit from short-term psychotherapy provided by trained professionals. Patients whose pain is particularly difficult to manage and who develop symptoms of clinical depression or adjustment disorder should be referred to a psychiatrist or psychologist for diagnosis. The relationship between poorly controlled pain, depression, and thoughts of suicide should not be ignored.

Support Groups and Pastoral Counseling

Because many patients benefit from peer support groups, clinicians should be aware of locally active groups and offer this information to patients and their families. Pastoral counseling members of the health care team should participate in meetings to discuss patients' needs and treatment. They should also be a source of information on community resources for spiritual care and social support.

Antineoplastic Interventions

Radiation Therapy

Local, half-body, or whole-body radiation enhances the effectiveness of analgesic drug and other noninvasive therapy by directly affecting the cause of pain (i.e., reducing primary and metastatic tumor bulk).¹¹⁰ Single or multifraction regimens of external-beam radiation therapy are equally effective when radiation is administered for pain relief; however, retreatment is needed somewhat more often after single-fraction therapy.¹¹¹ Dosages must be chosen to achieve a

balance between the amount of radiation required to kill tumor cells and that which would adversely affect normal cells or allow the repair of damaged tissue.

A single intravenous injection of beta particle-emitting agents such as iodine, phosphorus-32-orthophosphate, and strontium, as well as the investigational new drugs rhenium and samarium can relieve pain of widespread bony metastases. Half the patients so treated respond to a second treatment if pain recurs.¹¹²

Radiofrequency Ablation

Radiofrequency ablation (RFA) of painful osteolytic bony metastases may provide pain relief. In a nonconsecutive 27-month period, 43 patients from 9 sites across the United States and Europe underwent RFA. Of the 43 patients, 41 (95%) experienced a decrease in worst pain (at least 2 points on an 11-point scale) that continued for up to 24 hours. After peaking at week 1, the morphine equivalent daily dose decreased significantly at weeks 8 and 12, before rising again at week 24. Three patients experienced adverse events that included a second-degree skin burn at the grounding pad site, transient bladder and bowel incontinence after treatment of a sacral lesion, and an acetabular fracture 6 weeks after RFA of a lesion involving the ileum, ischium, and acetabulum. Other uncontrolled case reports confirm these findings.¹¹³ Further study to determine potential risks and benefits may be warranted.

Surgery

Curative excision or palliative debulking of a tumor has potential to reduce pain directly, relieve symptoms of obstruction or compression, and improve prognosis, even increasing long-term survival. Oncologic surgeons and other health care providers should be familiar with the interactions of chemotherapy, radiation therapy, and surgical interventions to avoid or anticipate iatrogenic complications. They should also recognize characteristic pain syndromes that follow specific surgical procedures.

Invasive Interventions

Less-invasive analgesic approaches should precede invasive palliative approaches; however, for a minority of patients in whom behavioral, physical, and drug therapy do not alleviate pain, invasive therapies are useful.

Nerve Blocks

Control of otherwise intractable pain can be achieved by the application of a local anesthetic or neurolytic agent. Nerve blocks are performed for several reasons:

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- **Diagnostic:** To determine the source of pain (e.g., somatic versus sympathetic pathways).
- **Therapeutic:** To treat painful conditions that respond to nerve blocks (e.g., celiac block for pain of pancreatic cancer).
- **Prognostic:** To predict the outcome of long-lasting interventions (e.g., infusions, neurolysis, rhizotomy).
- **Preemptive:** To prevent procedure-related pain.

A single injection of a nondestructive agent such as lidocaine or bupivacaine, alone or in combination with an anti-inflammatory corticosteroid for a longer-lasting effect, can provide local relief from nerve or root compression. Placement of an infusion catheter at a sympathetic ganglion extends the sympathetic blockade from hours to days or weeks. Destructive agents such as ethanol or phenol can be used to effect neurolysis at sites identified by local anesthesia as appropriate for permanent pain relief and may also be used to cause destruction of central nervous system structures. The efficacy of neurolytic sympathetic blocks may vary depending on the underlying pain mechanisms involved. For patients with multiple pain mechanisms, neurolytic sympathetic blocks may serve as adjuvant techniques to analgesic medications.

Neurosurgery

Neurosurgery can be performed to implant devices to deliver drugs or to electrically stimulate neural structures. Surgical ablation of pain pathways should, like neurolytic blockade, be reserved for situations in which other therapies are ineffective or poorly tolerated. In general, the choice of neurosurgical procedure is based on location and type of pain (somatic, visceral, deafferentation), the patient's general condition and life expectancy, and the expertise and follow-up available.

Management of Procedural Pain

Many diagnostic and therapeutic procedures are painful to patients. Treat anticipated procedure-related pain prophylactically and integrate pharmacologic and nonpharmacologic interventions in a complementary style.

Use local anesthetics and short-acting opioids to manage procedure-related pain, allowing adequate time for the drug to achieve full therapeutic effect. Anxiolytics and sedatives may be used to reduce anxiety or to produce sedation.

Cognitive-behavioral interventions, such as imagery or relaxation, are useful in managing procedure-related pain and anxiety. Patients generally tolerate procedures better when they are informed of what to expect.

Offer the option for a relative or friend to accompany the patient for support.

Geriatric Considerations

Like other adults, older patients require comprehensive assessment and aggressive management of cancer pain. Older patients are at risk for undertreatment of pain, however, because of underestimation of their sensitivity to pain, the expectation that they tolerate pain well, and misconceptions about their ability to benefit from the use of opioids. The following are issues that should be considered when assessing and treating cancer pain in older patients.

Multiple chronic diseases and sources of pain.

Age and complex medication regimens place them at increased risk for drug-drug and drug-disease interactions.

Visual, hearing, motor, and cognitive impairments.

The use of simple descriptive, numeric, and visual-analog pain-assessment instruments may be impeded. Cognitively impaired patients may require simpler scales and more frequent pain assessment.

Nonsteroidal anti-inflammatory drug (NSAID) side effects.

Although effective alone or as adjuncts to opioids, NSAIDs are more likely to cause gastric and renal toxicity and other drug reactions such as cognitive impairment, constipation, and headaches in older patients. Alternative NSAIDs (e.g., choline magnesium trisalicylate) or coadministration of misoprostol with NSAIDs should be considered to reduce gastric toxicity.

Opioid effectiveness.

Older persons tend to be more sensitive to the analgesic and central nervous system depressant effects of opioids. Peak opioid effects are generally greater and the duration of pain relief may be longer.

Patient-controlled analgesia.

Slower drug clearance and increased sensitivity to undesirable drug effects (e.g., cognitive impairment) indicate the need for cautious initial dosing and subsequent titration and monitoring of continuous parenteral infusions.

Alternative routes of administration.

Although useful for patients who have nausea or vomiting, the rectal route may be inappropriate for elderly or infirm patients who are physically unable to place the suppository in the rectum.

Postoperative pain control.

Following surgery, surgeons and other health care team members should maintain frequent direct contact with the elderly patient to reassess the quality of pain management.

Change of setting.

Reassessment of pain management and appropriate changes should be made whenever the elderly patient moves (e.g., from hospital to home or nursing home).

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Post-Test

1. Which of the following is NOT one of the identified barriers to effective pain management of cancer patients?
 - A. Poor assessment of pain by health care professionals.
 - B. Fear by patients that they will be thought of as a drug addict.
 - C. Inadequate reimbursement for cancer pain treatment
 - D. Increased potential for metastatic activity caused by opiate based medications.

2. A patient has been assessed using the Edmonton Staging System for Cancer Pain. Their scores are as follows: A3, B1, C2, D1, E2, F1, G2. What is this patient's prognosis for effective pain management?
 - A. Good
 - B. Intermediate
 - C. Poor
 - D. Unable to determine

3. Which medication is NOT classified as a Step 1 analgesic?
 - A. Fentanyl
 - B. Anaprox
 - C. Dolobid
 - D. Toradol

4. The most commonly used opioid for management of cancer pain is _____.
 - A. Hydromorphone
 - B. Morphine
 - C. Oxycodone
 - D. Methadone

5. Patients who take controlled-released oxycodone typically experience initial relief in ____ hour(s), and peak relief in ____ hours.
 - A. 1, 2-3
 - B. 2, 3-5
 - C. 3, 5-7
 - D. 4, 7-9

6. Which of the following is NOT a recommended route of administration for opioid medications?
 - A. Rectal
 - B. Transdermal
 - C. Parenteral
 - D. Intramuscular

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7. Which of the following is NOT a common side effect of opioids?
- A. Cognitive impairment
 - B. Respiratory depression
 - C. Bradykinesia
 - D. Constipation
8. Which of the following statements is TRUE?
- A. Cryotherapy is recommended for decreasing the inflammation over areas treated with radiation therapy.
 - B. During periods of acute pain, exercise should be limited to therapist performed passive range of motion.
 - C. During periods of immobilization, joints should be positioned to maintain maximal range of motion.
 - D. TENS is a low risk intervention for patients with cancer
9. Which of the following is NOT an example of a cognitive-behavioral intervention technique?
- A. Acupuncture
 - B. Slow rhythmic breathing
 - C. "Ball of energy" imagery
 - D. Praying
10. Which of the following statements is FALSE?
- A. NSAIDS are more likely to cause renal toxicity in older patients.
 - B. Older patients tend to be more sensitive to the central nervous system depressant effects of opioids.
 - C. Geriatric patients tend to have a relatively fast drug clearance and may require higher initial dosing of parenteral infusions.
 - D. Reassessment of pain status and appropriate plan modifications should be made whenever an elderly patient changes living environments.