

The Management of Cancer Pain

Nathan I. Cherny, MBBS

Abstract

Any therapeutic strategy developed for patients experiencing cancer pain depends on the goals of care, which can be broadly categorized as prolonging survival, optimizing comfort, and optimizing function. The relative priority of these goals for any individual should direct therapeutic decision-making.

By combining primary treatments, systemic analgesic agents, and other techniques, most cancer patients can achieve satisfactory relief of pain. In cases where pain appears refractory to these interventions, invasive anesthetic or neurosurgical maneuvers may be necessary, and sedation may be offered to those with unrelied pain at the end of life.

The principles of analgesic therapy are presented, as well as the practical issues involved in drug administration, ranging from calculating dosage to adverse effects, and, when necessary, how to switch and/or combine therapies. Adjuvant analgesics, which are drugs indicated for purposes other than relief of pain but which may have analgesic effects, are also listed and discussed in some detail.

Surgical and neurodestructive techniques, such as rhizotomy or cordotomy, although not frequently required or performed, represent yet other options for patients with unremitting pain and diminished hope of relief.

Although cancer pain can be a complex medical problem arising from multiple sources, patients should be assured that suffering is not inevitable and that relief is attainable. (CA Cancer J Clin 2000;50:70-116.)

Pain is among the most prevalent symptoms experienced by patients with cancer.¹ The success of cancer pain therapy—which depends on the ability of the clinician to assess the presenting problems, identify and evaluate pain syndromes, and formulate a plan for comprehensive continuing care—requires familiarity with a range of therapeutic options (Table 1) and an approach to long-term care that is responsive to the changing needs of the patient.

The formulation of an effective therapeutic strategy for the management of pain and other symptoms is predicated on a comprehensive assessment of the patient. Such an assessment should clarify the characteristics of the pain, including its impact on function and psychological well-being; identify the pain syndrome and the putative mechanisms that may underlie the pain; define and evaluate both the nature and extent of the underlying disease; and characterize concurrent problems (physical, psychological, and social) that are contributing, or may soon contribute, to patient distress.

The particular therapeutic strategy that evolves from this information depends on the goals of care. These goals can generally be grouped into three broad categories: 1) Prolonging survival, 2) optimizing comfort, and 3) optimizing function. The relative priority of these goals provides an essential context for

Dr. Cherny is Director of Cancer Pain and Palliative Medicine in the Department of Medical Oncology at Shaare Zedek Medical Center, Jerusalem, Israel. He is also a consultant to Roxanne Laboratories and Teva Pharmaceuticals.

This article is also available online at <http://www.ca-journal.org>.

Table 1
Analgesic Therapies for Cancer Pain

Therapy	Examples
Primary Therapy	Chemotherapy Radiotherapy Hormone therapy Immunotherapy Surgery Antibiotics
Systemic Analgesic Pharmacotherapy	Non-opioid analgesics Opioids Adjuvant analgesics
Anesthetic Techniques	Intraspinal opioids ± local anesthetic Chemical rhizotomy Somatic neurolysis Sympathetic blockade
Neurosurgical Techniques	Rhizotomy Cordotomy Cingulotomy Pituitary ablation
Physiatric Techniques	Orthoses Physical therapy
Psychological Techniques	Relaxation training Distraction techniques
Neurostimulatory Techniques	Transcutaneous electrical nerve stimulation Acupuncture

therapeutic decision-making.

Most cancer patients can attain satisfactory relief of pain through an approach that incorporates primary treatments, systemic analgesic therapy, and at times, other non-invasive techniques (such as psychological or rehabilitative interventions). Some patients whose pain remains inadequately relieved may benefit from invasive anesthetic or neurosurgical treatments and, occasionally, sedation may be considered for patients with re-

fractory pain at the end of life.

Primary Therapy

The assessment process may reveal a cause for the pain that is amenable to primary therapy (i.e., therapy directed at the cause of the pain). This therapy may improve comfort, function, or duration of survival. For example, pain generated by tumor infiltration may respond to antineoplastic treatment with surgery, radiothera-

py, or chemotherapy; and pain caused by infections may be relieved with antibiotic therapy or drainage procedures. Specific analgesic treatments are usually required as adjuncts to the primary therapy.

RADIOTHERAPY

The analgesic effectiveness of radiotherapy is documented by abundant data and favorable clinical experiences in the treatment of painful bone metastases,² epidural neoplasm,³ and headache due to cerebral metastases.⁴ Data are lacking in other settings, however, and the use of radiotherapy is largely anecdotal. For example, results of radiotherapy for perineal pain due to low sacral plexopathy appear to be encouraging,⁵ and hepatic radiotherapy (e.g., 2,000 to 3,000 cGy) can be well tolerated and effective for the pain of hepatic capsular distention in 50% to 90% of patients.⁶

CHEMOTHERAPY

Despite a paucity of data concerning the specific analgesic benefits of chemotherapy, there is a strong clinical impression that tumor shrinkage is generally associated with relief of pain. Although there are some reports of analgesia even in the absence of significant tumor shrinkage,^{7,8} the likelihood of a favorable effect on pain is generally related to the likelihood of tumor response. In all situations, the decision to administer chemotherapy solely for the treatment of symptoms should be promptly reconsidered unless the patient demonstrates a clearly favorable balance between relief and adverse effects.

SURGERY

Surgery may have a role in the relief of symptoms caused by specific problems, such as obstruction of a hollow viscus, unstable bony structures, and compression of neural tissues.⁹ The potential benefits must be weighed against the risks of surgery, the anticipated length of hospitalization and convalescence, and the predicted duration of benefit.¹⁰ Clinical expe-

rience has generally been most favorable when surgery has been used to stabilize pathological fractures,¹¹ relieve bowel obstructions, or drain symptomatic ascites. Large volume (up to five to 10 liters) paracentesis, for example, may provide prompt and prolonged relief from the pain and discomfort of tense ascites,¹² with a small risk of hypotension^{12,13} or hypoproteinemia.¹⁴ Radical surgery to excise locally advanced disease in patients with no evidence of metastatic spread may be palliative and may potentially increase the survival of some patients.^{15,16}

ANTIBIOTIC THERAPY

Antibiotics may provide analgesia when the source of the pain, such as in cellulitis, chronic sinus infections, pelvic abscess, pyonephrosis, and osteitis pubis, involves infection. In some cases, infection may be occult and is confirmed only by the symptomatic relief provided by empiric treatment with these drugs.¹⁷

Systemic Analgesic Pharmacotherapy

Analgesic pharmacotherapy is the mainstay of cancer pain management. Based on clinical convention, analgesic drugs can be classified into three groups: 1) the non-opioid analgesics, 2) the opioid analgesics, and 3) adjuvant analgesics, which are agents with other primary indications that can provide effective analgesia in specific circumstances.

PRINCIPLES OF THE "ANALGESIC LADDER"

An expert committee convened by the Cancer Unit of the World Health Organization (WHO) developed a useful approach to drug selection for cancer pain that has become known as the "analgesic ladder."¹⁸ Emphasizing that pain intensity should be the prime consideration in analgesic selection, the approach advocates three basic steps (Fig.):

Step 1) Patients with mild-to-moder-

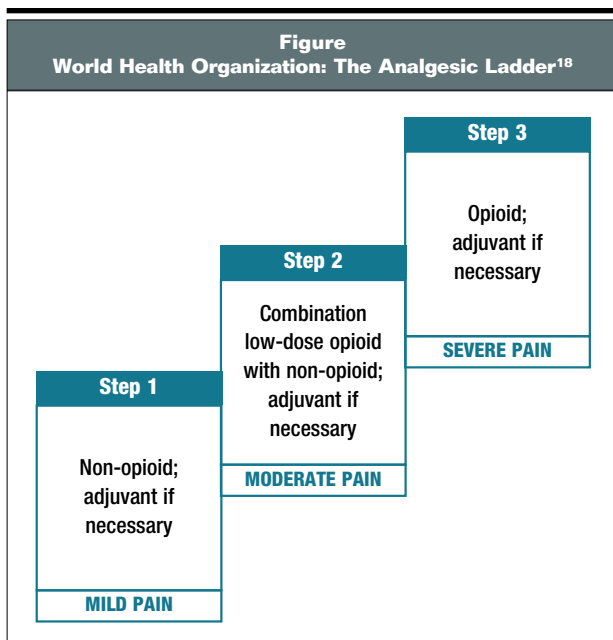
ate cancer-related pain should be treated with non-opioid analgesics, which should be combined with adjuvant analgesics if a specific indication for these exists.

Step 2) Patients who are relatively intolerant and present with moderate-to-severe pain, or who fail to achieve adequate relief after a trial of a non-opioid analgesic, should be treated with an opioid conventionally used to treat pain of this intensity. Traditionally, this has been accomplished using

a combination product containing a non-opioid (e.g., aspirin or acetaminophen) and an opioid (such as codeine, oxycodone, or propoxyphene). These compounds can also be coadministered with adjuvant analgesics.

Step 3) Patients who present with severe pain, or who fail to achieve adequate relief following appropriate administration of drugs on the second rung of the “analgesic ladder,” should receive an opioid agonist conventionally used for pain of this intensity. This drug may also be combined with a non-opioid analgesic or an adjuvant drug.

Despite evidence from a series of validation studies demonstrating that this approach, combined with appropriate dosing guidelines, provides adequate relief to 70% to 90% of patients,¹⁹ the strategy has come under criticism. A review of the validation studies concluded that there was a lack of evidence for the long-



term efficacy of the three-step approach.²⁰ Additionally, the recent development of low-dose formulations of pure opioid agonists traditionally used for severe pain and the introduction of other types of analgesic agents such as tramadol, has blurred the distinction between steps 2 and 3.

Notwithstanding these reservations, the two guiding principles of the ladder, namely, that analgesic selection should be primarily determined by the severity of the pain and that adjuvant analgesics should be used when necessary, remain sound and continue to be widely endorsed.^{19,21-23}

NON-OPIOID ANALGESICS

The non-opioid analgesics [aspirin, acetaminophen, and the non-steroidal anti-inflammatory drugs (NSAIDs)] are useful alone for mild-to-moderate pain (Step 1 of the analgesic ladder) and provide additive analgesia when combined with opioid drugs in the treatment of more severe

pain. Unlike opioid analgesics, the non-opioid analgesics have a “ceiling” effect for analgesia and produce neither tolerance nor physical dependence.

The non-opioid analgesics constitute a heterogeneous group of compounds that differ in chemical structure but share many pharmacological actions (Table 2). Some of these agents, such as aspirin and the NSAIDs, inhibit the enzyme cyclo-oxygenase and consequently block the biosynthesis of prostaglandins, inflammatory mediators known to sensitize peripheral nociceptors.²⁴ A central mechanism has also been described,²⁴ and appears to predominate in acetaminophen analgesia.²⁵

Adverse Effects

The safe administration of non-opioid analgesics requires familiarity with their potential adverse effects. Aspirin and the other NSAIDs have a broad spectrum of potential toxicity, with bleeding diathesis due to inhibition of platelet aggregation, gastroduodenopathy (including peptic ulcer disease), and renal impairment being the most common.²⁶ Less common adverse effects include confusion, precipitation of cardiac failure, and exacerbation of hypertension. Particular caution should be exercised when these agents are administered to patients at increased risk of adverse effects, such as the elderly, those with blood clotting disorders, predilection to peptic ulceration, impaired renal function, and those receiving concurrent corticosteroid therapy.

The risk of gastrointestinal bleeding can be minimized by appropriate drug selection and the use of peptic cytoprotective agents. It has recently been discovered that there are at least two isoforms of cyclo-oxygenase with distinct roles in analgesia and toxicity.²⁴ Cyclo-oxygenase-1 is responsible for the synthesis of the protective prostaglandins that preserve the integrity of the stomach lining and maintain normal renal function in a compromised kidney; cyclo-oxygenase-2 is an inducible

enzyme involved in inflammation, pain, and fever. Recently, a range of relatively selective cyclo-oxygenase-2 inhibitors, including meloxicam, nimesulide, rofecoxib, and celecoxib, have been introduced and approved as analgesics. Early data indicate that while these agents are equianalgesic with the non-selective inhibitors, they are associated with less mucosal and renal morbidity.²⁷

Among the conventional NSAIDs, the non-acetylated salicylates, including choline magnesium trisalicylate and sal-salate,²⁸ which have lesser effects on platelet aggregation and no effect on bleeding time at the usual clinical doses, are preferred in patients with tendencies to peptic ulceration or bleeding.

Data from randomized trials support the use of omeprazole,²⁹ misoprostol,³⁰ or famotidine,³¹ as the preferred agents for the prevention of NSAID-related peptic ulceration. In contrast, acetaminophen rarely produces gastrointestinal toxicity and there are no adverse effects on platelet function. Hepatic toxicity is possible, however, and patients with chronic alcoholism and liver disease can develop severe hepatotoxicity at the usual therapeutic doses of acetaminophen.³²

Dosing

A minimal effective analgesic dose, ceiling dose, or toxic dose for any individual patient with cancer pain is unknown. Doses may, in fact, be higher or lower than the usual dose ranges recommended for the drug involved. Recommended doses are usually derived from studies performed in relatively healthy patients who have an inflammatory disease, a population clearly dissimilar from those with cancer pain, who often have coexistent organ failure and who may be receiving other medications concurrently. Given that the effects of these drugs are (at least partially) dose-dependent, administration of NSAIDs should begin with low initial doses, followed, if necessary, with gradual dose escalation. Based on clinical experi-

Table 2
Non-opioid Analgesics

Chemical Class	Generic Name
Non-Acidic	Acetaminophen Nabumetone Nemesulide Meloxicam Surgery Antibiotics
Acidic Salicylates	Aspirin Diflunisal Choline magnesium trisalicylate Salsalate
Propionic Acids	Ibuprofen Naproxen Fenoprofen Ketoprofen Flurbiprofen Suprofen
Acetic Acids	Indomethacin Tolmentin Sulindac Diclofenac Ketorolac
Oxicams	Piroxicam
Fenemates	Mefenamic acid Meclofenamic acid

ence, an upper limit for dose titration is usually set at 1.5 to 2.0 times the standard recommended dose of the drug in question. As failure with one NSAID does not preclude success with another, sequential trials of several NSAIDs may be useful to identify a drug with a favorable balance between analgesia and side effects.

Opioid Analgesics

A trial of systemic opioid therapy should be administered to all cancer patients

with pain of moderate or greater severity, regardless of the pain mechanism. Although somatic and visceral pain appear to be relatively more responsive to opioid analgesics than is neuropathic pain, a neuropathic mechanism does not confer "opioid resistance" or "opioid unresponsiveness." Appropriate dose escalation of opioid agents will identify many patients with neuropathic pain who can achieve adequate relief with these drugs.^{33,34}

Optimal use of opioid analgesics requires a sound understanding of the gen-

eral principles of opioid pharmacology, the pharmacological characteristics of each of the commonly used drugs, and principles of administration, including drug selection, routes of administration, dosing and dose titration, and prevention and management of adverse effects.

General Principles of Opioid Pharmacology

Classification: Opioid compounds can be divided into agonist, agonist-antagonist, and antagonist classes based on their interactions with the various receptor subtypes (Table 3). The pure agonists are most commonly used in the management of cancer pain. The mixed agonist-antagonist opioids (pentazocine, nalbuphine, and butorphanol) and the partial agonist opioids (buprenorphine and probably dezocine), on the other hand, play a minor role in the management of cancer pain because of the existence of a ceiling effect for analgesia, the potential for precipitating withdrawal in patients physically dependent on opioid agonists, and in the case of mixed agonist-antagonists, the problem of dose-dependent psychomimetic side effects that exceed those of pure agonist drugs.³⁵

Dose-Response Relationship: The pure agonist opioids do not have a ceiling dose per se; as the dose is raised, analgesic effects increase in a semi log-linear function, until either analgesia is achieved or the patient develops dose-limiting adverse effects such as nausea, vomiting, confusion, sedation, myoclonus, or respiratory depression. In practice, the efficacy of any particular drug in a specific patient will be determined by the degree of analgesia produced following dose escalation through a range limited by the development of adverse effects.³³

Relative Potency and Equianalgesic Doses: Relative analgesic potency is the ratio of the dose of two analgesics required to produce the same analgesic ef-

fect. By convention, the relative potency of each of the commonly used opioids is based on comparison with 10 mg of parenteral morphine. Equianalgesic dose information (Table 4) provides guidelines for dose selection when the drug or route of administration is changed, and is generally useful as a reference point. Equianalgesic doses should not be considered standard starting doses nor should they be considered a firm guideline when switching between opioid agents. Numerous variables may influence the appropriate dose for individual patients, including pain severity, prior opioid exposure (and the degree of cross-tolerance this confers), age, route of administration, level of consciousness, and metabolic abnormalities.

Recently, data have emerged indicating that the relative potency of methadone may have been previously underestimated. It appears that the methadone:morphine equianalgesic ratio is curvilinear rather than linear: At low doses of morphine (30 to 200 mg oral morphine), it is 1:4-1:6 and at high doses (greater than 300 mg oral morphine), 1:10-1:12.³⁶

Opioid Agonists (Table 3)

Codeine: Codeine is the most commonly used opioid analgesic for the management of mild-to-moderate pain, and is generally formulated in combination with aspirin or acetaminophen. Its plasma half-life and duration of action is usually in the range of two to four hours. Recently, it has been demonstrated that the analgesic effect of codeine is at least partly dependent on the metabolism of codeine to morphine by the genetic polymorphic cytochrome P-450 CYP2D6 (sparteine oxygenase). Approximately 7% of Caucasians lack CYP2D6 activity (poor metabolizers) due to inheritance of two non-functional alleles; in these people, codeine has a diminished analgesic effect.³⁷

Dihydrocodeine: Dihydrocodeine is an equianalgesic codeine analogue, and in

Table 3
Analgesic Opioids Classified
By Receptor Interactions

Agonists

Codeine
 Oxycodone
 Hydrocodone
 Dihydrocodeine
 Heroin
 Oxymorphone
 Meperidine
 Levorphanol
 Hydromorphone
 Methadone
 Fentanyl
 Sufentanil
 Alfentanil
 Propoxyphene

Partial Agonists

Buprenorphine
 Dezocine

Agonist/Antagonists

Pentazocine
 Butorphanol
 Nalbuphine

the US, is only available in combination with acetaminophen or aspirin. A single-agent sustained-release formulation has recently been developed. As with codeine, poor metabolizers of sparteine experience diminished analgesia with dihydrocodeine.³⁸

Hydrocodone: Hydrocodone has an oral analgesic potency that is approximately half that of oral morphine. It is available in a combination tablet that incorporates 10 mg hydrocodone with 1,000 mg acetaminophen.³⁹ Hydrocodone is metabolized to morphine by cytochrome P-450 CYP2D6 to hydromorphone and, consequently, poor metabolizers derive only a diminished analgesic effect.

Oxycodone: Oral oxycodone has a high bioavailability (60%) and an analgesic

potency that is 25% to 50% greater than that of morphine.⁴⁰ Oral oxycodone, in combination with aspirin or acetaminophen in products that provide 5 mg of oxycodone per tablet, is a useful drug for treatment of moderate pain, as described in Step 2 of the "analgesic ladder." Single-agent tablet or syrup formulations of oxycodone are also available, doses of which can be adjusted to effectively manage severe pain. Recently, sustained-release formulations have been developed with an eight-to-12-hour duration of action, which is suitable for the management of both moderate and severe pain.^{40,41} In some countries, oxycodone pectinate is available as a rectal suppository, which has a delayed absorption and prolonged duration of effect.

Propoxyphene (Dextropropoxyphene):

Propoxyphene is a congener of methadone. It is metabolized to norpropoxyphene, which has a long half-life and is associated with excitatory effects, including tremulousness and seizures. These effects are dose-related and are not a clinical problem at doses typically administered for moderate pain (50 to 100 mg every four hours).⁴² Rarely, propoxyphene may induce a hepatotoxic reaction,⁴³ and potentially dangerous drug interactions have been reported when propoxyphene has been administered together with carbamazepine, warfarin, or alcohol.

Morphine: Based on its availability and the clinician's familiarity with its use, morphine has been designated as the prototypical agent for Step 3 of the "analgesic ladder."¹⁹ Its availability in a wide range of formulations—injectable, immediate- and controlled-release tablets, immediate- and controlled-release rectal suppositories, immediate-release syrup, and controlled-release suspension—is unique among the pure opioid agonists and contributes to the great flexibility of this agent.

**Table 4
Opioid Agonist Drugs**

Drug	<i>Dose (mg) Equianalgesic to 10 mg IM Morphine</i>		Half-life (hr)	Duration of Action (hr)	Comments
	IM	PO			
Codeine	130	200	2-3	2-4	Usually combined with a non-opioid.
Oxycodone	15	20-30	2-3	2-4	Combined with a non-opioid or as a controlled-release tablet
Propoxyphene	100	50	2-3	2-4	Usually combined with non-opioid. Norpropoxyphene toxicity may cause seizures.
Morphine	10	30	2-3	3-4	Multiple routes of administration available. Controlled-release available. M6G accumulation in renal failure.
Hydromorphone	2-3	7.5	2-3	2-4	Multiple routes available.
Methadone	1-3	2-6	15-190	4-8	Plasma accumulation may lead to delayed toxicity. Dosing should be initiated on a PRN basis.
Meperidine	75	300	2-3	2-4	Low oral bioavailability. Normeperidine toxicity limits utility. Contraindicated in patients with renal failure and those receiving MAO inhibitors.
Oxymorphone	1	10 (PR)	2-3	3-4	No oral formulation available. Less histamine release.
Levorphanol	2	4	12-15	4-8	Plasma accumulation may lead to delayed toxicity.
Fentanyl Transdermal System		(Empirically) fentanyl 100 mcg/h =2-4 mg/h IV morphine	Transdermal	48-72	Patches available to deliver 25, 50,75, and 100 mcg/hr
Key: mg=milligrams; IM=intramuscular; PO=orally; hr=hours; PRN=as needed; PR=per rectum; mcg=micrograms; MAO=monoamine oxidase					

Morphine usually has a half-life and duration of action of two to four hours. Morphine undergoes hepatic glucuronidation at the 3 and 6 positions, and the metabolites are excreted by the kidneys. Morphine-3-glucuronide (M3G), the major metabolite of morphine,⁴⁴ is not an analgesic. Rather, data suggest that M3G has a role in the production of dose-related adverse effects, such as hyperalgesia/allodynia and myoclonus.⁴⁵ Morphine-6-glucuronide (M6G), on the other hand, binds to opioid receptors and produces potent opioid effects in animals.^{46,47} In humans, however, analgesia has been observed with intrathecal administration⁴⁸ of M6G but not after intravenous administration.⁴⁹ Renal excretion of M6G is related to creatinine clearance.⁵⁰ In some patients with impaired renal function, high concentrations of M6G have been associated with toxicity,⁵¹⁻⁵³ suggesting the need for enhanced vigilance when administering morphine to patients with renal impairment.

The relative potency of intramuscular versus oral morphine is somewhat controversial. Although single-dose studies of morphine in postoperative cancer patients demonstrated an intramuscular-to-oral potency ratio of 1:6,⁵⁴ both bioavailability data⁵⁵ and surveys of patients receiving the drug chronically suggest that a ratio of 1:3 or 1:2 is more appropriate for routine use.⁵⁶

Hydromorphone: Hydromorphone is a versatile opioid with a short half-life that can be administered by oral, rectal, parenteral, and intraspinal routes.⁵⁷ Its solubility, high bioavailability (78%) by continuous subcutaneous infusion,⁵⁸ and the availability of a high-concentration (10 mg/cc) preparation, make it particularly suitable for subcutaneous infusion. A sustained-release formulation of oral hydromorphone with a duration of action of eight to 12 hours has recently become available.^{41,59} Although the equianalgesic ratio of parenteral morphine to hydro-

morphone has traditionally been quoted as 7:1, recent data suggest that it is probably closer to 4:1.^{60,61}

Meperidine (Pethedine): Meperidine is an opioid agonist with a short half-life and a profile of potential adverse effects that limits its utility. Meperidine is N-demethylated to normeperidine, an active metabolite with twice the convulsant potency and half the analgesic potency of its parent compound. The half-life of normeperidine is 12 to 16 hours, approximately four to five times the half-life of meperidine.

Accumulation of normeperidine after repetitive dosing of meperidine can result in central nervous system toxicity characterized by subtle adverse mood effects, tremulousness, multifocal myoclonus, and, occasionally, seizures.⁶² Although accumulation of normeperidine is most likely to affect the elderly and patients with overt renal disease, toxicity is sometimes observed in younger patients with normal renal function. The most serious toxicity associated with meperidine is normeperidine-induced seizures. Naloxone does not reverse this effect, and theoretically could precipitate seizures in meperidine-treated patients by blocking the depressant action of meperidine and allowing the convulsant activity of normeperidine to become manifest. If naloxone must be administered to a patient receiving meperidine, it should be diluted and slowly titrated while appropriate seizure precautions are taken. Meperidine may also be toxic if administered to patients receiving monoamine oxidase inhibitors. This combination may produce a syndrome characterized by hyperpyrexia, muscle rigidity, and seizures that may occasionally be fatal.⁶³ The pathophysiology of this syndrome is related to excess availability of serotonin at the 5-HT_{1A}-receptor in the central nervous system.

Fentanyl: Fentanyl is a semi-synthetic

opioid characterized by high potency, lipophilicity, and a short half-life after bolus administration. The development of a transdermal system has broadened its clinical utility for the management of cancer pain.⁶⁴ Parenteral fentanyl is used as a premedication for painful procedures⁶⁵ and in continual infusion either intravenously⁶⁶ or by the subcutaneous route.⁶⁷ A recently approved oral transmucosal formulation may be particularly useful in the management of "break-through" pain in cancer patients.⁶⁸

Oxymorphone: Oxymorphone is a potent lipophilic congener of morphine with a short half-life that is available as injectable and rectal formulations in the US. Substantial experience has been reported using oxymorphone for intravenous or subcutaneous Patient Controlled Analgesia.⁶⁹ The rectal formulation is approximately equipotent with parenteral morphine. Oxymorphone is less likely to induce histamine release than is morphine, and may have particular utility for patients who develop itch in response to other opioids.⁷⁰

Methadone: Methadone is a synthetic opioid with a very long plasma half-life of approximately 24 hours (range, 13 to more than 100 hours).⁷¹ Despite this long half-life, many patients require dosing at a four-to-eight-hour interval to maintain analgesic effects.⁷² After treatment is initiated or the dose is increased, plasma concentration rises for a prolonged period, which may be associated with delayed onset of side effects. Serious adverse effects can be avoided if the initial period of dosing is accomplished with "as needed" administration.⁷³ When steady-state has been achieved, scheduled dose frequency should be determined by the duration of analgesia following each dose. Oral and parenteral preparations of methadone are available. Subcutaneous infusion has been reported to cause local skin toxicity and is not recommended.⁷⁴

The equianalgesic dose ratio of morphine to methadone has been a matter of confusion and controversy. Recent data from crossover studies with morphine and methadone and hydromorphone and methadone indicate that methadone is much more potent than previously described in literature, and that the ratio correlates with total opioid dose administered before switching to methadone.³⁶ Among patients receiving low doses of morphine (30 to 300 mg oral morphine), the equianalgesic ratio for oral methadone to oral morphine is 1:4 to 1:6 and at high doses (more than 300 mg oral morphine), 1:10 to 1:12.³⁶

Levorphanol: Levorphanol is a morphine congener with a long half-life (12 to 16 hours) that is available in both oral and parenteral formulations. It is five times more potent than morphine and has an oral:parenteral relative potency ratio of 2:1. Like methadone, drug accumulation may follow the initiation of therapy or dose escalation. Levorphanol is used commonly as a second-line agent in patients with chronic pain who cannot tolerate morphine.

FACTORS IN OPIOID SELECTION

The factors that influence opioid selection in chronic pain states include pain intensity, pharmacokinetic and formulary considerations, previous adverse effects, and the presence of co-existing disease.

Pain Intensity

Traditionally, patients with moderate pain have been treated with a combination product containing acetaminophen or aspirin plus codeine, dihydrocodeine, hydrocodone, oxycodone, or propoxyphene. The doses of these combination products can be increased until the maximum dose of the non-opioid co-analgesic is attained (e.g., 4,000 mg acetaminophen); beyond this dose, the opioid in the combination product could be increased as a single agent, or the patient could be switched to

an opioid conventionally used for strong pain. In recent years, new opioid formulations have been developed that may improve the convenience of drug administration for patients with moderate pain, including controlled-release formulations of codeine, dihydrocodeine, oxycodone, morphine, and tramadol.

Patients who present with severe pain are usually treated with morphine, hydromorphone, oxycodone, oxymorphone, fentanyl, methadone, or levorphanol.

Pharmacokinetic and Formulary Considerations

Opioid agonists with short half-lives (morphine, hydromorphone, fentanyl, oxycodone, or oxymorphone) are generally favored because they are easier to titrate than drugs with longer half-lives that require longer periods to approach steady-state plasma concentrations. Morphine is generally preferred as it has a short half-life and is easy to titrate in its immediate-release form; it is also available as a controlled-release preparation that allows an eight-to-12-hour dosing interval. The opioids with long half-lives, methadone and levorphanol, are not usually considered first-line agents. They can be more difficult to titrate and present challenging management problems if delayed toxicity develops as a result of gradually rising plasma concentrations following dose increments.

As noted previously, the mixed agonist-antagonist opioids (pentazocine, nalbuphine, and butorphanol) and the partial agonist opioids (buprenorphine and probably dezocine) are not preferred in the management of cancer pain.³⁵ Similarly, the pharmacological characteristics of meperidine limit its role in the cancer population.

When opioids cannot be given orally, the availability of other routes of administration becomes an important consideration in opioid selection. For instance, oxymorphone is available only as a rectal

suppository or for injection; fentanyl is only available for transdermal or parenteral administration; and oxycodone is only available for oral administration.

Response to Previous Therapy with Opioids

The patient's response to previous trials of opioid therapy is always important. If an opioid is well tolerated, the agent is usually continued unless difficulties in dose titration occur or the required dose cannot be administered conveniently. If the patient is opioid-naïve and has strong pain, morphine is generally recommended because of the range of available formulations and widespread physician familiarity. A switch to an alternative opioid is considered if the patient develops dose-limiting toxicity that precludes adequate relief of pain without excessive side effects, or if a specific formulation, not available for the current drug, is either needed or may substantially improve the convenience of opioid administration.

Some patients will require sequential trials of several different opioids before an effective and well tolerated drug is identified.⁷⁵⁻⁷⁷ The existence of incomplete cross-tolerance to various opioid effects (analgesia and side effects) underlies the utility of such sequential trials. It is strongly recommended that clinicians be familiar with at least three opioid drugs used in the management of severe pain and have the ability to calculate appropriate starting doses using equianalgesic dosing data.

Co-existing Disease

The presence of liver disease may decrease the clearance and increase the bioavailability and half-lives of meperidine, pentazocine, and propoxyphene, resulting in higher-than-normal plasma concentrations. Mild or moderate hepatic impairment has only minor impact on morphine clearance; however, advanced disease may be associated with reduced elimination.⁷⁸

Patients with renal impairment may accumulate the active metabolites of propoxyphene (norpropoxyphene), meperidine (normeperidine), and morphine (M6G). In the setting of renal failure or unstable renal function, titration of these drugs requires caution and close monitoring; alternative opioids are often recommended.

ROUTE OF ADMINISTRATION

Routes of systemic administration may be classified according to degree of invasiveness. Opioids should be administered by the least invasive and safest route that provides adequate analgesia. In a survey of patients with advanced cancer, more than half required two or more routes of administration prior to death, and almost a quarter required three or more.⁷⁹

Non-invasive Routes of Opioid Administration

Usually, the oral route of opioid administration is preferred in routine practice. Alternative routes are necessary for patients who have impaired swallowing or gastrointestinal dysfunction, for those who require a very rapid onset of analgesia, or for those who are unable to manage either the logistics or side effects associated with the oral route.⁷⁵ For patients requiring very high doses, the oral route may not be practically feasible due to the excessive number of tablets or high volumes of oral solution that are necessary.⁷⁵

Non-invasive alternatives to the oral route for relatively intolerant patients include the rectal, transdermal, and sublingual routes. Rectal suppositories containing oxycodone, hydromorphone, oxymorphone, and morphine have been formulated, and controlled-release morphine tablets can be also administered per rectum.⁸⁰ The potency of opioids administered rectally is approximately equivalent to that achieved by the oral route.⁵⁶

Fentanyl is the only opioid available as a transdermal preparation. The fentanyl transdermal system consists of a

drug reservoir that is separated from the skin by a copolymer membrane that controls the rate of drug delivery to the skin surface such that the drug is released into the skin at a nearly constant amount per unit time. The dosing interval for each system is usually 72 hours⁸¹ but some patients require a 48-hour schedule.⁶⁴ Transdermal patches capable of delivering 25, 50, 75, and 100 mcg/hr are available, and multiple patches may be used simultaneously if patients require higher doses. At the present time, the limitations of the transdermal delivery system include its cost and the requirement for an alternative short-acting opioid for breakthrough pain. Recent data from controlled studies indicate that the transdermal administration of fentanyl is associated with a lower incidence of constipation than is morphine and is often preferred.⁸²⁻⁸⁴

Sublingual absorption of any opioid could potentially yield clinical benefit, but bioavailability is very poor with drugs that are not highly lipophilic and the likelihood of an adequate response is low.⁸⁵ Sublingual buprenorphine, a relatively lipophilic partial agonist, can provide adequate relief of mild to moderate cancer pain.⁸⁶ Anecdotally, sublingual morphine has also been reported to be effective, although this drug has poor sublingual absorption⁸⁵ and efficacy may be related, in part, to swallowing of the dose. Both fentanyl and methadone are relatively well absorbed through the buccal route,⁸⁵ and sublingual administration of an injectable formulation is occasionally used in the relatively intolerant patient who transiently loses the option of oral dosing. Overall, however, the sublingual route has limited value due to the lack of available formulations, poor absorption of most drugs, and the inability to deliver high doses or prevent swallowing of the dose.

An oral transmucosal formulation of fentanyl, which incorporates the drug into a candy base that is absorbed across the buccal mucosa, has recently been ap-

proved for the management of breakthrough pain. This formulation is rapidly absorbed and achieves blood levels and time to peak effect that are comparable to parenterally administered fentanyl. Indeed, the time to onset of effect is five to 10 minutes.^{68,87} Studies in cancer patients suggested that it is useful and that it can provide rapid and very effective relief of breakthrough pain.^{68,87} Formulations incorporating 200, 400, 800, and 1,600 mcg have been approved by the FDA and are now available. The most common adverse effects associated with this formulation are somnolence, nausea, and dizziness.

Invasive Routes of Opioid Administration

A parenteral route for opioid administration must be considered when the oral route is precluded or when there is need for rapid onset of analgesia, or a more convenient regimen. Repeated parenteral bolus injections, which may be administered by the intravenous, intramuscular, or subcutaneous routes, may be useful in some patients, but are often compromised by the occurrence of prominent "bolus" effects (toxicity at peak concentration and/or pain breakthrough at the trough). Repetitive intramuscular injections are a common practice, but because they are painful and offer no pharmacokinetic advantage, their use is not recommended. Repeated bolus doses without frequent skin punctures can be accomplished through the use of an indwelling intravenous or subcutaneous infusion device. To deliver repeated subcutaneous injections, a 25-to-27-gauge infusion device (a "butterfly") can be left under the skin for up to a week.⁸⁸

Intravenous bolus administration provides the most rapid onset and shortest duration of action. Time to peak effect correlates with the lipid solubility of the opioid and ranges from two to five minutes for methadone to 15 to 30 minutes for morphine and hydromorphone. This approach is most commonly used to

treat very severe pain, in which case, intravenous doses can be repeated at an interval as brief as that determined by the time to peak effect, until adequate relief is achieved.⁸⁹

Continuous parenteral infusions are useful for many patients who cannot be maintained on oral opioids. Long-term infusions may be administered intravenously or subcutaneously. In practice, the major indication for continuous infusion occurs among patients who are unable to swallow or absorb opioids. Continuous infusion is also used in some patients whose high opioid requirement renders oral treatment impractical.

Ambulatory patients can easily use continuous subcutaneous infusion. A recent study demonstrated that the bioavailability of hydromorphone is 78% by this route,⁵⁸ and clinical experience suggests that dosing may be initiated in a manner identical to that used with continuous intravenous infusion.⁹⁰ A range of pumps is available varying in complexity, cost, and ability to provide patient-controlled "rescue doses" as adjuncts to the continuous basal infusion.⁸⁸

Opioids suitable for continuous subcutaneous infusion must be soluble, well absorbed, and nonirritant. Extensive experience has been reported with heroin, hydromorphone, oxymorphone, morphine, and fentanyl.⁸⁸ Methadone, however, appears to be relatively irritating and is not preferred.⁷⁴ To maintain the comfort of an infusion site, the subcutaneous infusion rate should not exceed three to five cc/hr. Patients who require high doses may benefit from the use of concentrated solutions. A high concentration hydromorphone formulation (10 mg/cc) is available commercially, for example, and the organic salt of morphine, morphine tartrate, is available in some countries as an 80-mg/cc solution. In selected cases, concentrated opioid solutions can be compounded specifically for continuous subcutaneous infusion.

Subcutaneous infusion, like repeat-

ed subcutaneous bolus injections, can usually be administered using a 27-gauge "butterfly" needle. The infraclavicular and anterior chest sites provide the greatest freedom of movement for patients, but other sites may be used. A single infusion site can often be maintained for five to seven days. Occasionally, patients develop focal erythematous swelling at the site of injection;⁹¹ this is a common complication with methadone⁷⁴ and has also been described with morphine and hydromorphone.⁹¹ This type of focal swelling must be distinguished, however, from injection site abscess formation, which may require antibiotic therapy, and in some cases, surgical drainage.

Continuous subcutaneous delivery of drug combinations may be indicated when nausea, anxiety, or agitation accompanies pain. An antiemetic, neuroleptic, or anxiolytic agent may be combined with an opioid, provided that it is nonirritant, miscible, and stable in combined solution. Experience has been reported with metoclopramide, haloperidol, scopolamine, cyclizine, methotrimeprazine, chlorpromazine, and midazolam.^{92,93}

In some circumstances, continuous intravenous infusion may be the most appropriate parenteral route. This approach may be indicated, for example, when very high doses are required, when methadone is used parenterally, or when the patient has developed injection site reactions. If continuous intravenous infusion is to be administered on a long-term basis, placement of a permanent central venous line is recommended.⁹⁴

CHANGING ROUTES OF ADMINISTRATION

The switch between oral and parenteral routes should be guided by knowledge of relative potency (Table 4) to avoid subsequent over- or under-dosing. In calculating the equianalgesic dose, the potencies of the intravenous, subcutaneous, and intramuscular routes are considered equiva-

lent. In recognition of the imprecision of the accepted equianalgesic doses and the risk of toxicity from potential overdose, a modest reduction in the equianalgesic dose is prudent. Implementing the change in a stepwise fashion (i.e., slowly reducing the parenteral dose and increasing the oral dose over a two-to-three-day period) can minimize the problems associated with switching the route of administration.

SCHEDULING OPIOID ADMINISTRATION

The schedule of opioid administration should be individualized to optimize the balance between patient comfort and convenience. "Around-the-clock" dosing and "as needed" dosing both have a place in clinical practice.

"Around-The-Clock" Dosing

Patients with continuous or frequent pain generally benefit from scheduled "around-the-clock" dosing, which can provide continuous relief by preventing the pain from recurring. Clinical vigilance is required, however, when this approach is used in patients with no previous opioid exposure and when administering drugs that have long half-lives (methadone or levorphanol) or produce metabolites with long half-lives (e.g., M6G and norpropoxyphene). In the latter situations, delayed toxicity may develop as plasma drug (or metabolite) concentrations rise toward steady-state levels.

Most patients who receive an "around-the-clock" opioid regimen should also be provided a so-called "rescue dose," which is a supplemental dose offered on an "as needed" basis to treat pain that breaks through the regular schedule. The frequency with which the rescue dose can be offered depends on the route of administration and the time to peak effect for the particular drug. Oral rescue doses are usually offered up to every one to two hours and parenteral doses can be offered as frequently as every 15 to 30 minutes.

Clinical experience suggests that the initial size of the rescue dose should be equivalent to approximately 50% to 100% of the dose administered every four hours for oral or parenteral bolus medications, or 50% to 100% of the hourly infusion rate for patients receiving continuous infusions. Alternatively, this may be calculated as 5% to 15% of the 24-hour baseline dose. The magnitude of the rescue dose should be individualized, and some patients with low baseline pain but severe exacerbations may require rescue doses that are substantially higher.⁹⁵ The drug used for the rescue dose is usually identical to that administered on a scheduled basis. In the case of transdermal fentanyl, however, an alternative opioid with a short half-life is recommended for the rescue dose.

The integration of around-the-clock dosing with rescue doses provides a method for safe and rational stepwise dose escalation, which is applicable to all routes of opioid administration. Patients who require more than four to six rescue doses per day should generally undergo escalation of the baseline dose. The quantity of the rescue medication consumed can be used to guide the dose increment. Alternatively, each dose increment can be set at 33% to 50% of the pre-existing dose. In all cases, escalation of the baseline dose should be accompanied by a proportionate increase in the rescue dose, so that the size of the supplemental dose remains a constant percentage of the fixed dose (Table 5).

Controlled-Release Drug Formulations

Controlled-release opioid preparations can reduce the inconvenience associated with around-the-clock administration of drugs with a short duration of action. Currently, controlled-release formulations are available for administration by the oral, transdermal, and rectal routes. Clinical experience has been greatest with oral controlled-release morphine preparations that have an eight-to-12-

hour duration of effect. Over recent years, the range of controlled-release formulations has substantially expanded and now includes once-daily morphine preparations;⁹⁶ controlled-release morphine suppositories⁹⁷ and suspension;⁹⁸ transdermal fentanyl;^{82,99} controlled-release oxycodone tablets;⁴¹ hydromorphone;⁴¹ codeine; and dihydrocodeine.¹⁰¹

Most patients who are given a controlled-release opioid should also be provided with a rescue dose of an immediate-release opioid to treat pain that breaks through the regular controlled-release schedule (Table 5).

Clinical experience suggests that controlled-release morphine should not be used for rapid dose titration in patients with severe pain. The time required (at least 24 hours) to approach steady-state plasma concentration after dosing is initiated or changed may complicate efforts to rapidly identify the appropriate dose. Repeat dose adjustments for patients with severe pain are performed more efficiently with a short-acting morphine preparation, which may then be changed to a controlled-release preparation when the effective around-the-clock dose is identified. This switch from short-acting morphine to controlled-release morphine should be a milligram-to-milligram conversion, which results in the same total around-the-clock dose of the opioid.

"As Needed" Dosing

In some situations, opioid administration on an "as needed" basis, without an around-the-clock dosing regimen, may be beneficial. In the opioid-naïve patient, "as needed" dosing may provide additional safety during the initiation of opioid therapy, particularly when rapid dose escalation is needed or when therapy with a long half-life opioid, such as methadone or levorphanol, is begun.⁷³ "As needed" dosing may also be appropriate for patients who have rapidly decreasing analgesic requirements or intermittent pain separated by pain-free intervals.

Patient Controlled Analgesia

Patient controlled analgesia (PCA) generally refers to a technique of parenteral drug administration in which the patient controls an infusion device that delivers a bolus of analgesic drug "on demand," according to parameters set by the physician. Use of a PCA device allows the patient to overcome variations in both pharmacokinetic and pharmacodynamic factors by carefully titrating the rate of opioid administration to meet individual analgesic needs.¹⁰² Although it should be recognized that the use of oral rescue doses is, in fact, a form of PCA,⁷³ the term is not commonly applied to this situation.

Long-term PCA in cancer patients is most commonly achieved via the subcutaneous route using an ambulatory infusion device.^{88,102} In most cases, PCA is added to a basal infusion rate and acts essentially as a rescue dose.¹⁰² Rare patients have benefited from PCA alone to manage episodic pains characterized by an onset so rapid that an oral dose could not provide sufficiently prompt relief.¹⁰³ Long-term intravenous PCA can be used for patients who require doses that cannot be comfortably tolerated via the subcutaneous route or in those who develop local reactions to subcutaneous infusion. PCA has also been applied with spinally administered opioids¹⁰⁴ and non-opioid approaches such as nitrous oxide.¹⁰⁵

DOSE SELECTION AND TITRATION

Selecting a Starting Dose

A patient who is relatively intolerant, having had only some exposure to an opioid for moderate pain from the second rung of the analgesic ladder, should generally begin one of the opioids typically used for severe pain at a dose equivalent to five to 10 mg morphine intramuscularly every four hours.⁵⁶ If morphine is used, an oral-to-intramuscular relative potency ratio of 2:1 to 3:1 is conventional.⁵⁶ When patients on higher doses of opioids are switched to an alternative opioid drug, the starting dose of the new drug

should be reduced to 50% to 75% of the equianalgesic dose to account for incomplete cross-tolerance.

Dose Adjustment

Adjustment of the opioid dose is essential at the start of therapy and is usually necessary throughout the course of therapy. At all times, inadequate relief should be addressed through gradual escalation of dose until adequate analgesia is reported or intolerable and unmanageable side effects supervene. Because opioid response increases linearly with the log of the dose, a dose increment of less than 30% to 50% is not likely to significantly improve analgesia. Doses can become extremely large during this process of titration. The absolute dose is immaterial as long as administration is not compromised by excessive side effects, inconvenience, discomfort, or cost.

Patients vary greatly in the opioid dose required to manage pain^{79,106,107} and some patients require very high doses of systemic opioids to control pain.^{108,109} A survey of patients with advanced cancer observed that the average daily opioid requirement was equivalent to 400 to 600 mg of intramuscular morphine; approximately 10% of patients in the survey required greater than 2,000 mg, and one patient required more than 35,000 mg per 24 hours.⁷⁹

Rate of Dose Titration

The rate of dose titration depends on the severity of the pain, the medical condition of the patient, and the goals of care. Patients who present with very severe pain are sometimes best managed by repeated parenteral administration of a dose every 15 to 30 minutes until pain is partially relieved.⁸⁹ Empiric guidelines have been proposed for the calculation of hourly maintenance dosing after this parenteral loading has been accomplished with a short half-life opioid such as morphine, hydromorphone, or fentanyl;¹¹⁰ these guidelines, which can be reasonably

Table 5
Stepwise Escalation of Morphine Sulfate

Oral Immediate-Release Morphine Sulfate		
Step*	mg every 4 hr ATC	Rescue Dose (mg)
1	15	7.5 PRN q 1 hr
2	30	15.0 PRN q 1 hr
3	45	22.5 PRN q 1 hr
4	60	30.0 PRN q 1 hr
5	90	45.0 PRN q 1 hr
Oral Controlled-Release Morphine Sulfate (immediate-release rescue dose)		
Step*	mg ATC	Immediate-Release Rescue Dose (mg)
1	30 every 12	7.5 PRN every 1hr
2	30 every 8	15.0 PRN every 1hr
3	60 every 12	15.0 PRN every 1hr
4	100 every 12	30.0 PRN every 1hr
5	100 every 8	45.0 PRN every 1hr
Continuous Morphine Infusion		
Step*	mg/hr	Rescue Dose (mg)
1	3	2.0 PRN every 30 min
2	5	2.5 PRN every 30 min
3	7	3.5 RN every 30 min
4	10	5.0 PRN every 30 min
5	15	7.5 PRN every 30 min
<p>*Suggested indications for progression from one step to the next include: 1) Requirement of more than two rescue doses in any four-hour interval or 2) Requirement of more than six rescue doses in 24 hours</p>		
<p>Examples of stepwise dose escalation for morphine sulfate administered as oral immediate-release preparation, oral controlled-release, and continuous infusion.</p>		
<p>Key: hr=hour; ATC=around the clock; PRN=as needed</p>		

extrapolated to the cancer population, recommend that the starting hourly maintenance dose of the short half-life opioid can be approximated by dividing the total loading dose by twice the elimination half-life of the drug. For example, the starting maintenance dose for a patient who has required a total intravenous loading dose of 60 mg of morphine sulfate (half-life, approximately three hours) to achieve adequate relief, would be 10 mg per hour.

Patients with moderate pain may not require a loading dose of the opioid, but rather the initiation of a regular dose with provision for rescue doses and gradual dose titration. In this situation, dose increments of 30% to 50% can be administered at intervals greater than those required to reach steady-state following each change (Table 5). The dose of morphine (tablets or elixir), hydromorphone, or oxycodone can be increased on a twice daily basis, and the dose of controlled-release oral morphine or transdermal fentanyl can be increased every 24 to 48 hours.

The Problem of Tolerance

The need for escalating doses is a complex phenomenon. Most patients reach a dose that remains constant for prolonged periods.^{106,111} When the need for dose escalation arises, any of a variety of distinct processes may be involved. Clinical experience suggests that disease progression¹¹¹⁻¹¹⁴ and increasing psychological distress¹¹⁵ are much more common than true analgesic tolerance.

In true pharmacologic tolerance, which presumably involves changes at the receptor level, continued drug administration itself induces an attenuation of effect. Clinically, tolerance to the non-analgesic effects of opioids appears to occur commonly,¹¹⁶ albeit at varying rates for different effects. For example, tolerance to respiratory depression, somnolence, and nausea generally develops rapidly, whereas tolerance to opioid-induced constipation develops very slowly,

if at all.¹¹⁶ Tolerance to these opioid side effects is not a clinical problem, and indeed, is a desirable outcome that allows effective dose titration to proceed.

The induction of true analgesic tolerance, which could compromise the utility of treatment, can only be said to occur if a patient manifests the need for increasing opioid doses in the absence of other factors (e.g., progressive disease) that would explain the increase in pain. Extensive clinical experience suggests that most patients who require dose escalation to manage increasing pain have demonstrable progression of disease.¹¹²⁻¹¹⁴

Together, these observations suggest several important conclusions:

- True pharmacological tolerance to the analgesic effects of opioids is not a common clinical problem.
- Concern about tolerance should not impede the use of opioids early in the course of the disease.
- Worsening pain in a patient receiving a stable dose of opioids should not be attributed to tolerance, but should be assessed as presumptive evidence of disease progression or, less commonly, increasing psychological distress.

MANAGEMENT OF ADVERSE EFFECTS

Successful opioid therapy requires that the benefits of analgesia and other desired effects clearly outweigh treatment-related adverse effects.

The pathophysiological mechanisms that contribute to adverse opioid effects are incompletely understood. The appearance of these effects depends on a number of factors, including patient age, extent of disease, concurrent organ dysfunction, other drugs, prior opioid exposure, and the route of drug administration. In general, data are lacking from controlled studies that compare the adverse effects of one opioid analgesic with another, or that compare the adverse effects produced by the same opioid given by different routes of administration.

Adverse Drug Interactions

In patients with advanced cancer, side effects due to drug combinations are common. The potential for additive side effects and serious toxicity from drug combinations must be recognized. The sedative effect of an opioid may add to that produced by numerous other centrally acting drugs, such as anxiolytics, neuroleptics, and antidepressants. Likewise, drugs with anticholinergic effects probably worsen the constipatory effects of opioids. As noted previously, a severe adverse reaction, including excitation, hyperpyrexia, convulsions, and death, has been reported after the administration of meperidine to patients treated with a monoamine oxidase inhibitor.¹¹⁷

Gastrointestinal Side Effects

The gastrointestinal adverse effects of opioids are common. In general, they are characterized by a weak dose-response relationship.

Constipation: Constipation is the most common adverse effect of chronic opioid therapy.¹¹⁸ The likelihood of opioid-induced constipation is so great that, for most patients, laxative medications should be prescribed prophylactically. Recent studies have demonstrated a reduced incidence of constipation among patients treated with transdermal fentanyl compared with those treated with oral morphine.⁸²⁻⁸⁴

There have been no controlled comparisons of the various laxatives used to manage opioid-induced constipation and published recommendations are based entirely on anecdotal experience (Table 6). Combination therapy is frequently used, particularly co-administration of a softening agent (docusate) and a cathartic (e.g., senna, bisacodyl, or phenolphthalein). The doses of these drugs should be increased as necessary, and an osmotic laxative (e.g., milk of magnesia) should be added if needed. Chronic lactulose therapy is an alternative that some pa-

tients prefer, and occasionally, patients are managed with intermittent colonic lavage using an oral bowel preparation such as "Golytely."[®]

Rare patients with refractory constipation may be given a trial of oral naloxone, which has a bioavailability less than 3% and presumably acts selectively on opioid receptors in the gut. Oral administration of a 3-to-5-mg dose reversed constipation without compromising analgesia or precipitating systemic withdrawal.¹¹⁹ Systemic withdrawal can be produced, however, if doses are escalated. Hence, the initial naloxone dose should be small (0.8 to 1.2 mg once or twice daily) and may be escalated slowly until either favorable effects occur or the patient develops abdominal cramps, diarrhea, or any other adverse effect. Preliminary data suggest that similar effects can be achieved with naltrexone.¹²⁰

Nausea and Vomiting: Opioids may produce nausea and vomiting through both central and peripheral mechanisms. These drugs stimulate the medullary chemoreceptor trigger zone, increase vestibular sensitivity, and have effects on the gastrointestinal tract that include increased gastric antral tone, diminished motility, and delayed gastric emptying.¹²¹ In ambulatory patients, the incidences of nausea and vomiting have been estimated to be 10% to 40% and 15% to 40%, respectively.¹²² The likelihood of these effects is greatest at the start of opioid therapy.

With the initiation of opioid therapy, patients should be informed that nausea can occur and that it is usually transitory and controllable. Tolerance typically develops within weeks. Routine prophylactic administration of an antiemetic is not necessary, except in patients with a history of severe opioid-induced nausea and vomiting,¹²³ but patients should have access to an antiemetic at the start of therapy if the need for one arises. Anecdotaly, the use of prochlorperazine or metoclopramide has usually been sufficient.

In patients with more severe or persistent symptoms, the most appropriate antiemetic treatment may be suggested by the clinical features.¹²⁴ For nausea associated with early satiety, bloating, or postprandial vomiting, all of which are features of delayed gastric emptying, metoclopramide is the most reasonable initial treatment. Patients with vertigo, or prominent movement-induced nausea, may benefit from the use of an antivertigenous drug such as prochlorperazine, scopolamine, or meclizine. If signs of gastroparesis or vestibular dysfunction are not prominent, treatment with prochlorperazine or metoclopramide is usually begun. Drug combinations are sometimes used and, in all cases, doses are escalated if initial treatment is unsuccessful. If these drugs are ineffective at relatively high doses, other options include trials of alternative opioids or treatment with antihistamines (e.g., diphenhydramine or hydroxyzine), other neuroleptics (e.g., haloperidol, chlorpromazine, or droperidol), benzodiazepines (e.g., lorazepam), steroids (e.g., dexamethasone) or the new serotonin antagonists (e.g., ondansetron).

Central Nervous System Side Effects:

The central nervous system side effects of opioids are generally dose-related, with specific patterns influenced by individual patient factors, duration of opioid exposure, and dose.

Sedation. Initiation of opioid therapy or significant dose escalation commonly induces sedation that persists until tolerance to this effect develops, usually in days to weeks. It is useful to forewarn patients, thereby reducing anxiety and cautioning avoidance of activities, such as driving, that may be dangerous if sedation occurs.¹²⁵ Some patients have a persistent problem with sedation, particularly if other confounding factors exist. These factors include the use of other sedating drugs or coexistent

diseases such as dementia, metabolic encephalopathy, or brain metastases. Management of persistent sedation is best accomplished with a stepwise approach (Table 7).

Both dextroamphetamine¹²⁶ and methylphenidate^{127,128} have been widely used in the treatment of opioid-induced sedation. There has also been some anecdotal experience with the related compound, pemoline, which has relatively minor sympathomimetic effects and is available in a chewable tablet.¹²⁹ Treatment with methylphenidate or dextroamphetamine is typically begun at 2.5 mg to 5.0 mg in the morning, repeated at midday if necessary to maintain effects until evening. Doses are then increased gradually if needed. Few patients require more than 40 mg per day in divided doses. At the doses used clinically, the risks associated with this treatment appear to be very small. This approach is relatively contraindicated among patients with cardiac arrhythmias, agitated delirium, paranoid personality, and past amphetamine abuse.

Confusion and Delirium. For patients and their families, confusion is a greatly feared effect of the opioid drugs. Mild cognitive impairment is common following the initiation of opioid therapy or dose escalation.¹³⁰ Similar to sedation, however, pure opioid-induced encephalopathy appears to be transient in most patients, lasting from days to a week or two. Although persistent confusion attributable to opioid alone occurs, the etiology of persistent delirium is usually related to the combined effect of the opioid and other contributing factors, including electrolyte disorders, neoplastic involvement of central nervous system, sepsis, vital organ failure, and hypoxemia.^{130,131} A stepwise approach to management (Table 8) often culminates in a trial of a neuroleptic drug. Haloperidol in low doses (0.5-1.0 mg orally or 0.25-0.5 mg intravenously or intramuscularly) is most commonly recommended because of its

Table 6
Laxative Medications

Class	Drug	Usual Starting Dose	Comments
Stool softeners	Docusate sodium	200 mg/day	
Osmotic agents	Lactulose Milk of magnesia	15-30 cc 30-60 cc	May cause abdominal cramps or flatulence
Stimulants	Senna Bisacodyl Phenolphthalein	2 tab 10-15 mg 60-120 mg	Delayed onset of action Delayed onset of action Allergic rash 5%
Bulk agents	Psyllium	4-6 g	May constipate if oral fluid intake is low
Oral lavage	"Golytely®"	100 cc tid	
Opioid antagonist	Oral naloxone	0.8-1.2 mg bid	Escalate dose by small steps until either favorable effect or the development of abdominal cramps, diarrhea, or signs of systemic withdrawal

efficacy and low incidence of cardiovascular and anticholinergic effects.

Respiratory Depression. Respiratory depression is potentially the most serious adverse effect of opioid therapy. Opioids may impair all phases of respiratory rate, minute volume, and tidal exchange. Commonly, a compensatory increase in respiratory rate obscures the degree of respiratory insufficiency initially produced by an opioid, and patients who appear to have normal respiration during opioid therapy may be predisposed to respiratory compromise if any pulmonary insult occurs. Clinically significant respiratory depression, however, is always accompanied by other signs of central nervous system depression, including sedation and mental clouding. Respiratory compromise ac-

companied by tachypnea and anxiety is never a primary opioid event.

With repeated opioid administration, tolerance appears to develop rapidly to the respiratory depressant effects of the opioid drugs.¹¹⁶ As a result, opioid analgesics can be used in the management of chronic cancer pain without significant risk of respiratory depression. Indeed, clinically important respiratory depression is a very rare event in the cancer patient whose opioid dose has been titrated against pain. When respiratory depression occurs in such patients, alternative explanations (e.g., pneumonia or pulmonary embolism) should be sought.

The ability to tolerate high doses of opioids is also related to the stimulatory effect of pain on respiration in a manner that is balanced against the depressant

Table 7
Management of
Opioid-Induced Sedation

- 1) Discontinue non-essential central nervous system depressant medications.
- 2) If analgesia is satisfactory, reduce opioid dose by 25%.
- 3) If analgesia is unsatisfactory, try addition of a psychostimulant, e.g., methylphenidate, dextroamphetamine, or pemoline
- 4) If somnolence persists, consider:
 - Addition of a co-analgesic that will allow reduction in opioid dose
 - Change to an alternative opioid drug
 - Change in opioid route to the intraspinal route (\pm local anesthetic)
 - Trial of other anesthetic or neurosurgical options

opioid effect. Opioid-induced respiratory depression can occur, however, if pain is suddenly eliminated (such as may occur following neurolytic procedures) and the opioid dose is not reduced.¹³²

When respiratory depression occurs in patients on chronic opioid therapy, administration of the specific opioid antagonist, naloxone, usually improves ventilation. This is true even if the primary cause of the respiratory event was not the opioid itself, but rather, an intercurrent cardiac or pulmonary process. A response to naloxone, therefore, should not be taken as evidence that the event was due to the opioid alone and an evaluation for these other processes should be instituted.

Naloxone can precipitate a severe abstinence syndrome and should be administered only if strongly indicated.¹³³ If the patient is bradypneic but readily arousable, and the peak plasma level of the last opioid dose has already been reached, the opioid should be withheld and the patient monitored until improved. If severe hypoventilation occurs (regardless of the associated factors that may be

contributing to respiratory compromise), or the patient is bradypneic and unarousable, naloxone should be administered. To reduce the risk of severe withdrawal following a period of opioid administration, dilute naloxone (1:10) should be used in doses titrated to respiratory rate and level of consciousness.^{134,135}

It is neither necessary nor desirable to reverse analgesia during the treatment of analgesic-induced respiratory depression. In the comatose patient, it may be prudent to place an endotracheal tube to prevent aspiration following administration of naloxone. As mentioned previously, naloxone should be used cautiously in patients who have received chronic meperidine therapy, as it may precipitate seizures. Rarely, naloxone administration may trigger the development of a non-cardiogenic pulmonary edema.¹³⁶

Multifocal Myoclonus. All opioid analgesics can produce involuntary muscular contractions called "myoclonus." Although the mechanism of this effect is not known, patients with advanced cancer often have multiple potentially contributory factors. The opioid effect is dose-related and is most prominent with meperidine, presumably as a result of metabolite accumulation.¹³⁷ Mild and infrequent myoclonus is common, and may resolve spontaneously with the development of tolerance to this effect. In occasional patients, myoclonus can be distressing or contribute to breakthrough pain that occurs with the involuntary movement. If the dose cannot be reduced due to persistent pain, consideration should be given to either switching to an alternative opioid^{75,76} or to symptomatic treatment with a benzodiazepine (particularly clonazepam or midazolam),¹³⁸ dantrolene,¹³⁹ or an anticonvulsant.

Other Effects: Urinary Retention. Opioid analgesics increase smooth muscle tone and can occasionally cause bladder spasm or urinary retention (due to an in-

Table 8
Management of
Opioid-Induced Delirium

- 1) Discontinue non-essential centrally acting medications.
- 2) If analgesia is satisfactory, reduce opioid dose by 25%.
- 3) Exclude sepsis or metabolic derangement.
- 4) Exclude involvement of tumor in central nervous system.
- 5) If delirium persists, consider:
 - Trial of neuroleptic (e.g., haloperidol)
 - Change to an alternative opioid drug
 - Change in opioid route to the intraspinal route (\pm local anesthetic)
 - Trial of other anesthetic or neurosurgical options

crease in sphincter tone). This is an infrequent problem that is usually observed in elderly male patients. Tolerance can develop rapidly but catheterization may be necessary to manage transient problems.

Pulmonary Edema. Non-cardiogenic pulmonary edema has been observed in patients treated with high, escalating opioid doses.¹⁴⁰ A clear cause-and-effect relationship with opioid use has not been established, but is suspected. The mechanism, if opioid-related, is obscure.

DEPENDENCE AND ADDICTION

Confusion about physical dependence and addiction augment the fear of opioid drugs and contribute substantially to the undertreatment of pain. To understand these phenomena as they relate to opioid pharmacotherapy for cancer pain, it is useful to first present a concept that might be called "therapeutic dependence." Patients who require a specific pharmacotherapy to control a symptom

or disease process are clearly dependent on the therapeutic efficacy of the drugs in question. Examples of this "therapeutic dependence" include the requirements of patients with congestive cardiac failure for cardiotoxic and diuretic medications, or the reliance of insulin-dependent diabetics on insulin therapy. In these patients, undermedication or withdrawal of treatment results in serious untoward consequences for the patient, the fear of which could conceivably induce aberrant psychological responses and drug-seeking behaviors. Patients with chronic cancer pain have an analogous relationship to their analgesic pharmacotherapy. This relationship may or may not be associated with the development of physical dependence, but is virtually never associated with addiction.

Physical Dependence

Owing to a pharmacological property of opioid drugs, physical dependence is defined by the development of an abstinence (withdrawal) syndrome following either abrupt dose reduction or administration of an antagonist. Despite the observation that physical dependence is most commonly observed in patients taking large opioid doses for a prolonged period of time, withdrawal has also been observed with low doses or short duration of treatment. Physical dependence rarely becomes a clinical problem if patients are warned to avoid abrupt discontinuation of the drug; if a tapering schedule is used should treatment cessation be indicated; and if opioid antagonist drugs (including agonist-antagonist analgesics) are avoided. Occasionally, patients who are switched from a pure agonist opioid to transdermal fentanyl will develop an abstinence syndrome within the first 24 hours, the mechanism of which is not understood.^{83,141}

Addiction

The term addiction refers to a psychological and behavioral syndrome character-

ized by a continued craving for an opioid drug to achieve a psychic effect (psychological dependence) and associated aberrant drug-related behaviors, such as compulsive drug-seeking, unsanctioned use or dose escalation, and use despite harm to self or others. Addiction should be suspected if patients demonstrate compulsive use, loss of control over drug use, and continuing use despite harm.

The medical use of opioids is very rarely associated with the development of addiction. In the largest prospective study, only four cases could be identified among 11,882 patients with no history of addiction who received at least one opioid preparation in the hospital setting.¹⁴² In a prospective study of 550 cancer patients who were treated with morphine for a total of 22,525 treatment days, only one patient developed problems related to substance abuse.¹¹¹ Health care providers, patients, and families often require vigorous and repeated reassurance that the risk of addiction is extremely small.

“Pseudo-addiction”

The distress engendered in patients who have a therapeutic dependence on analgesic pharmacotherapy but who continue to experience unrelieved pain is occasionally expressed in behaviors that mimic those of the addict, such as intense concern about opioid availability and unsanctioned dose escalation. Pain relief, usually produced by dose escalation, eliminates these aberrant behaviors and distinguishes the patient from the true addict. This syndrome has been termed “pseudo-addiction.”¹⁴³ Misunderstanding of these phenomena may lead the clinician to inappropriately stigmatize the patient with the label “addict,” which may compromise care and erode the doctor-patient relationship. In the setting of unrelieved pain, aberrant drug-related behaviors require careful assessment, renewed efforts to manage pain, and avoidance of stigmatizing labels.

PAIN THAT IS REFRACTORY TO SYSTEMIC OPIOID THERAPY

All patients who are candidates for opioid therapy should undergo a trial of systemic opioid administration guided by the foregoing principles. Some patients, however, fail to attain adequate relief despite escalation of the dose to levels associated with intolerable and unmanageable side effects. A stepwise strategy (Table 9) can be considered when dose escalation of a systemically administered opioid fails to yield a satisfactory result.

The first step in this strategy includes interventions that may improve the balance between the analgesic and adverse effects of systemic opioid therapy. If dose-limiting side effects cannot be ameliorated, it may be possible to reduce the requirement for opioid therapy by the concurrent use of an appropriate primary therapy or other non-invasive analgesic approach. The latter comprise pharmacological treatments (a non-opioid or an adjuvant analgesic) and a diverse group of psychological, rehabilitative, and neurostimulatory techniques (e.g., transcutaneous electrical nerve stimulation). An alternative approach, which has attracted much recent interest, is to switch to another opioid.⁷⁵⁻⁷⁷ This approach, commonly referred to as opioid rotation, is predicated on incomplete cross tolerance to analgesia and incomplete cross-sensitivity to adverse effects particularly sedation, cognitive impairment, delirium, nausea and vomiting, and myoclonus.⁷⁵

Patients unable to achieve a satisfactory analgesic outcome despite these interventions are candidates for the use of invasive analgesic techniques. The use of these approaches should be based on a careful evaluation of the likelihood and duration of analgesic benefit, the immediate risks and morbidity of the procedure (including the anticipated length of hospitalization), and the risks of long-term neurological sequelae. Anesthetic approaches using opioids or local anesthetics, such as epidural infusion, are usually consid-

ered first because they can reduce the requirement for systemically administered opioids without compromising neurologic function. Neurodestructive procedures that involve chemical or surgical neurolysis are very valuable in a small subset of patients; some of these procedures, such as celiac plexus blockade in patients with pancreatic cancer, may have a favorable enough risk:benefit ratio to warrant early application. Finally, some patients with advanced cancer who have comfort as the overriding goal of care, can elect to be deeply sedated rather than endure further trials of invasive analgesic therapy.

ADJUVANT ANALGESICS

The term "adjuvant analgesic" describes a drug that has a primary indication other than the treatment of pain but is analgesic in some conditions. In patients with cancer, these drugs may be combined with primary analgesics in any of the three steps of the analgesic ladder to improve outcomes for those who cannot otherwise attain an acceptable balance between relief and side effects. The potential utility of an adjuvant analgesic is usually suggested by the characteristics of the pain or by the existence of another symptom that may be amenable to a non-analgesic effect of the drug.

Whenever an adjuvant analgesic is selected, differences between the use of the drug for its primary indication and its use as an analgesic must be appreciated. As a dose-response relationship for analgesia has not been characterized for most of these drugs, dose titration is reasonable with virtually all. It is often useful to start with low initial doses to avoid early side effects. This approach may delay the onset of analgesia, however, and patients must be forewarned of this possibility to improve compliance with the therapy.

There is great interindividual variability in the response to such adjuvant analgesics. Although patient characteristics, such as advanced age or co-existent major organ failure, may increase the

likelihood of some (usually adverse) responses, neither favorable effects nor specific side effects can be reliably predicted in the individual patient. Furthermore, there is remarkable intraindividual variability in the response to different drugs, including to those within the same class. These observations suggest the potential utility of sequential trials of adjuvant analgesics. The process of sequential drug trials, like the use of low initial doses and dose titration, should be explained to the patient at the start of therapy to enhance compliance and reduce the distress that may occur if treatments fail.

In the management of cancer pain, adjuvant analgesics can be broadly classified into four groups based on conventional use: 1) Multipurpose adjuvant analgesics; 2) adjuvant analgesics used for neuropathic pain; 3) adjuvant analgesics used for bone pain; and 4) adjuvant analgesics used for visceral pain.

MULTIPURPOSE ADJUVANT AGENTS

Corticosteroids

Corticosteroids are among the most widely used adjuvant analgesics,¹⁴⁴ and have demonstrated analgesic effects that significantly improve quality of life. Corticosteroids have beneficial effects on appetite, nausea, mood, and malaise in the cancer population. Painful conditions that commonly respond to corticosteroids are listed in Table 10. The mechanism of analgesia produced by these drugs may involve anti-edema effects,¹⁴⁵ anti-inflammatory effects, and a direct influence on the electrical activity in damaged nerves.¹⁴⁶

The relative risks and benefits of the various corticosteroids are unknown and dosing is largely empirical. In the US, the most commonly used drug is dexamethasone, a choice that gains theoretical support from its relatively low mineralocorticoid effect. Dexamethasone also has been conventionally used to treat raised intracranial pressure and spinal cord compression. Prednisone,¹⁴⁷ methylprednisolone,^{148,149} and predni-

Table 9
Managing Dose-Limiting Toxicity Associated with Systemic Opioid Therapy: A Stepwise Strategy

Step	Intervention
1	<p>Non-invasive interventions to improve the therapeutic index of systemic opioid therapy:</p> <p>A) Treat dose-limiting opioid side effect</p> <p>B) Reduce opioid requirement by</p> <ul style="list-style-type: none"> • Appropriate primary therapy • Addition of non-opioid analgesic • Addition of an adjuvant analgesic • Use of cognitive or behavioral techniques • Use of an orthotic device or other physical medicine approach • Use of transcutaneous electrical nerve stimulation <p>C) Switch to a different opioid</p>
2	<p>Consider invasive interventions to lower systemic opioid requirement and preserve cognitive function.</p> <p>A) Regional analgesic techniques (spinal or intraventricular opioids)</p> <p>B) Neural blockade</p> <p>C) Neuroablative techniques</p> <p>D) Invasive neurostimulatory approach</p>
3	Consider increased sedation.

solone^{150,151} have also been used for other indications.

Patients with advanced cancer who experience pain and other symptoms may respond favorably to a relatively small dose of corticosteroid (e.g., dexamethasone 1 to 2 mg twice daily), although in some settings, a high-dose regimen may be appropriate. For example, patients with spinal cord compression, an acute episode of very severe bone pain, or neuropathic pain that cannot be promptly reduced with opioids, may respond dramatically to a short course of relatively high doses (e.g., dexamethasone 100 mg, followed initially by 96 mg per day in divided doses).¹⁵² This dose can be tapered over weeks, concurrent with initiation of other analgesic approaches, such as radiotherapy. Although high steroid doses

are more likely to lead to adverse effects, clinical experience with this approach has been favorable.

Although the effects produced by corticosteroids in patients with advanced cancer are often highly gratifying, side effects are potentially serious and increase with prolonged use.¹⁵³ In a study of advanced cancer patients who received chronically administered prednisolone or dexamethasone at varying doses, oropharyngeal candidiasis occurred in approximately one-third, edema or cushingoid habitus developed in almost one-fifth; dyspepsia, weight gain, neuropsychological changes, or ecchymoses were observed in 5% to 10%; the incidence of other adverse effects, such as hyperglycemia, myopathy, and osteoporosis was extremely low.¹⁴⁸

The risk of peptic ulcer is approximately doubled in patients chronically treated with corticosteroids. Co-administration of a corticosteroid with aspirin or an NSAID further increases the risk of gastroduodenopathy and is not recommended.¹⁵⁴ Active peptic ulcer disease, systemic infection, and unstable diabetes are relative contraindications to the use of corticosteroids as adjuvant analgesics.

Topical Local Anesthetics

Topical local anesthetics can be used in the management of painful cutaneous and mucosal lesions, and as a premedication prior to skin puncture. Controlled studies have demonstrated the effectiveness of eutectic mixture of 2.5% lidocaine and 2.5% prilocaine (EMLA) in reducing pain associated with venipuncture,¹⁵⁵ lumbar puncture,¹⁵⁶ and arterial puncture.¹⁵⁷ Anecdotally, it has also been used for painful ulcerating skin lesions.^{158,159} Viscous lidocaine is frequently used in the management of oropharyngeal ulceration.¹⁶⁰ Although the risk of aspiration appears to be very small, patients should use caution when eating after oropharyngeal anesthesia.

Neuroleptics

The role of neuroleptic drugs in the management of cancer pain is limited. Methotrimeprazine is a proven analgesic¹⁶¹ that is useful in bedridden patients with advanced cancer who experience pain associated with anxiety, restlessness, or nausea. In the US, methotrimeprazine is approved for intramuscular administration, but extensive experience indicates that it may also be given by continuous subcutaneous administration,¹⁶² subcutaneous bolus injection, or brief intravenous infusion (administration over 20 to 30 minutes). A prudent dosing schedule begins with 5 to 10 mg every six hours, or a comparable dose delivered by infusion, which is gradually increased as needed. Most patients will not require more than 20 to 50 mg

every six hours to gain the desired effects.

Benzodiazepines

There is very little evidence that benzodiazepines are analgesic in most clinical circumstances.¹⁶³ Anecdotal evidence supports a potential role for these agents in the management of muscle spasm, concomitant chronic pain and anxiety, and lancinating neuropathic pain, in which case, clonazepam and alprazolam are preferred.¹⁶⁴

ADJUVANTS FOR NEUROPATHIC PAIN

Neuropathic pains are generally less responsive to opioid therapy than are nociceptive pains. The therapeutic outcome of pharmacotherapy may be improved by the addition of an adjuvant medication selected for the particular clinical characteristics of the prevailing neuropathic pain problem. The distinction between continuous and lancinating neuropathic pain has important implications for the selection of an appropriate drug (Table 11).

Antidepressants

In cancer patients, antidepressant drugs are commonly used to manage continuous neuropathic pains that have not responded adequately to an opioid, and lancinating neuropathic pains that are refractory to opioids and other specific adjuvant agents.¹⁶⁵ The evidence for analgesic efficacy is greatest for the tertiary amine tricyclic drugs, such as amitriptyline, doxepin, and imipramine. The secondary amine tricyclic antidepressants (such as desipramine, clomipramine, and nortriptyline) have fewer side effects and are preferred when there is concern about sedation, anticholinergic effects, or cardiovascular toxicity.^{166,167} The selective serotonin uptake inhibitor antidepressants are much less effective in the management of neuropathic pain and are generally not recommended for this purpose.¹⁶⁵

The starting dose of a tricyclic antidepressant should be low, e.g., amitriptyline 10 mg in the elderly and 25 mg in

Table 10
Painful Conditions
Commonly Responding to
Corticosteroid Therapy

Raised intracranial pressure
Acute spinal cord compression
Superior vena cava syndrome
Metastatic bone pain
Neuropathic pain due to infiltration or compression by tumor
Symptomatic lymphedema
Hepatic capsular distention

younger patients. Doses can be increased every few days and the initial dosing increments are usually the same size as the starting dose. When doses have reached the usual effective range (e.g., amitriptyline 50 to 150 mg), it is prudent to observe effects for a week before continuing upward dose titration. Analgesia usually occurs within a week after achieving an effective dosing level. Although most patients can be treated with a single nighttime dose, some patients have less morning "hangover," and/or less late afternoon pain if doses are divided. It is reasonable to continue upward dose titration beyond the usual analgesic doses in patients who fail to achieve benefit and have no limiting side effects. Plasma drug concentration levels, if available, may provide useful information and should be followed during the course of therapy.

Oral Local Anesthetics

Occasionally, systemically administered local anesthetic drugs may be useful in the management of neuropathic pains characterized by either continuous or lancinating dysesthesias. Controlled trials have demonstrated the efficacy of tetracaine¹⁶⁸ and mexiletine^{169,170} and clinical evidence suggests similar effects may be achieved with flecainide¹⁷⁰ and subcutaneous lidocaine.¹⁷¹

Experience with oral local anesthetics in the cancer population is still limited,¹⁷⁰ and recommendations are largely empirical. It is reasonable to undertake a trial with an oral local anesthetic in patients with continuous dysesthesias who fail to respond adequately or who cannot tolerate the tricyclic antidepressants, and in patients with lancinating pains refractory to trials of anticonvulsant drugs and baclofen. Mexiletine is the safest of the oral local anesthetics¹⁷² and is preferred. Analgesic response to a trial of intravenous lidocaine (5 mg/kg, over 45 minutes) may predict the likelihood of response to oral mexiletine.¹⁶⁹ Dosing with mexiletine should usually be started at 100 to 150 mg per day. If intolerable side effects do not occur, the dose can be increased by a like amount every few days, until the usual maximum dose of 300 mg three times per day is reached. Plasma drug concentration levels, if available, can provide information similar to that described previously for the tricyclic antidepressants.

Clonidine

Clonidine is an alpha-2 adrenergic agonist that has established analgesic effects when administered by the spinal route¹⁷³ and limited activity by the oral or transdermal routes.¹⁷⁴ In cancer patients, a trial of oral or transdermal clonidine can be considered in the management of continuous neuropathic pain refractory to opioids and other adjuvants.

Capsaicin

Occasionally, patients will benefit from the topical application of capsaicin, which depletes peptides in small primary afferent neurons, including those that are putative mediators of nociceptive transmission (e.g., substance P).¹⁷⁵ Analgesic effects have been observed in postherpetic neuralgia, painful peripheral neuropathies, and post-mastectomy pain.¹⁷⁶⁻¹⁷⁹ Although the dose-response relationship has not been evaluated in controlled studies,

Table 11
Adjuvant Analgesics For Neuropathic Pain
Based On Clinical Characteristics

Continuous Pain	Lancinating Pain
Antidepressants	Anticonvulsant Drugs
Amitriptyline	Carbamazepine
Doxepin	Phenytoin
Imipramine	Clonazepam
Desipramine	Valproate
Nortriptyline	Baclofen
	Oral Local Anesthetics
Oral Local Anesthetics	
Mexiletine	
Clonidine	
Capsaicin	

a far lesser extent, in those with neuropathic pains characterized solely by continuous dysesthesias. Although most practitioners prefer to begin with carbamazepine because of the very good response rate observed in trigeminal neuralgia,¹⁶⁴ this drug must be used cautiously in cancer patients with thrombocytopenia, those at risk for marrow failure (e.g., following chemotherapy), and those whose blood counts must be monitored to determine disease status. If carbamazepine is used, a

complete blood count should be obtained prior to the start of therapy, after two and four weeks, and every three to four months thereafter. A leukocyte count below 4,000 is usually considered a contraindication to treatment, and a decline to less than 3,000, or an absolute neutrophil count of less than 1,500 during therapy should prompt discontinuation of the drug.

Other anticonvulsant drugs may also be useful for patients with lancinating dysesthesias following nerve injury. Published reports and clinical experience support trials with gabapentin,¹⁸¹ phenytoin,¹⁶⁴ clonazepam,¹⁶⁴ and valproate.¹⁶⁴

When anticonvulsant drugs are used as adjuvant analgesics, dosing should be initiated on the basis of guidelines customarily employed in the treatment of seizures. Low initial doses are appropriate for carbamazepine, valproate, and clonazepam, and the administration of phenytoin often begins with the presumed therapeutic dose (e.g., 300 mg per day) or a prudent oral loading regimen (e.g., 500

data from phase 2 studies of 0.075% and 0.025% capsaicin preparations suggest that it would be reasonable to use the higher concentration for either the initial trial or a subsequent trial following failure of the lower concentration product. Application is often complicated by a burning sensation. This wanes spontaneously in some patients and can be reduced in others with the prior use of an oral analgesic or cutaneous application of lidocaine 5% ointment. A proportion of patients report intolerable burning and cannot use the drug. In those who tolerate the drug, at least four applications per day for four weeks represent an adequate trial.

Anticonvulsant Drugs

Selected anticonvulsant drugs appear to be analgesic for the lancinating dysesthesias that characterize diverse types of neuropathic pain.^{164,180} Clinical experience also supports the use of these agents in patients with paroxysmal neuropathic pains that may not be lancinating, and to

mg twice, separated by hours). When low initial doses are used, dose escalation may continue until a favorable effect occurs, intolerable side effects supervene, or the plasma drug concentration has reached a predetermined level, which is customarily at the upper end of the therapeutic range for seizure management. This approach is empirical, as there are no data relating plasma concentration to analgesic effects. The variability in the response to these drugs is great, and sequential trials in patients with persistent pain are amply justified by clinical experience.

Baclofen

Baclofen is a GABA-agonist that has proven efficacy in the treatment of trigeminal neuralgia,¹⁸² and is therefore commonly tried in the management of paroxysmal neuropathic pains of any type. Baclofen dosing is generally undertaken in a manner similar to that used for treating spasticity, its primary indication. A starting dose of 5 mg two to three times per day is gradually escalated to 30 to 90 mg per day, and sometimes higher if side effects do not occur. The most common adverse effects are sedation and confusion. Failure of a prolonged trial of baclofen requires dose tapering prior to discontinuation due to the potential for a withdrawal syndrome.

N-Methyl-D-Aspartate Antagonists

Limited data suggest that an N-methyl-D-aspartate (NMDA) antagonist may be useful in the management of neuropathic pain states. Experience has been reported with ketamine administered by subcutaneous infusion, starting with 0.1 to 0.3 mg/kg/hr.^{183,184} This approach is worthy of consideration in difficult pain states. The oral bioavailability of ketamine is low and this route is not recommended. Other drugs with NMDA-antagonist activity have been evaluated and there is some evidence of analgesic efficacy for amantadine¹⁸⁵ and dextromethorphan.¹⁸⁶

Calcitonin

Subcutaneous injection of calcitonin (100 to 200 I.U. per day) has been shown to be an active analgesic in the management of continuous neuropathic phantom limb pain.¹⁸⁷ Experience with this drug in the treatment of neuropathic pain is very limited and should be considered only after trials of other drugs have failed.

Pimozide

Pimozide, a phenothiazine neuroleptic with activity against lancinating neuropathic pain, is rarely used in the cancer setting. Given its high incidence of adverse effects, including physical and mental slowing, tremor, and slight parkinsonian symptoms,¹⁸⁸ it also should be considered following failed trials with other drugs.

ADJUVANT ANALGESICS FOR BONE PAIN

Anti-inflammatory Drugs

The management of bone pain frequently requires the integration of opioid therapy with multiple ancillary approaches. Although a meta-analysis of NSAID therapy in cancer pain that reviewed data from 1,615 patients in 21 trials found no specific efficacy in bone pain and analgesic effects equivalent only to "weak" opioids,¹⁸⁹ some patients appear to benefit greatly from the addition of such a drug. Corticosteroids are often advocated in difficult cases.¹⁴⁴

Bisphosphonates

Bisphosphonates are analogues of inorganic pyrophosphate that inhibit osteoclast activity and reduce bone resorption in a variety of illnesses. Controlled and uncontrolled trials of intravenous pamidronate in patients with advanced cancer have demonstrated significant reduction of bone pain.¹⁹⁰ The analgesic effect of pamidronate appears to be dose- and schedule-dependent: A dose response is evident at doses between 15 and 30 mg per week, and it appears that 30 mg every two weeks is less effective than 60 mg every four weeks.¹⁹⁰ Whereas similar

effects have been observed with orally administered clodronate,^{191,192} a study that evaluated sodium etidronate demonstrated no beneficial effects.¹⁹³ On balance, the data are sufficient to recommend a trial of one of these agents in patients with refractory bone pain; currently, the evidence for analgesic effects is best for parenterally administered pamidronate or oral clodronate.

Radiopharmaceuticals

Radiolabeled agents that are absorbed into areas of high bone turnover have been evaluated as potential therapies for metastatic bone disease. Such an approach has the advantage of addressing all sites of involvement with relatively selective absorption, thus limiting radiation exposure to normal tissues. Excellent clinical responses with acceptable hematological toxicity have been observed with a range of radiopharmaceuticals. Systemically administered phosphorus-32 has long been known to be an effective agent in the management of metastatic bone pain, and recent studies have demonstrated efficacy without substantial myelosuppression.^{194,195} The best studied and most commonly used radionuclide is strontium-89. Large, prospectively randomized clinical trials have demonstrated its efficacy as a first-line therapy¹⁹⁶ or as an adjuvant to external-beam radiotherapy.¹⁹⁷ This approach is contraindicated in patients who have a platelet count less than 60,000 or a white cell count less than 2.4,¹⁹⁸ and is not advised for patients with very poor performance status.¹⁹⁹ Using another approach, bone-seeking radiopharmaceuticals, which link a radioisotope with a bisphosphonate compound, have been synthesized. Positive experience has been reported with samarium-153-ethylenediaminetetramethylene phosphonic acid,²⁰⁰ and rhenium-186-hydroxyethylidene diphosphonate.²⁰¹

Calcitonin

There is limited evidence that repeated doses of subcutaneous calcitonin can reduce bone pain.^{202,203} Nonetheless, it is reasonable to consider a trial with this drug (e.g., salmon calcitonin 100 to 200 I.U. twice daily subcutaneously for several weeks) in refractory cases.

ADJUVANTS FOR VISCERAL PAIN

There are limited data that support the potential efficacy of a range of adjuvant agents for the management of bladder spasm, tenesmoid pain, and colicky intestinal pain. Oxybutynin chloride, a tertiary amine with anticholinergic and papaverine-like, direct muscular antispasmodic effects, is often helpful for bladder spasm pain,²⁰⁴ as is flavoxate.²⁰⁵ Based on limited clinical experience and in vitro evidence that prostaglandins play a role in bladder smooth-muscle contraction, a trial of NSAIDs may be justified for patients with painful bladder spasms,²⁰⁶ and limited data support a trial of intravesical capsaicin.^{207,208}

There is no well established pharmacotherapy for painful rectal spasms, although a recent double-blind study demonstrated that nebulized salbutamol can reduce the duration and severity of attack.²⁰⁹ There is also some anecdotal support for trials of diltiazem,²¹⁰ clonidine,²¹¹ chlorpromazine,¹⁶¹ and benzodiazepines.²¹² Colicky pain due to inoperable bowel obstruction has been treated empirically with intravenous scopolamine (hyoscine) butylbromide²¹³⁻²¹⁵ and sublingual scopolamine (hyoscine) hydrobromide.²¹⁶ Limited data support the use of octreotide for this indication as well.²¹⁷

In the management of pain due to pancreatic cancer, there is limited evidence supporting the effectiveness of the somatostatin analogues, such as octreotide²¹⁷ or lanreotide,²¹⁸ as well as the oral administration of trypsin.²¹⁹ It is speculated that these effects are mediated by reduction in pancreatic exocrine secretion.

Other Non-invasive Analgesic Techniques

PSYCHOLOGICAL THERAPIES

Psychological approaches are an integral part of the care of the cancer patient with pain. All patients can benefit from psychological assessment and support, and some are good candidates for specific psychological intervention. Cognitive-behavioral interventions can help some patients decrease the perception of distress engendered by the pain through the development of new coping skills and the modification of thoughts, feelings, and behaviors.²²⁰ Relaxation techniques may be able to reduce muscular tension and emotional arousal, or enhance pain tolerance.²²¹ Other approaches reduce anticipatory anxiety that may lead to avoidance behaviors, or lessen the distress associated with the pain.²²² Successful implementation of these approaches in the cancer population requires a cognitively intact patient and a dedicated, well-trained practitioner.²²³

PHYSIATRIC TECHNIQUES

Physiatric techniques can be used to optimize the function of the patient with chronic cancer or to enhance analgesia through application of modalities such as electrical stimulation, heat, or cryotherapy. The treatment of lymphedema by use of wraps, pressure stockings, or pneumatic pump devices can both improve function and relieve pain and heaviness.^{224,225} The use of orthotic devices can immobilize and support painful or weakened structures, and assistive devices can be of great value to patients with pain precipitated by weight bearing or ambulation.

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION

The mechanisms by which transcutaneous electrical nerve stimulation reduces pain are not well defined; local neural blockade and activation of a central inhibitory system have been pro-

posed as explanations. Clinical experience suggests that this modality can be a useful adjunct in the management of mild to moderate musculoskeletal or neuropathic pain.²²⁶

Invasive Analgesic Techniques

ANESTHETIC AND NEUROSURGICAL TECHNIQUES

The results of the WHO "analgesic ladder" validation studies suggest that 10% to 30% of patients with cancer pain do not achieve a satisfactory balance between relief and side effects using systemic pharmacotherapy alone.¹⁹ Anesthetic and neurosurgical techniques (Table 12) may reduce or eliminate the requirement for systemically administered opioids to achieve adequate analgesia.

Consideration of invasive approaches requires a word of caution. Interpretation of data regarding the use of alternative analgesic approaches and extrapolation to the presenting clinical problem requires care. The literature is characterized by a lack of uniformity in patient selection, inadequate reporting of previous analgesic therapies, inconsistencies in outcome evaluation, and paucity of long-term follow-up. Furthermore, reported outcomes in the literature may not predict the outcomes of a procedure performed by a physician who has more limited experience with the techniques involved.

When indicated, the use of invasive and neurodestructive procedures should be considered on the basis of the likelihood and duration of analgesic benefit, the immediate and long-term risks, the likely duration of survival, the availability of local expertise, and the anticipated length of hospitalization.

For most pain syndromes, there exists a range of techniques that may theoretically be applied. The following principles are important in selecting a procedure:

1. Ablative procedures should be deferred as long as pain relief can be

achieved with non-ablative modalities.

2. The procedure most likely to be effective should be selected. If there is a choice, however, the one with the fewest and least serious adverse effects is preferred.

3. In progressive stages of cancer, pain is likely to be multifocal and a procedure aimed at a single locus of pain, even if completed flawlessly, is unlikely to provide complete pain relief until death. A realistic and sound goal is a lasting reduction in pain to a level that is manageable by pharmacotherapy with minimal side effects.

4. Whenever possible, an anesthetic block should be used to predict the efficacy of neurolysis prior to the actual procedure.

5. All procedures should be performed by a physician who is experienced in the specific intervention.

In general, regional analgesic techniques such as intraspinal opioid and local anesthetic administration or intrapleural local anesthetic administration, are usually considered first because they do not compromise neurological integrity. Neurodestructive procedures, however, are valuable in a small subset of patients; and some of these procedures, such as celiac plexus blockade in patients with pancreatic cancer, may have a favorable enough risk:benefit ratio that early treatment is warranted.

REGIONAL ANALGESIA

Epidural and Intrathecal Opioids

The delivery of low opioid doses near the sites of action in the spinal cord may decrease supraspinally mediated adverse effects. In the absence of randomized trials that compare the various intraspinal techniques with other analgesic approaches, the indications for the spinal route remain empirical, although they are based on relative therapeutic index. One survey reported that only 16 of 1,205 cancer patients with pain required intraspinal therapy.²²⁷ Compared to neuroablative ther-

apies, spinal opioids have the advantage of preserving sensation, strength, and sympathetic function. Contraindications include bleeding diathesis, profound leukopenia, and sepsis. A temporary trial of spinal opioid therapy should be performed to assess the potential benefits of this approach before implantation of a permanent catheter.

Opioid selection for intraspinal delivery is influenced by several factors. Hydrophilic drugs, such as morphine and hydromorphone, have a prolonged half-life in cerebrospinal fluid and significant rostral redistribution.²²⁸ Lipophilic opioids, such as fentanyl and sufentanil, have less rostral redistribution and may be preferable for segmental analgesia at the level of spinal infusion. The addition of a low concentration of a local anesthetic, such as 0.125% to 0.25% bupivacaine, to an epidural²²⁹ or intrathecal opioid²³⁰⁻²³² has been demonstrated to increase analgesic effect without increasing toxicity. Other agents have also been co-administered with intraspinal opioids, including clonidine,²³³ octreotide,²³⁴ ketamine,^{235,236} and calcitonin,²³⁷ but additional studies are required to assess their potential utility.

There have been no trials comparing the intrathecal and epidural routes in cancer pain although extensive experience has been reported with each approach. Longitudinal studies of epidural or intrathecal opioid infusions for cancer pain suggest that the risks associated with these techniques are similar.^{104,238,239} These procedures are associated with potentially substantial morbidity and should be performed and monitored by well trained clinicians.

Intraventricular Opioids

A growing international experience suggests that the administration of low doses of an opioid (particularly morphine) into the cerebral ventricles can provide long-term analgesia in selected patients.^{240,241} This technique has been used for patients

Table 12
Invasive Analgesic Techniques According to the Site of Pain

Site	Procedure
Face (Unilateral)	Gasserian gangliolysis Trigeminal neurolysis Intraventricular opioid
Pharyngeal	Glossopharyngeal neurolysis Intraventricular opioid
Arm/Brachial Plexus	Spinal opioid±local anesthetic Chemical rhizotomy Surgical rhizotomy
Chest Wall	Spinal opioid±local anesthetic Intercostal neurolysis Paravertebral neurolysis Chemical rhizotomy Surgical rhizotomy
Abdominal (Somatic)	Spinal opioid±local anesthetic Chemical rhizotomy Surgical rhizotomy Cordotomy (unilateral pain)
Upper Abdomen (Visceral)	Celiac plexus neurolysis
Low Abdomen (Visceral)	Hypogastric neurolysis Ganglion impar neurolysis
Perineum	Spinal opioid±local anesthetic Chemical rhizotomy Surgical rhizotomy Transsacral S4 neurolysis
Pelvis+lower limb	Spinal opioid±local anesthetic Chemical rhizotomy Surgical rhizotomy
Unilateral Lower Quadrant	Cordotomy
Multifocal or generalized pain	Pituitary ablation Cingulotomy

with upper body or head pain, or severe diffuse pain and has been generally very well tolerated. Schedules have included both intermittent injection via an Ommaya reservoir^{240,241} and continual infusion using an implanted pump.²⁴²

Regional Local Anesthetic

Several authors have described the use of intrapleural local anesthetics in the management of chronic post-thoracotomy pain²⁴³ and cancer-related pains involving the head, neck, chest, arms, and upper ab-

dominal viscera.^{244,245} Although a single bolus may provide prolonged analgesia, continuous infusion of local anesthetic has been recommended for patients with chronic pain due to advanced cancer.²⁴⁶ For patients with localized upper limb pain, intermittent infusion of bupivacaine through an interscalene brachial plexus catheter may be of benefit.²⁴⁷

ANESTHETIC TECHNIQUES FOR SYMPATHETICALLY MAINTAINED PAIN AND VISCERAL PAIN

Celiac Plexus Block

Neurolytic celiac plexus blockade can be considered in the management of pain caused by neoplastic infiltration of the upper abdominal viscera, including the pancreas, upper retroperitoneum, liver, gall bladder, and proximal small bowel.^{248,249} In addition to an extensive anecdotal experience, this technique is supported by two controlled studies of the percutaneous approach^{250,251} and a controlled trial of intraoperative neurolysis.²⁵² Reported analgesic response rates in patients with pancreatic cancer are 50% to 90%, and the reported duration of effect is generally one to 12 months.^{248,249} Given the generally favorable response to this approach, and supportive data from two small studies,^{250,251} some clinicians recommend this intervention at an early stage; other experts differ and recommend celiac plexus block only for patients who do not maintain an adequate balance between analgesia and side effects from an oral opioid.²⁴⁸

Common transient complications include postural hypotension and diarrhea. Rarely, the procedure can produce a paraplegia due to an acute ischemic myelopathy (probably caused by involvement of Adamkiewicz's artery).^{253,254} Posterior spread of neurolytic solution can occasionally lead to involvement of lower thoracic and lumbar somatic nerves, which can potentially result in a neuropathic pain syndrome. Other uncommon

complications include pneumothorax and retroperitoneal hematoma.

Sympathetic Blocks for Pelvic Visceral Pain

Limited anecdotal experience has been reported with two sympathetic blocking techniques. Phenol ablation of the superior hypogastric nerve plexus, which lies anterior to the sacral promontory, has been reported to relieve the pain of chronic cancer arising from the descending colon and rectum and the lower genitourinary structures in 40% to 80% of patients.^{255,256} Similarly, neurolysis of the ganglion impar (ganglion of Walther, a solitary retroperitoneal structure at the sacrococcygeal junction that marks the termination of the paired paravertebral sympathetic chains) has been reported to relieve visceral sensations referred to the rectum, perineum, or vagina caused by locally advanced cancers of the pelvic visceral structures.²⁵⁷⁻²⁵⁹

Sympathetic Blockade of Somatic Structures

Sympathetically maintained pain syndromes may be relieved by interruption of sympathetic outflow to the affected region of the body. Lumbar sympathetic blockade should be considered for sympathetically maintained pain involving the legs, and stellate ganglion blockade may be useful for sympathetically maintained pain involving the face or arms.²⁶⁰

NEUROABLATIVE TECHNIQUES FOR SOMATIC AND NEUROPATHIC PAIN

Rhizotomy

Segmental or multisegmental destruction of the dorsal sensory roots (rhizotomy), achieved by surgical section, chemical neurolysis, or radiofrequency lesion, can be an effective method of pain control for patients with otherwise refractory localized pain syndromes. These techniques are most commonly used in the management of chest wall pain due to tumor invasion of somatic and neural structures.²⁶¹

Other indications include refractory upper limb, lower limb, pelvic, or perineal pain.²⁶²

Chemical rhizotomy, produced by the instillation of a neurolytic solution into either the epidural or intrathecal space,²⁶¹ can be performed at any level up to the mid-cervical region, above which the spread of neurolytic agent to the medullary centers carries an unacceptable risk of cardiorespiratory collapse. To minimize the risk of excessive spread and lysis beyond the target segments, catheter tip position should be confirmed radiographically and phenol should be injected in small volumes (1 to 2 ml).²⁶³

Satisfactory analgesia is achieved in about 50% of patients,²⁶¹ and the average duration of relief is three to four months with a wide range of distribution. Adverse effects can be related to the injection technique (e.g., spinal headache, infection, and arachnoiditis) or to the destruction of non-nociceptive nerve fibers. Specific complications of the procedure depend on the site of neurolysis. For example, the complications of lumbosacral neurolysis include paresis (5% to 20%), sphincter dysfunction (5% to 60%), impairment of touch and proprioception, and dysesthesias. Although neurological deficits are usually transient, the risk of increased disability through weakness, sphincter incompetence, and loss of positional sense suggests that these techniques should be reserved for patients with limited function and preexisting urinary diversion. Patient counseling and informed consent regarding risk are essential.

Neurolysis of Primary Afferent Nerves or Their Ganglia

Neurolysis of primary afferent nerves may also provide significant relief for selected patients with localized pain. The utility of these approaches is limited by the potential for concurrent motor or sphincteric dysfunction. Refractory unilateral facial or pharyngeal pain may

be amenable to trigeminal neurolysis (gasserian gangliolysis) or glossopharyngeal neurolysis.^{264,265} Unilateral pain involving the tongue or floor of the mouth may be amenable to blockade of the sphenopalatine ganglion.²⁶⁶ Intercostal or paravertebral neurolysis is an alternative to rhizotomy for patients with chest wall pain. Unilateral shoulder pain may be amenable to suprascapular neurolysis.²⁶⁷ Arm pain that is more extensive may be effectively relieved by brachial plexus neurolysis, but this approach will result in extreme motor weakness.²⁶⁸ Anecdotally, refractory leg pain has been relieved without compromise of motor function by injection of 10 ml of 10% phenol into the psoas muscle sheath.²⁶⁹ Severe somatic pain limited to the perineum may be treated by neurolysis of the S4 nerve root via the ipsilateral posterior sacral foramen, a procedure that carries minimal risk of motor or sphincter dysfunction.²⁷⁰

Regeneration of peripheral nerves is sometimes accompanied by the development of neuropathic pain, although the threat of postablative dysesthesia is of limited consequence when life expectancy is very limited or intractable pain already exceeds the limits of tolerance.

Cordotomy

During cordotomy, the anterolateral spinothalamic tract is ablated to produce contralateral loss of pain and temperature sensibility.^{271,272} The patient with severe unilateral pain arising in the torso or lower extremity is most likely to benefit from this procedure.^{271,272} Impressive results have also been observed in patients with chest wall pain.²⁷² The percutaneous technique is generally preferred;^{271,272} open cordotomy is usually reserved for patients who are unable to lie in the supine position or are not cooperative enough to undergo a percutaneous procedure.

Significant pain relief is achieved in more than 90% of patients during the period immediately following cordoto-

my.^{271,272} Fifty percent of surviving patients have recurrent pain after one year.²⁷³ Repeat cordotomy can sometimes be effective. The neurological complications of cordotomy include paresis, ataxia, and bladder and "mirror-image" pain.²⁷² Although complications are usually transient, they may be protracted and disabling in approximately 5% of cases.²⁷² Rarely, patients with a long duration of survival (greater than 12 months) develop a delayed-onset dysesthetic pain.²⁷³ The most serious potential complication is respiratory dysfunction, which may occur in the form of phrenic nerve paralysis or as sleep-induced apnea.^{274,275} Because of the latter concern, bilateral high cervical cordotomies or a unilateral cervical cordotomy ipsilateral to the site of the only functioning lung are not recommended.

Pituitary Ablation

Pituitary ablation by chemical or surgical hypophysectomy has been reported to relieve diffuse and multifocal pain syndromes that have been refractory to opioid therapy and are unsuitable for any regional neuroablative procedure.^{276,277} Relief of pain due to both hormone-dependent and hormone-independent tumors has been observed.^{276,277}

Cingulotomy

Anecdotal reports also support the efficacy of magnetic resonance imaging-guided stereotactic cingulotomy in the management of diffuse pain syndromes that have been refractory to opioid therapy.^{278,279} Although this appears to be a safe procedure with minimal neurological or psychological morbidity, the duration of analgesia is often limited,^{278,279} the mode of action is unknown, and the procedure is rarely considered.

SEDATION AS PAIN THERAPY

Through the vigilant application of analgesic care, pain is often relieved adequately without compromising the sentience or function of the patient beyond

that caused by the natural disease process itself. Occasionally, however, this cannot be achieved and pain is perceived to be "refractory." The term refractory pain is used to describe pain that remains distressing despite efforts to alleviate it by means that do not compromise global perception and conscious function.²⁸⁰ In deciding that a pain is refractory, the clinician must perceive that the further application of standard interventions are either 1) incapable of providing adequate relief, 2) associated with excessive and intolerable acute or chronic morbidity, or 3) unlikely to provide relief within a tolerable time frame. In such situations, sedation may be the only therapeutic option capable of providing adequate relief. This approach is described as "sedation in the management of refractory symptoms at the end of life."²⁸

Traditionally, the ethical justification of sedation has been based on "the doctrine of double effect," which distinguishes between the compelling primary intended therapeutic effect (to relieve suffering) and the foreseeable but unavoidable adverse effects (the loss of interactional function and the potential for accelerating death).^{280,281} There is a significant problem with this justification insofar as the death of the patient at the end of a long and difficult illness is not always an untoward or adverse outcome. Indeed, in Jewish tradition, there is a blessing for a "timely" death ("Baruch Dayan Ha Emet," Blessed is the Supreme Judge). Critics of this justification have claimed that at best "double effect" is often claimed disingenuously²⁸² or, at worst, it has become a meaningless mantra recited by cynical surreptitious practitioners of euthanasia cloaked as benevolent clinicians.²⁸³

The justification for sedation in this setting is more effectively asserted on the basis that it is goal appropriate and proportionate. At the end of life, when the overwhelming goal of care is the preservation of patient comfort, the provision

of adequate relief of symptoms must be pursued even in the setting of a narrow therapeutic index for the necessary palliative treatments. In this context, sedation is a medically indicated and proportionate therapeutic response to refractory symptoms that cannot be otherwise relieved. Appeal to patients' rights also underwrites the moral legitimacy of sedation in the management of otherwise intolerable pain at the end of life. Patients have a right, recently affirmed by the Supreme Court, to palliative care in response to unrelieved suffering.²⁸⁴


A survey of homecare patients treated by the palliative care service of the Italian National Cancer Institute found that 31 of 120 terminally ill patients developed otherwise unendurable symptoms that required deep sedation for adequate relief.²⁸⁵ In a retrospective survey of 100 patients who died in an inpatient palliative care ward, Fainsinger et al²⁸⁶ found that six patients required sedation for adequate pain control prior to death. An additional two patients who may have benefited from sedation died with severe uncontrolled pain. In a retrospective survey of 36 patients treated with opioid infusions for pain, Portenoy et al²⁸⁷ reported that approximately one-third were unable to achieve adequate analgesia without excessive sedation.

Once symptoms are deemed to be refractory by clinical consensus, it is appropriate to present this option to the patient or his or her surrogate. The offer of sedation made in such a setting can demonstrate the clinician's commitment to the relief of suffering; can enhance trust in the doctor-patient relationship;

and can influence the patient's appraisal of his or her capacity to cope. Indeed, patients commonly decline sedation, acknowledging that symptoms will be incompletely relieved but secure in the knowledge that if the situation becomes intolerable, this option remains available. Other patients reaffirm comfort as the predominating consideration and request the initiation of sedation.

The published literature describing the use of sedation in the management of refractory symptoms at the end of life is anecdotal and refers to the use of opioids, neuroleptics, benzodiazepines, barbiturates, and propofol.²⁸⁰ In the absence of relative efficacy data, guidelines for drug selection are empirical. Irrespective of the agent or agents selected, administration initially requires dose titration to achieve adequate relief, followed subsequently by provision of ongoing therapy to ensure maintenance of effect.

Conclusion

The goal of analgesic therapy in patients with cancer is to optimize analgesia with the minimum of side effects and inconvenience. Currently available techniques can provide adequate relief to a vast majority of patients. Most will require ongoing pain treatment, and analgesic requirements often change as the disease progresses. Patients with refractory pain, or unremitting suffering related to other losses or distressing symptoms, should have access to specialists in pain management or palliative medicine who can provide an approach capable of addressing these complex problems. 

References

1. In Bonica JJ: *The Management of Pain*, 2nd ed. Philadelphia, Lea & Febiger, 1990, pp 400-460.
2. Janjan NA: Radiation for bone metastases: Conventional techniques and the role of systemic radiopharmaceuticals. *Cancer* 1997;80:1628-1645.
3. Bates T: A review of local radiotherapy in the treatment of bone metastases and cord compression. *Int J Radiat Oncol Biol Phys* 1992;23:217-221.
4. Vermeulen SS: Whole brain radiotherapy in the treatment of metastatic brain tumors. *Semin Surg Oncol* 1998;14:64-69.
5. Dobrowsky W, Schmid AP: Radiotherapy of presacral recurrence following radical surgery for rectal carcinoma. *Dis Colon Rectum* 1985;28:917-919.

6. Leibel SA, Pajak TF, Massullo V, et al: A comparison of misonidazole sensitized radiation therapy to radiation therapy alone for the palliation of hepatic metastases: Results of a Radiation Therapy Oncology Group randomized prospective trial. *Int J Radiat Oncol Biol Phys* 1987;13:1057-1064.
7. Rothenberg ML: New developments in chemotherapy for patients with advanced pancreatic cancer. *Oncology (Huntingt)* 1996;10:18-22.
8. Thatcher N, Anderson H, Betticher DC, Ranson M: Symptomatic benefit from gemcitabine and other chemotherapy in advanced non-small cell lung cancer: Changes in performance status and tumour-related symptoms. *Anticancer Drugs* 1995; (6 Suppl) 6:39-48.
9. Harris JK, Sutcliffe JC, Robinson NE: The role of emergency surgery in malignant spinal extradural compression: assessment of functional outcome. *Br J Neurosurg* 1996;10:27-33.
10. Boraas MC: Palliative surgery. *Semin Oncol* 1985;12:368-374.
11. Algan SM, Horowitz SM: Surgical treatment of pathologic hip lesions in patients with metastatic disease. *Clin Orthop* 1996;(332):223-231.
12. Ross GJ, Kessler HB, Clair MR, et al: Sonographically guided paracentesis for palliation of symptomatic malignant ascites. *AJR Am J Roentgenol* 1989;153:1309-1311.
13. Cruikshank DP, Buchsbaum HJ: Effects of rapid paracentesis. Cardiovascular dynamics and body fluid composition. *JAMA* 1973;225:1361-1362.
14. Lifshitz S, Buchsbaum HJ: The effect of paracentesis on serum proteins. *Gynecol Oncol* 1976;4:347-353.
15. Avradopoulos KA, Vezzeridis MP, Wanebo HJ: Pelvic exenteration for recurrent rectal cancer. *Adv Surg* 1996;29:215-233.
16. Estes NC, Thomas JH, Jewell WR, et al: Pelvic exenteration: A treatment for failed rectal cancer surgery. *Am Surg* 1993;59:420-422.
17. Coyle N, Portenoy RK.: Infection as a cause of rapidly increasing pain in cancer patients. *J Pain Symptom Manage* 1991; 6:266-269.
18. World Health Organization: *Cancer Pain Relief*. Geneva, World Health Organization, 1986.
19. World Health Organization: *Cancer Pain Relief: With a guide to opioid availability*, 2nd ed. Geneva, World Health Organization, 1996.
20. Jadad AR, Browman GP: The WHO analgesic ladder for cancer pain management. Stepping up the quality of its evaluation. *JAMA* 1995;274:1870-1873.
21. American Pain Society. *Principles of Analgesic Use in the Treatment Acute Pain and Chronic Cancer Pain. A Concise Guide to Medical Practice*. (3rd ed.) Skokie, Illinois: American Pain Society, 1992.
22. Agency for Health Care Policy and Research. *Management of cancer pain: Adults*. Cancer Pain Guideline Panel. *Am Fam Physician* 1994; 49:1853-1868.
23. *Cancer Pain Assessment and Treatment Curriculum Guidelines*. The Ad Hoc Committee on Cancer Pain of the American Society of Clinical Oncology. *J Clin Oncol* 1992;10:1976-1982.
24. Vane JR, Botting RM: Anti-inflammatory drugs and their mechanism of action. *Inflamm Res* 1998; 47 Suppl 2:S78-87.
25. Piletta P, Porchet HC, Dayer P: Central analgesic effect of acetaminophen but not of aspirin. *Clin Pharmacol Ther* 1991;49:350-354.
26. Lehmann T, Day RO, Brooks PM: Toxicity of antirheumatic drugs. *Med J Aust* 1997;166:378-383.
27. Hawkey CJ: COX-2 inhibitors. *Lancet* 1999;353:307-314.
28. Johnson JR, Miller AJ: The efficacy of choline magnesium trisilicylate (CMT) in the management of metastatic bone pain: A pilot study. *Palliat Med* 1994;8:129-135.
29. Hawkey CJ: Progress in prophylaxis against non-steroidal anti-inflammatory drug-associated ulcers and erosions. Omeprazole NSAID Steering Committee. *Am J Med* 1998;104:67S-74S; discussion 9S-80S.
30. Valentini M, Cannizzaro R, Poletti M, et al: Nonsteroidal antiinflammatory drugs for cancer pain: Comparison between misoprostol and ranitidine in prevention of upper gastrointestinal damage. *J Clin Oncol* 1995;13:2637-2642.
31. Taha AS, Hudson N, Hawkey CJ, et al: Famotidine for the prevention of gastric and duodenal ulcers caused by nonsteroidal antiinflammatory drugs. *N Engl J Med* 1996;334:1435-1439.
32. Makin AJ, Williams R: Acetaminophen-induced hepatotoxicity: Predisposing factors and treatments. *Adv Intern Med* 1997;42:453-483.
33. Portenoy RK, Foley KM, Inturrisi CE: The nature of opioid responsiveness and its implications for neuropathic pain: New hypotheses derived from studies of opioid infusions. *Pain* 1990;43:273-286.
34. Hanks GW, Forbes K: Opioid responsiveness. *Acta Anaesthesiol Scand* 1997;41:154-158.
35. Cherny NI: Opioid analgesics: Comparative features and prescribing guidelines. *Drugs* 1996; 51:713-737.
36. Ripamonti C, Groff L, Brunelli C, et al: Switching from morphine to oral methadone in treating cancer pain. What is the equianalgesic dose ratio? *J Clin Oncol* 1998;16:3216-3221.
37. Sindrup SH, Brosen K: The pharmacogenetics of codeine hypoalgesia. *Pharmacogenetics* 1995;5:335-346.
38. Fromm MF, Hofmann U, Griese EU, Mikus G: Dihydrocodeine: A new opioid substrate for the polymorphic CYP2D6 in humans. *Clin Pharmacol Ther* 1995;58:374-382.
39. Hopkinson JH 3d: Vicodin, a new analgesic: Clinical evaluation of efficacy and safety of repeated doses. *Curr Ther Res Clin Exp* 1978;24:633-645.
40. Heiskanen T, Kalso E: Controlled-release oxycodone and morphine in cancer related pain. *Pain* 1997;73:37-45.
41. Hagen NA, Babul N: Comparative clinical efficacy and safety of a novel controlled-release oxycodone formulation and controlled-release hydromorphone in the treatment of cancer pain. *Cancer* 1997;79:1428-1437.
42. Mercadante S, Salvaggio L, Dardanoni G, et al:

- Dextropropoxyphene versus morphine in opioid-naïve cancer patients with pain. *J Pain Symptom Manage* 1998;15:76-81.
43. Rosenberg WM, Ryley NG, Trowell JM, et al: Dextropropoxyphene induced hepatotoxicity: A report of nine cases. *J Hepatol* 1993;19:470-474.
44. Sawe J, Svensson JO, Rane A: Morphine metabolism in cancer patients on increasing oral doses—no evidence for autoinduction or dose-dependence. *Br J Clin Pharmacol* 1983;16:85-93.
45. Christrup LL: Morphine metabolites. *Acta Anaesthesiol Scand* 1997; 41:116-122.
46. Pasternak GW, Bodnar RJ, Clark JA, Inturrisi CE: Morphine-6-glucuronide, a potent mu agonist. *Life Sci* 1987; 41:2845-2849.
47. Gong QL, Hedner T, Hedner J, et al: Antinociceptive and ventilatory effects of the morphine metabolites: Morphine-6-glucuronide and morphine-3-glucuronide. *Eur J Pharmacol* 1991;193:47-56.
48. Grace D, Fee JP: A comparison of intrathecal morphine-6-glucuronide and intrathecal morphine sulfate as analgesics for total hip replacement. *Anesth Analg* 1996;83:1055-1059.
49. Lotsch J, Kobal G, Stockmann A, et al: G: Lack of analgesic activity of morphine-6-glucuronide after short-term intravenous administration in healthy volunteers. *Anesthesiology* 1997;87:1348-1358.
50. Osborne R, Joel S, Grebenik K, et al: M: The pharmacokinetics of morphine and morphine glucuronides in kidney failure. *Clin Pharmacol Ther* 1993;54:158-167.
51. Hagen NA, Foley KM, Cerbone DJ, et al: Chronic nausea and morphine-6-glucuronide. *J Pain Symptom Manage* 1991;6:125-128.
52. Osborne RJ, Joel SP, Slevin ML: Morphine intoxication in renal failure: the role of morphine-6-glucuronide. *Br Med J (Clin Res Ed)* 1986; 292:1548-1549.
53. Sjogren P, Dragsted L, Christensen CB: Myoclonic spasms during treatment with high doses of intravenous morphine in renal failure. *Acta Anaesthesiol Scand* 1993; 37:780-782.
54. Houde RW, Wallenstein SL, Beaver WT: Clinical measurement of pain. In: de Stevens G, ed. *Analgesics*. New York, Academic Press, 1965, pp 75-122.
55. Hasselstrom J, Sawe J: Morphine pharmacokinetics and metabolism in humans. Enterohepatic cycling and relative contribution of metabolites to active opioid concentrations. *Clin Pharmacokin* 1993;24:344-354.
56. Morphine in cancer pain: Modes of administration. Expert Working Group of the European Association for Palliative Care. *BMJ* 1996; 312: 823-826.
57. Houde RW. Clinical analgesic studies of hydromorphone. in: Foley KM, Inturrisi CE, (eds): *Opioid Analgesics in the Management of Clinical Pain*. Advances in Pain Research and Therapy, vol 8. New York, Raven Press, 1986, pp 129-136.
58. Moulin DE, Kreeft JH, Murray-Parsons N, Bouquillon AI: Comparison of continuous subcutaneous and intravenous hydromorphone infusions for management of cancer pain. *Lancet* 1991;337: 465-468.
59. Bruera E, Sloan P, Mount B, et al: A randomized, double-blind, double-dummy, crossover trial comparing the safety and efficacy of oral sustained-release hydromorphone with immediate-release hydromorphone in patients with cancer pain. Canadian Palliative Care Clinical Trials Group. *J Clin Oncol* 1996;14:1713-1717.
60. Collins JJ, Geake J, Grier HE, et al: Patient-controlled analgesia for mucositis pain in children: a three- period crossover study comparing morphine and hydromorphone. *J Pediatr* 1996;129:722-728.
61. Lawlor P, Turner K, Hanson J, Bruera E: Dose ratio between morphine and hydromorphone in patients with cancer pain: A retrospective study. *Pain* 1997; 72:79-85.
62. Szeto HH, Inturrisi CE, Houde R, Saal S, et al: Accumulation of normeperidine, an active metabolite of meperidine, in patients with renal failure of cancer. *Ann Intern Med* 1977; 86:738-741.
63. Sporer KA: The serotonin syndrome. Implicated drugs, pathophysiology and management. *Drug Saf* 1995;13:94-104.
64. Jeal W, Benfield P: Transdermal fentanyl. A review of its pharmacological properties and therapeutic efficacy in pain control. *Drugs* 1997;53: 109-138.
65. Agency for Health Care Policy and Research: *Acute Pain Management: Operative or Medical Procedures and Trauma*. Rockville, Md., U.S. Dept. of Health and Human Services, 1992. AHCPR publication no. 92-0032.
66. Lenz KL, Dunlap DS: Continuous fentanyl infusion: Use in severe cancer pain. *Ann Pharmacother* 1998; 32:316-319.
67. Paix A, Coleman A, Lees J, et al: Subcutaneous fentanyl and sufentanil infusion substitution for morphine intolerance in cancer pain management. *Pain* 1995; 63:263-269.
68. Farrar JT, Cleary J, Rauck R, et al: Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo- controlled trial for treatment of breakthrough pain in cancer patients. *J Natl Cancer Inst* 1998;90:611-616.
69. Sinatra RS, Harrison DM: Oxymorphone in patient-controlled analgesia. *Clin Pharm* 1989;8:541, 544.
70. Hermens JM, Ebertz JM, Hanifin JM, Hirshman CA: Comparison of histamine release in human skin mast cells induced by morphine, fentanyl, and oxymorphone. *Anesthesiology* 1985;62:124-129.
71. Ripamonti C, Zecca E, Bruera E: An update on the clinical use of methadone for cancer pain. *Pain* 1997;70:109-115.
72. Grochow L, Sheidler V, Grossman S, et al: Does intravenous methadone provide longer lasting analgesia than intravenous morphine? A randomized, double-blind study. *Pain* 1989;38:151-157.
73. Mercadante S, Sapio M, Serretta R, Caligara M: Patient-controlled analgesia with oral methadone in cancer pain: Preliminary report. *Ann Oncol*

- 1996;7:613-617.
74. Bruera E, Fainsinger R, Moore M, et al: Local toxicity with subcutaneous methadone. Experience of two centers. *Pain* 1991;45:141-143.
 75. Cherny NJ, Chang V, Frager G, et al: Opioid pharmacotherapy in the management of cancer pain: a survey of strategies used by pain physicians for the selection of analgesic drugs and routes of administration. *Cancer* 1995;76:1283-1293.
 76. de Stoutz ND, Bruera E, Suarez-Almazor M: Opioid rotation for toxicity reduction in terminal cancer patients. *J Pain Symptom Manage* 1995;10:378-384.
 77. Fallon M: Opioid rotation: Does it have a role? [editorial]. *Palliat Med* 1997; 11:177-178.
 78. Hasselstrom J, Eriksson S, Persson A, et al: The metabolism and bioavailability of morphine in patients with severe liver cirrhosis. *Br J Clin Pharmacol* 1990;29:289-297.
 79. Coyle N, Adelhardt J, Foley KM, Portenoy RK: Character of terminal illness in the advanced cancer patient: Pain and other symptoms during the last four weeks of life. *J Pain Symptom Manage* 1990; 5:83-93.
 80. Kaiko RF, Fitzmartin RD, Thomas GB, Goldenheim PD: The bioavailability of morphine in controlled-release 30-mg tablets per rectum compared with immediate-release 30-mg rectal suppositories and controlled-release 30-mg oral tablets. *Pharmacotherapy* 1992;12:107-113.
 81. Varvel JR, Shafer SL, Hwang SS, et al: Absorption characteristics of transdermally administered fentanyl. *Anesthesiology* 1989;70:928-934.
 82. Ahmedzai S, Brooks D: Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. The TTS-Fentanyl Comparative Trial Group. *J Pain Symptom Manage* 1997; 13:254-261.
 83. Donner B, Zenz M, Tryba M, Strumpf M: Direct conversion from oral morphine to transdermal fentanyl: A multicenter study in patients with cancer pain. *Pain* 1996; 64:527-534.
 84. Payne R, Mathias SD, Pasta DJ, et al: Quality of life and cancer pain: Satisfaction and side effects with transdermal fentanyl versus oral morphine. *J Clin Oncol* 1998;16:1588-1593.
 85. Weinberg DS, Inturrisi CE, Reidenberg B, et al: Sublingual absorption of selected opioid analgesics. *Clin Pharmacol Ther* 1988;44:335-342.
 86. De Conno F, Ripamonti C, Sbanotto A, Barletta L: A clinical note on sublingual buprenorphine. *J Palliat Care* 1993;9:44-46.
 87. Christie JM, Simmonds M, Patt R, et al: Dose-titration, multicenter study of oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients using transdermal fentanyl for persistent pain. *J Clin Oncol* 1998; 16:3238-3245.
 88. Coyle N, Cherny NI, Portenoy RK: Subcutaneous opioid infusions at home. *Oncology (Huntingt)* 1994; 8:21-7; discussion 31-2, 37.
 89. Hagen NA, Elwood T, Ernst S: Cancer pain emergencies: A protocol for management. *J Pain Symptom Manage* 1997;14:45-50.
 90. Nelson KA, Glare PA, Walsh D, Groh ES: A prospective, within-patient, crossover study of continuous intravenous and subcutaneous morphine for chronic cancer pain. *J Pain Symptom Manage* 1997;13:262-267.
 91. Bruera E, Macmillan K, Selmser P, MacDonald RN: Decreased local toxicity with subcutaneous diamorphine (heroin): A preliminary report. *Pain* 1990;43:91-94.
 92. Drummond SH, Peterson GM, Galloway JG, Keefe PA: National survey of drug use in palliative care. *Palliat Med* 1996; 10:119-124.
 93. Lichter I, Hunt E: Drug combinations in syringe drivers. *N Z Med J* 1995;108:224-226.
 94. Brant JM: The use of access devices in cancer pain control. *Semin Oncol Nurs* 1995;11:203-212.
 95. Lyss AP: Long-term use of oral transmucosal fentanyl citrate (OTFC) for breakthrough pain in cancer patients (Meeting abstract). *Proc Annu Meet Am Soc Clin Oncol*, 1997;16:A144.
 96. Broomhead A, Kerr R, Tester W, et al: Comparison of a once-a-day sustained-release morphine formulation with standard oral morphine treatment for cancer pain. *J Pain Symptom Manage* 1997;14:63-73.
 97. Bruera E, Fainsinger R, Spachynski K, et al: Clinical efficacy and safety of a novel controlled-release morphine suppository and subcutaneous morphine in cancer pain: A randomized evaluation. *J Clin Oncol* 1995;13:1520-1527.
 98. Forman WB, Portenoy RK, Yanagihara RH, et al: A novel morphine sulphate preparation: clinical trial of a controlled-release morphine suspension in cancer pain. *Palliat Med* 1993;7:301-306.
 99. Wong JO, Chiu GL, Tsao CJ, Chang CL: Comparison of oral controlled-release morphine with transdermal fentanyl in terminal cancer pain. *Acta Anaesthesiol Sin* 1997;35:25-32.
 100. Dhaliwal HS, Sloan P, Arkininstall WW, et al: Randomized evaluation of controlled-release codeine and placebo in chronic cancer pain. *J Pain Symptom Manage* 1995;10:612-623.
 101. Aitken HA, Clark EC, McArdle CS, et al: Evaluation of two formulations of dihydrocodeine using patient-controlled analgesia. *Anaesthesia* 1990;45:535-537.
 102. Ripamonti C, Bruera E: Current status of patient-controlled analgesia in cancer patients. *Oncology (Huntingt)* 1997; 11:373-80, 83-4; discussion 84-86.
 103. Portenoy RK, Hagen NA: Breakthrough pain: Definition, prevalence and characteristics. *Pain* 1990;41:273-281.
 104. Gestin Y, Vainio A, Pegurier AM: Long-term intrathecal infusion of morphine in the home care of patients with advanced cancer. *Acta Anaesthesiol Scand* 1997;41:12-17.
 105. Keating Hr, Kundrat M: Patient-controlled analgesia with nitrous oxide in cancer pain. *J Pain Symptom Manage* 1996;11:126-130.
 106. Mercadante S, Dardanoni G, Salvaggio L, et al: Monitoring of opioid therapy in advanced cancer pain patients. *J Pain Symptom Manage* 1997;13: 204-212.
 107. Boisvert M, Cohen SR: Opioid use in advanced

- malignant disease: Why do different centers use vastly different doses? A plea for standardized reporting. *J Pain Symptom Manage* 1995; 10:632-638.
108. Collins JJ, Grier HE, Kinney HC, Berde CB: Control of severe pain in children with terminal malignancy. *J Pediatr* 1995;126:653-657.
109. Fitzgibbon DR, Ready LB: Intravenous high-dose methadone administered by patient controlled analgesia and continuous infusion for the treatment of cancer pain refractory to high-dose morphine. *Pain* 1997; 73:259-621.
110. Edwards WT: Optimizing opioid treatment of postoperative pain. *J Pain Symptom Manage* 1990;5:324-36.
111. Schug SA, Zech D, Grond S, et al: A long-term survey of morphine in cancer pain patients. *J Pain Symptom Manage* 1992;7:259-266.
112. Portenoy RK: Tolerance to opioid analgesics: clinical aspects. *Cancer Surv* 1994;21:49-65.
113. Collin E, Poulain P, Gauvain-Piquard A, et al: Is disease progression the major factor in morphine 'tolerance' in cancer pain treatment? *Pain* 1993;55:319-326.
114. Paice JA: The phenomenon of analgesic tolerance in cancer pain management. *Oncol Nurs Forum* 1988;15:455-460.
115. Coyle N, Breitbart W, Weaver S, Portenoy R: Delirium as a contributing factor to "crescendo" pain: Three case reports. *J Pain Symptom Manage* 1994;9:44-47.
116. Foley KM: Clinical tolerance to opioids. In Basbaum AI, Besson JM (eds): *Towards a new pharmacotherapy of pain: report of the Dahlem Workshop*. New York, Wiley, 1991 pp 181-204.
117. Browne B, Linter S: Monoamine oxidase inhibitors and narcotic analgesics. A critical review of the implications for treatment. *Br J Psychiatry* 1987;151:210-212.
118. Fallon M, O'Neill B: ABC of palliative care. Constipation and diarrhoea. *BMJ* 1997; 315:1293-1296.
119. Sykes NP: An investigation of the ability of oral naloxone to correct opioid-related constipation in patients with advanced cancer. *Palliat Med* 1996;10:135-144.
120. Yuan CS, Foss JF, Osinski J, et al: The safety and efficacy of oral methylalntrexone in preventing morphine-induced delay in oral-cecal transit time. *Clin Pharmacol Ther* 1997;61:467-475.
121. Rogers M, Cerda JJ: The narcotic bowel syndrome. *J Clin Gastroenterol* 1989;11:132-135.
122. Campora E, Merlini L, Pace M, et al: The incidence of narcotic-induced emesis. *J Pain Symptom Manage* 1991;6:428-430.
123. Walsh TD: Prevention of opioid side effects. *J Pain Symptom Manage* 1990;5:362-367.
124. Lichter I: Nausea and vomiting in patients with cancer. *Hematol Oncol Clin North Am* 1996; 10:207-220.
125. Vainio A, Ollila J, Matikainen E, et al: Driving ability in cancer patients receiving long-term morphine analgesia. *Lancet* 1995;346:667-670.
126. Forrest WH, Jr., Brown BW, Jr., Brown CR, et al: Dextroamphetamine with morphine for the treatment of postoperative pain. *N Engl J Med* 1977;296:712-715.
127. Wilwerding MB, Loprinzi CL, Mailliard JA, et al: A randomized, crossover evaluation of methylphenidate in cancer patients receiving strong narcotics. *Support Care Cancer* 1995; 3:135-138.
128. Bruera E, Fainsinger R, MacEachern T, Hanson J: The use of methylphenidate in patients with incident cancer pain receiving regular opiates. A preliminary report. *Pain* 1992;50:75-77.
129. Breitbart W, Mermelstein H: Pemoline. An alternative psychostimulant for the management of depressive disorders in cancer patients. *Psychosomatics* 1992;33:352-356.
130. Bruera E, Miller L, McCallion J, et al: Cognitive failure in patients with terminal cancer: a prospective study. *J Pain Symptom Manage* 1992;7:192-195.
131. Pereira J, Hanson J, Bruera E: The frequency and clinical course of cognitive impairment in patients with terminal cancer. *Cancer* 1997;79: 835-842.
132. Wells CJ, Lipton S, Lahuerta J: Respiratory depression after percutaneous cervical anterolateral cordotomy in patients on slow-release oral morphine [letter]. *Lancet* 1984; 1:739.
133. Manfredi PL, Ribeiro S, Chandler SW, Payne R: Inappropriate use of naloxone in cancer patients with pain. *J Pain Symptom Manage* 1996;11:131-134.
134. Goldfrank L, Weisman RS, Errick JK, Lo MW: A dosing nomogram for continuous infusion intravenous naloxone. *Ann Emerg Med* 1986;15: 566-570.
135. Bradberry JC, Raebel MA: Continuous infusion of naloxone in the treatment of narcotic overdose. *Drug Intell Clin Pharm* 1981;15:945-950.
136. Schwartz JA, Koenigsberg MD: Naloxone-induced pulmonary edema. *Ann Emerg Med* 1987;16:1294-1296.
137. Goetting MG, Thirman MJ: Neurotoxicity of meperidine. *Ann Emerg Med* 1985;14:1007-1009.
138. Holdsworth MT, Adams VR, Chavez CM, et al: Continuous midazolam infusion for the management of morphine-induced myoclonus. *Ann Pharmacother* 1995; 29:25-29.
139. Mercadante S: Dantrolene treatment of opioid-induced myoclonus. *Anesth Analg* 1995; 81:1307-1308.
140. Bruera E, Miller MJ: Non-cardiogenic pulmonary edema after narcotic treatment for cancer pain. *Pain* 1989;39:297-300.
141. Zenz M, Donner B, Strumpf M: Withdrawal symptoms during therapy with transdermal fentanyl (fentanyl TTS)? *J Pain Symptom Manage* 1994; 9:54-55.
142. Porter J, Jick H: Addiction rare in patients treated with narcotics. *N Engl J Med* 1980;302:123.
143. Weissman DE, Haddox JD: Opioid pseudoaddiction—an iatrogenic syndrome. *Pain* 1989;36: 363-366.
144. Watanabe S, Bruera E: Corticosteroids as adjuvant analgesics. *J Pain Symptom Manage*

- 1994;9:442-445.
145. Yamada K, Ushio Y, Hayakawa T, et al: Effects of methylprednisolone on peritumoral brain edema. A quantitative autoradiographic study. *J Neurosurg* 1983;59:612-619.
146. Devor M, Govrin-Lippmann R, Raber P: Corticosteroids suppress ectopic neural discharge originating in experimental neuromas. *Pain* 1985;22:127-137.
147. Tannock I, Gospodarowicz M, Meakin W, et al: Treatment of metastatic prostatic cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response. *J Clin Oncol* 1989;7:590-597.
148. Hanks GW, Trueman T, Twycross RG: Corticosteroids in terminal cancer—A prospective analysis of current practice. *Postgrad Med J* 1983;59:702-706.
149. Bruera E, Roca E, Cedaro L, et al: Action of oral methylprednisolone in terminal cancer patients: A prospective randomized double-blind study. *Cancer Treat Rep* 1985;69:751-754.
150. Twycross RG, Guppy D: Prednisolone in terminal breast and bronchogenic cancer. *Practitioner* 1985;229:57-59.
151. Willox JC, Corr J, Shaw J, et al: Prednisolone as an appetite stimulant in patients with cancer. *Br Med J (Clin Res Ed)* 1984;288:27.
152. Sorensen S, Helweg-Larsen S, Mouridsen H, Hansen HH: Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: A randomised trial. *Eur J Cancer* 1994;30A:22-27.
153. Twycross R: The risks and benefits of corticosteroids in advanced cancer. *Drug Saf* 1994;11:163-178.
154. Ellershaw JE, Kelly MJ: Corticosteroids and peptic ulceration. *Palliat Med* 1994;8:313-319.
155. Sharma SK, Gajraj NM, Sidawi JE, Lowe K: EMLA cream effectively reduces the pain of spinal needle insertion. *Reg Anesth* 1996;21:561-564.
156. Holdsworth MT, Raisch DW, Winter SS, et al: Differences among raters evaluating the success of EMLA cream in alleviating procedure-related pain in children with cancer. *Pharmacotherapy* 1997;17:1017-1022.
157. Taddio A, Ohlsson A, Einarsen TR, et al: A systematic review of lidocaine-prilocaine cream (EMLA) in the treatment of acute pain in neonates. *Pediatrics* 1998;101:E1.
158. Robins G, Farr PM: Pain relief with Emla of ulcerating lesions in mycosis fungoides [letter]. *Br J Dermatol* 1997;136:287.
159. Stegman MB, Stoukides CA: Resolution of tumor pain with EMLA cream. *Pharmacotherapy* 1996;16:694-697.
160. Carnel SB, Blakeslee DB, Oswald SG, Barnes M: Treatment of radiation- and chemotherapy-induced stomatitis. *Otolaryngol Head Neck Surg* 1990;102:326-330.
161. Patt RB, Proper G, Reddy S: The neuroleptics as adjuvant analgesics. *J Pain Symptom Manage* 1994;9:446-453.
162. Oliver DJ: The use of methotrimeprazine in terminal care. *Br J Clin Pract* 1985;39:339-340.
163. Reddy S, Patt RB: The benzodiazepines as adjuvant analgesics. *J Pain Symptom Manage* 1994;9:510-514.
164. McQuay H, Carroll D, Jadad AR, et al: Anticonvulsant drugs for management of pain: A systematic review. *BMJ* 1995;311:1047-1052.
165. McQuay HJ, Tramer M, Nye BA, et al: A systematic review of antidepressants in neuropathic pain. *Pain* 1996;68:217-227.
166. Max MB, Kishore-Kumar R, Schafer SC, et al: Efficacy of desipramine in painful diabetic neuropathy: A placebo-controlled trial. *Pain* 1991;45:3-9; discussion 1-2.
167. Gomez-Perez FJ, Rull JA, Dies H, et al: Nortriptyline and fluphenazine in the symptomatic treatment of diabetic neuropathy. A double-blind cross-over study. *Pain* 1985;23:395-400.
168. Lindstrom P, Lindblom U: The analgesic effect of tocainide in trigeminal neuralgia. *Pain* 1987;28:45-50.
169. Galer BS, Harle J, Rowbotham MC: Response to intravenous lidocaine infusion predicts subsequent response to oral mexiletine: A prospective study. *J Pain Symptom Manage* 1996;12:161-167.
170. Chong SF, Bretscher ME, Mailliard JA, et al: Pilot study evaluating local anesthetics administered systemically for treatment of pain in patients with advanced cancer. *J Pain Symptom Manage* 1997;13:112-117.
171. Brose WG, Cousins MJ: Subcutaneous lidocaine for treatment of neuropathic cancer pain. *Pain* 1991;45:145-148.
172. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. *N Engl J Med* 1989; 321:406-412.
173. De Kock M, Wiederkehr P, Laghmiche A, Scholtes JL: Epidural clonidine used as the sole analgesic agent during and after abdominal surgery. A dose-response study. *Anesthesiology* 1997; 86:285-292.
174. Owen MD, Fibuch EE, McQuillan R, Millington WR: Postoperative analgesia using a low-dose, oral-transdermal clonidine combination: Lack of clinical efficacy. *J Clin Anesth* 1997;9:8-14.
175. Dubner R: Topical capsaicin therapy for neuropathic pain. *Pain* 1991;47:247-248.
176. Watson CP: Topical capsaicin as an adjuvant analgesic. *J Pain Symptom Manage* 1994;9:425-433.
177. Watson CP, Tyler KL, Bickers DR, et al: A randomized vehicle-controlled trial of topical capsaicin in the treatment of postherpetic neuralgia. *Clin Ther* 1993;15:510-526.
178. Ellison N, Loprinzi CL, Kugler J, et al: Phase III placebo-controlled trial of capsaicin cream in the management of surgical neuropathic pain in cancer patients. *J Clin Oncol* 1997;15:2974-2980.
179. Effect of treatment with capsaicin on daily activities of patients with painful diabetic neuropathy. Capsaicin Study Group. *Diabetes Care* 1992;15:159-165.

180. Swerdlow M. The use of anticonvulsants in the management of cancer pain. Erdmann W, Oyama T, Pernak MJ (eds): *The Pain Clinic I. Proceedings of the First International Symposium*. Utrecht, The Netherlands, VNU Science Press, 1985.
181. Merren MD: Gabapentin for treatment of pain and tremor: A large case series. *South Med J* 1998;91:739-744.
182. Fromm GH: Baclofen as an adjuvant analgesic. *J Pain Symptom Manage* 1994;9:500-509.
183. Mercadante S: Ketamine in cancer pain: an update. *Palliat Med* 1996;10:225-230.
184. Mercadante S, Lodi F, Sapio M, et al: Long-term ketamine subcutaneous continuous infusion in neuropathic cancer pain. *J Pain Symptom Manage* 1995;10:564-568.
185. Pud D, Eisenberg E, Spitzer A, et al: The NMDA receptor antagonist amantadine reduces surgical neuropathic pain in cancer patients: a double blind, randomized, placebo controlled trial. *Pain* 1998;75:349-354.
186. Nelson KA, Park KM, Robinovitz E, et al: High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. *Neurology* 1997;48:1212-1218.
187. Jaeger H, Maier C: Calcitonin in phantom limb pain: a double-blind study. *Pain* 1992;48:21-27.
188. Lechin F, van der Dijs B, Lechin ME, et al: Pimozide therapy for trigeminal neuralgia. *Arch Neurol* 1989;46:960-963.
189. Eisenberg E, Berkey CS, Carr DB, et al: Efficacy and safety of nonsteroidal antiinflammatory drugs for cancer pain: A meta-analysis. *J Clin Oncol* 1994;12:2756-2765.
190. Strang P: Analgesic effect of bisphosphonates on bone pain in breast cancer patients: A review article. *Acta Oncol* 1996;5:50-54.
191. Ernst DS, Brasher P, Hagen N, et al: A randomized, controlled trial of intravenous clodronate in patients with metastatic bone disease and pain. *J Pain Symptom Manage* 1997;13:319-326.
192. Robertson AG, Reed NS, Ralston SH: Effect of oral clodronate on metastatic bone pain: a double-blind, placebo-controlled study. *J Clin Oncol* 1995;13:2427-430.
193. Smith JA, Jr: Palliation of painful bone metastases from prostate cancer using sodium etidronate: Results of a randomized, prospective, double-blind, placebo-controlled study. *J Urol* 1989;141:85-87.
194. Silberstein EB, Elgazzar AH, Kapilivsky A: Phosphorus-32 radiopharmaceuticals for the treatment of painful osseous metastases. *Semin Nucl Med* 1992;22:17-27.
195. Burnet NG, Williams G, Howard N: Phosphorus-32 for intractable bony pain from carcinoma of the prostate. *Clin Oncol (R Coll Radiol)* 1990;2:220-223.
196. Robinson RG, Preston DF, Schiefelbein M, Baxter KG: Strontium 89 therapy for the palliation of pain due to osseous metastases. *JAMA* 1995;274:420-424.
197. Porter AT, McEwan AJ, Powe JE, et al: Results of a randomized phase-III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer. *Int J Radiat Oncol Biol Phys* 1993;25:805-813.
198. Powsner RA, Zietman AL, Foss FM: Bone marrow suppression after strontium-89 therapy and local radiation therapy in patients with diffuse marrow involvement. *Clin Nucl Med* 1997;22:147-150.
199. Schmeler K, Bastin K: Strontium-89 for symptomatic metastatic prostate cancer to bone: recommendations for hospice patients. *Hosp J* 1996;11:1-10.
200. Resche I, Chatal JF, Pecking A, et al: A dose-controlled study of ¹⁵³Sm-ethylenediaminetetramethylenephosphonate (EDTMP) in the treatment of patients with painful bone metastases. *Eur J Cancer* 1997;33:1583-1591.
201. Limouris GS, Shukla SK, Condi-Paphiti A, et al: Palliative therapy using rhenium-186-HEDP in painful breast osseous metastases. *Anticancer Res* 1997;17:1767-1772.
202. Blomqvist C, Elomaa I, Porkka L, et al: Evaluation of salmon calcitonin treatment in bone metastases from breast cancer—a controlled trial. *Bone* 1988;9:45-51.
203. Kadow C, Gingell JC: Salmon calcitonin for bone pain in patients with metastatic carcinoma of the prostate. A pilot study. *Br J Clin Pract* 1988;42:24-25.
204. Paulson DF: Oxybutynin chloride in control of post-trasarethral vesical pain and spasm. *Urology* 1978;11:237-238.
205. Baert L. Controlled double-blind trial of flavoxate in painful conditions of the lower urinary tract. *Curr Med Res Opin* 1974;2:631-635.
206. Abrams PH, Feneley RC: The action of prostaglandins on smooth muscle of the human urinary tract in vitro. *Br J Urol* 1975;47:909-915.
207. Lazeri M, Beneforti P, Benaim G, et al: Intravesical capsaicin for treatment of severe bladder pain: A randomized placebo controlled study. *J Urol* 1996;156:947-952.
208. Barbanti G, Maggi CA, Beneforti P, et al: Relief of pain following intravesical capsaicin in patients with hypersensitive disorders of the lower urinary tract. *Br J Urol* 1993;71:686-691.
209. Eckardt VF, Dodt O, Kanzler G, Bernhard G: Treatment of proctalgia fugax with salbutamol inhalation. *Am J Gastroenterol* 1996;91:686-689.
210. Boquet J, Moore N, Lhuintre JP, Boismare F: Diltiazem for proctalgia fugax [letter]. *Lancet* 1986;1:1493.
211. Swain R. Oral clonidine for proctalgia fugax. *Gut* 1987;28:1039-1040.
212. Hanks GW: Psychotropic drugs. *Postgrad Med J* 1984;60:881-885.
213. Ventafridda V, Ripamonti C, Caraceni A, et al: The management of inoperable gastrointestinal obstruction in terminal cancer patients. *Tumori* 1990;76:389-393.
214. De Conno F, Caraceni A, Zecca E, et al: Continuous subcutaneous infusion of hyoscine butylbromide reduces secretions in patients with gastrointestinal obstruction. *J Pain Symptom Manage* 1991;6:484-486.

215. Baines MJ: ABC of palliative care. Nausea, vomiting, and intestinal obstruction. *BMJ* 1997; 315:1148-1150.
216. Baines MJ: Management of intestinal obstruction in patients with advanced cancer. *Ann Acad Med Singapore* 1994;23:178-182.
217. Mercadante S: The role of octreotide in palliative care. *J Pain Symptom Manage* 1994;9:406-411.
218. Canobbio L, Boccardo F, Cannata D, et al: Treatment of advanced pancreatic carcinoma with the somatostatin analogue BIM 23014. Preliminary results of a pilot study. *Cancer* 1992;69:648-650.
219. Ihse I, Permerth J: Enzyme therapy and pancreatic pain. *Acta Chir Scand* 1990;156:281-283.
220. Spiegel D, Moore R: Imagery and hypnosis in the treatment of cancer patients. *Oncology (Huntingt)* 1997;11:1179-1189; discussion 1189-1195.
221. Arathuzik D: Effects of cognitive-behavioral strategies on pain in cancer patients. *Cancer Nurs* 1994;17:207-214.
222. Turk DC, Feldman CS: Noninvasive approaches to pain control in terminal illness: The contribution of psychological variables. *Hosp J* 1992;8:1-23.
223. Fishman B: The cognitive behavioral perspective on pain management in terminal illness. *Hosp J* 1992;8:73-88.
224. Marcks P: Lymphedema. Pathogenesis, prevention, and treatment. *Cancer Pract* 1997;5:32-38.
225. Brennan MJ, DePompolo RW, Garden FH: Focused review: postmastectomy lymphedema. *Arch Phys Med Rehabil* 1996;77:S74-S80.
226. Sykes J, Johnson R, Hanks GW: ABC of palliative care. Difficult pain problems. *BMJ* 1997;315:867-869.
227. Hogan Q, Haddox JD, Abram S, et al: Epidural opiates and local anesthetics for the management of cancer pain. *Pain* 1991;46:271-279.
228. Brose WG, Tanelian DL, Brodsky JB, et al: CSF and blood pharmacokinetics of hydromorphone and morphine following lumbar epidural administration. *Pain* 1991; 45:11-15.
229. Du Pen SL, Williams AR: Management of patients receiving combined epidural morphine and bupivacaine for the treatment of cancer pain. *J Pain Symptom Manage* 1992;7:125-127.
230. Nitescu P, Sjoberg M, Appelgren L, Curelaru I: Complications of intrathecal opioids and bupivacaine in the treatment of "refractory" cancer pain. *Clin J Pain* 1995;11:45-62.
231. Sjoberg M, Nitescu P, Appelgren L, Curelaru I: Long-term intrathecal morphine and bupivacaine in patients with refractory cancer pain. Results from a morphine:Bupivacaine dose regimen of 0.5:4.75 mg/ml. *Anesthesiology* 1994;80:284-297.
232. Mercadante S: Intrathecal morphine and bupivacaine in advanced cancer pain patients implanted at home. *J Pain Symptom Manage* 1994;9:201-207.
233. Eisenach JC, DuPen S, Dubois M, et al: Epidural clonidine analgesia for intractable cancer pain. The Epidural Clonidine Study Group. *Pain* 1995;61:391-399.
234. Penn RD, Paice JA, Kroin JS: Octreotide: a potent new non-opiate analgesic for intrathecal infusion. *Pain* 1992;49:13-19.
235. Yang CY, Wong CS, Chang JY, Ho ST: Intrathecal ketamine reduces morphine requirements in patients with terminal cancer pain. *Can J Anaesth* 1996;43:379-383.
236. Yaksh TL: Epidural ketamine: a useful, mechanistically novel adjuvant for epidural morphine? *Reg Anesth* 1996;21:508-513.
237. Blanchard J, Menk E, Ramamurthy S, Hoffman J: Subarachnoid and epidural calcitonin in patients with pain due to metastatic cancer. *J Pain Symptom Manage* 1990;5:42-45.
238. Hassenbusch SJ, Stanton-Hicks M, Covington EC, et al: Long-term intraspinal infusions of opioids in the treatment of neuropathic pain. *J Pain Symptom Manage* 1995;10:527-543.
239. Nitescu P, Appelgren L, Linder LE, et al: Epidural versus intrathecal morphine-bupivacaine: assessment of consecutive treatments in advanced cancer pain. *J Pain Symptom Manage* 1990;5:18-26.
240. Karavelis A, Foroglou G, Selviaridis P, Fountzilias G: Intraventricular administration of morphine for control of intractable cancer pain in 90 patients. *Neurosurgery* 1996;39:57-61.
241. Cramond T, Stuart G: Intraventricular morphine for intractable pain of advanced cancer. *J Pain Symptom Manage* 1993;8:465-473.
242. Dennis GC, DeWitty RL: Long-term intraventricular infusion of morphine for intractable pain in cancer of the head and neck. *Neurosurgery* 1990;26:404-407; discussion 407-408.
243. Symreng T, Gomez MN, Rossi N: Intrapleural bupivacaine v saline after thoracotomy—effects on pain and lung function—a double-blind study. *J Cardiothorac Anesth* 1989;3:144-149.
244. Dionne C: Tumour invasion of the brachial plexus: management of pain with intrapleural analgesia [letter]. *Can J Anaesth* 1992;39:520-521.
245. Lema MJ, Myers DP, De Leon-Casasola O, Penetrante R: Pleural phenol therapy for the treatment of chronic esophageal cancer pain. *Reg Anesth* 1992;17:166-170.
246. Myers DP, Lema MJ, de Leon-Casasola OA, Bacon DR: Interpleural analgesia for the treatment of severe cancer pain in terminally ill patients. *J Pain Symptom Manage* 1993;8:505-510.
247. Cooper MG, Keneally JP, Kinchington D: Continuous brachial plexus neural blockade in a child with intractable cancer pain. *J Pain Symptom Manage* 1994;9:277-281.
248. Caraceni A, Portenoy RK: Pain management in patients with pancreatic carcinoma. *Cancer* 1996;78:639-653.
249. Eisenberg E, Carr DB, Chalmers TC: Neurolytic celiac plexus block for treatment of cancer pain: a meta-analysis [published erratum appears in *Anesth Analg* 1995 Jul; (81):1:213]. *Anesth Analg* 1995;80:290-295.
250. Kawamata M, Ishitani K, Ishikawa K, et al: Comparison between celiac plexus block and morphine treatment on quality of life in patients with pancreatic cancer pain. *Pain* 1996; 64:597-602.
251. Mercadante S: Celiac plexus block versus analgesics in pancreatic cancer pain. *Pain* 1993;52:

- 187-192.
252. Lillemoe KD, Cameron JL, Kaufman HS, et al: Chemical splanchnicectomy in patients with unresectable pancreatic cancer. A prospective randomized trial. *Ann Surg* 1993;217:447-55; discussion 56-57.
253. Hayakawa J, Kobayashi O, Murayama H: Paraplegia after intraoperative celiac plexus block. *Anesth Analg* 1997;84:447-448.
254. Wong GY, Brown DL: Transient paraplegia following alcohol celiac plexus block. *Reg Anesth* 1995;20:352-355.
255. Plancarte R, de Leon-Casasola OA, El-Helaly M, et al: Neurolytic superior hypogastric plexus block for chronic pelvic pain associated with cancer. *Reg Anesth* 1997;22:562-568.
256. Plancarte R, Amescua C, Patt RB, Aldrete JA: Superior hypogastric plexus block for pelvic cancer pain. *Anesthesiology* 1990;73:236-239.
257. Plancarte R, Velazquez R, Patt RB: Neurolytic block of the sympathetic axis. In: Patt RB (ed): *Cancer Pain*. Philadelphia: Lippincott, 1993, pp 377-425.
258. Wemm K, Jr., Saberski L: Modified approach to block the ganglion impar (ganglion of Walther) [letter]. *Reg Anesth* 1995;20:544-545.
259. Nebab EG, Florence IM: An alternative needle geometry for interruption of the ganglion impar [letter]. *Anesthesiology* 1997;86:1213-1214.
260. Lamcraft G, Cousins MJ: Neural blockade in chronic and cancer pain. *Int Anesthesiol Clin* 1997;35:131-153.
261. Patt RB, Reddy S: Spinal neurolysis for cancer pain: Indications and recent results. *Ann Acad Med Singapore* 1994;23:216-220.
262. Saris SC, Silver JM, Vieira JF, Nashold BS, Jr: Sacrococcygeal rhizotomy for perineal pain. *Neurosurgery* 1986;19:789-793.
263. Salmon JB, Finch PM, Lovegrove FT, Warwick A: Mapping the spread of epidural phenol in cancer pain patients by radionuclide admixture and epidural scintigraphy. *Clin J Pain* 1992;8:18-22.
264. Ischia S, Luzzani A, Polati E: Retrogasserian glycerol injection: A retrospective study of 112 patients. *Clin J Pain* 1990;6:291-296.
265. Rizzi R, Terrevoli A, Visentin M: Long-term results of alcoholization and thermocoagulation of trigeminal nerve for cancer pain. Erdmann W, Oyama T, Pernak MJ (eds): *The Pain Clinic I*. Proceedings of the First International Symposium. Utrecht, The Netherlands, VNU Science Press, 1985.
266. Prasanna A, Murthy PS: Sphenopalatine ganglion block and pain of cancer [letter]. *J Pain Symptom Manage* 1993;8:125.
267. Meyer-Witting M, Foster JM: Suprascapular nerve block in the management of cancer pain. *Anaesthesia* 1992;47:626.
268. Neill RS: Ablation of the brachial plexus. Control of intractable pain, due to a pathological fracture of the humerus. *Anaesthesia* 1979;34:1024-1027.
269. Calava JM, Patt RB, Reddy S, et al: Psoas sheath chemical neurolysis for management of intractable leg pain from metastatic liposarcoma. *Clin J Pain* 1996;12:69-75.
270. Robertson DH: Transsacral neurolytic nerve block. An alternative approach to intractable perineal pain. *Br J Anaesth* 1983;55:873-875.
271. Stuart G, Cramond T: Role of percutaneous cervical cordotomy for pain of malignant origin. *Med J Aust* 1993;158:667-670.
272. Sanders M, Zuurmond W: Safety of unilateral and bilateral percutaneous cervical cordotomy in 80 terminally ill cancer patients. *J Clin Oncol* 1995;13:1509-1512.
273. Cowie RA, Hitchcock ER: The late results of antero-lateral cordotomy for pain relief. *Acta Neurochir (Wien)* 1982;64:39-50.
274. Chevrolet JC, Reverdin A, Suter PM, et al: Ventilatory dysfunction resulting from bilateral anterolateral high cervical cordotomy. Dual beneficial effect of aminophylline. *Chest* 1983;84:112-115.
275. Polatty RC, Cooper KR: Respiratory failure after percutaneous cordotomy. *South Med J* 1986;79:897-899.
276. Gonski A, Sackelariou R: Cryohypophysectomy for the relief of pain in malignant disease. *Med J Aust* 1984;140:140-142.
277. Levin AB, Ramirez LL: Treatment of cancer pain with hypophysectomy: Surgical and chemical. *Adv Pain Res Ther* 1984;7:631-645.
278. Wong ET, Gunes S, Gaughan E, et al: Palliation of intractable cancer pain by MRI-guided cingulotomy. *Clin J Pain* 1997;13:260-263.
279. Hassenbusch SJ, Pillay PK, Barnett GH: Radiofrequency cingulotomy for intractable cancer pain using stereotaxic guided by magnetic resonance imaging. *Neurosurgery* 1990;27:220-223.
280. Cherny NI, Portenoy RK: Sedation in the management of refractory symptoms: Guidelines for evaluation and treatment. *J Palliat Care* 1994;10:31-38.
281. Latimer EJ: Ethical decision-making in the care of the dying and its applications to clinical practice. *J Pain Symptom Manage* 1991; 6:329-336.
282. Quill TE, Dresser R, Brock DW: The rule of double effect—a critique of its role in end-of-life decision making. *N Engl J Med* 1997;337:1768-1771.
283. Orentlicher D: The Supreme Court and physician-assisted suicide—rejecting assisted suicide but embracing euthanasia. *N Engl J Med* 1997;337:1236-1239.
284. Burt RA: The Supreme Court speaks—not assisted suicide but a constitutional right to palliative care. *N Engl J Med* 1997;337:1234-1236.
285. Ventafridda V, Ripamonti C, De Conno F, et al: Symptom prevalence and control during cancer patients' last days of life. *J Palliat Care* 1990;6:7-11.
286. Fainsinger R, Miller MJ, Bruera E, et al: Symptom control during the last week of life on a palliative care unit. *J Palliat Care* 1991;7:5-11.
287. Portenoy RK, Moulin DE, Rogers AG, et al: Intravenous infusion of opioids in cancer-related pain: review of cases and guidelines for use. *Adv Pain Res Ther* 1986;8:413-424.