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Assessment and Management of Cancer Pain

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PREVALENCE OF CANCER PAIN

It is estimated that from 30% to 50% of patients actively undergoing cancer therapy and from 60% to 90% of patients with advanced cancer have pain (Foley, 1979; Bonica, 1990; Twycross and Fairfield, 1982; World Health Organization, 1986; Levin et al., 1985). Approximately 50% of children in an inpatient pediatric cancer center and about 25% of outpatients experience pain (Miser et al., 1987). The World Health Organization Cancer Pain Relief Program indicates that approximately 5 million people worldwide suffer from cancer-related pain on a daily basis, and fully 25% of them die at home or in a hospital without relief (World Health Organization, 1990).

It is important to assess the effects of pain on the quality of life in multidimensional terms, and the development of valid and reliable measurement instruments for this purpose is currently an area of intense research (Aaronson, 1988). A number of validated tools have been used to track pain and other symptom intensity, such as the Edmonton Symptom Assessment System (ESAS) and The University of Texas M. D. Anderson Cancer Center Symptom Inventory (MDASI). It is useful to assess pain in conjunction with other symptoms so that appropriate treatment can be planned.

The loss of function, fear of death, and a multitude of other psychosocial ramifications of cancer and pain are intertwined. The term *suffering* has been used in this context to describe the overall negative impact of cancer on the life of the individual (Portenoy, 1990), and, while it must be recognized that pain is only one aspect of suffering, it is often a major one. Comprehensive management of the cancer patient with pain requires that all of the factors associated with the quality of life of the person as a whole be considered.

UNDERTREATMENT OF CANCER PAIN

It is a sad fact that pain is not satisfactorily managed for many cancer patients. For example, in one published study, 1308 patients were surveyed at 54 treatment sites participating in the Eastern Cooperative Oncology Group to evaluate the prevalence of pain and the adequacy of its treatment (Cleeland et al., 1994). In this study, 67% of patients reported daily pain and took analgesics daily. However, 42% of these patients had negative pain index scores, which are measures of the adequacy of analgesic therapy for pain. These scores match the severity of the patient's reported pain with the potency of the analgesic(s) prescribed. Not surprisingly, the patients who reported the most pain also reported the poorest function. At particular risk for undertreatment were patients of African-American, Hispanic American, and other minority ethnic groups, females, patients over the age of 70 years, and those who reported pain but had "good" performance status scores.

Results such as these and the significant variability in treatment outcomes for cancer pain management documented from a variety of sources led to the development of federal guidelines relating to the management of cancer pain published in the mid-1990s

(Jacox et al., 1994). The guidelines emphasize the need to adequately assess the causes of pain and to treat pain aggressively in an approach that individualizes therapy for each patient.

Barriers to Optimal Cancer Pain Management

Despite the increased knowledge of pain mechanisms, improved methods for treating generalized and specific pain syndromes, and an increased number of professional and government organizations dedicated to disseminating this information, an inordinate number of patients with pain experience inadequate relief. Reasons that account for this are *(1)* cultural and societal barriers to the adequate and appropriate use of opioids, *(2)* a general lack of awareness among healthcare providers of advances in opioid pharmacology culled from long-term studies in cancer patients experiencing chronic pain, and *(3)* the negative influence of state healthcare disciplinary boards and state and federal drug enforcement agencies on drug prescribing and dispensing practices (Hill, 1990). These situations alternately interdigitate to effect undertreatment of pain during the course of an individual's treatment. Each discrete reason, or a combination thereof, may exert a dominant influence at any given time during the course of a patient's pain treatment. For example, pain relief may initially be inadequate because of the physician's knowledge deficit about the pharmacology of opioids, but later in the course of treatment may be inadequate because of fear of regulatory sanctions.

All these difficulties specifically relate to the use of opioids. Yet, difficulty in achieving adequate pain control occurs most frequently with pain that is diffuse and of such intensity that it can be relieved only with these drugs. No similar limitations or restrictions are placed on other treatment modalities, nor are they associated with the same emotional milieu as found when opioids are a part of the treatment picture. Therefore, nonopioid treatment modalities are used with impunity to achieve the optimum benefit that can be attained with them.

Two of the above factors, cultural and societal barriers and government regulatory barriers, demonstrate how extramedical influences, by contributing to pain undertreatment, can be detrimental to providing quality medical care. The third reason, knowledge deficits about medical advances, demonstrates how difficult it is to replace information that has been ingrained into the accepted body of medical knowledge. This knowledge is, however, based on limited clinical studies and a restricted pain model, whereas the new information is based on more appropriate clinical studies carried out in an appropriate pain model—the cancer patient in pain.

This section explicates how the various interdictions to efficacious pain therapy interfere with adequate pain treatment and offers recommendations for overcoming this interference.

Cultural and Societal Barriers

The use of opioids by patients who take them for legitimate medical use is confused with the illegal abuse of them by individuals who take them for recreational nonmedical purposes. The dominance of the illegitimate image of these drugs in the minds of both healthcare professionals and the public is so pervasive that their effective use as drugs with a legitimate medical purpose is overshadowed. Patients have often been made to feel like criminals or morally inferior beings for taking these drugs. This general confusion frequently leads to physicians prescribing inappropriately low doses at intervals that exceed the effectiveness of the drugs. Patients who are undertreated in this manner become desperate for relief and often resort to behavior that mimics the drug seeker, prompting healthcare providers to label them as "addicts." Weissman and Haddox (1989) have coined the term "pseudoaddiction" for this iatrogenically created behavior.

Physicians' prescribing practices are strongly influenced by peer pressure. Despite an adequate knowledge of the pharmacokinetics and pharmacodynamics of opioid drugs, physicians often prescribe in the same manner as their peers even though this entails prescribing the wrong dose of the drug and for an interval that is inappropriately long, particularly for cancer patients. This widespread practice sets the standard for prescribing opioids in a given community, a practice that results in undertreatment and inadequately relieved pain. Drug regulatory agencies use a community standard to judge an individual physician's prescribing practices. Therefore, a physician who prescribes a proper dose of an opioid may be judged to be outside the normal standard of practice and subject to sanctions, including the loss of his or her license to practice medicine. Unfortu-

nately, community standards often perpetuate undertreatment of pain.

Healthcare professionals have an irrational fear of causing psychological dependency (addiction) to drugs. Chronic use of opioids per se is, however, not synonymous with addiction. While patients who require chronic opioids for pain relief can become physiologically dependent on the opioid and experience an abstinence or withdrawal reaction if the drug is abruptly discontinued (reflecting the normal pharmacologic action of all opioids), addiction only results when a person becomes psychologically dependent on an opioid. Addiction is also a social condition, associated with a destructive life-style. The psychologically dependent individual has a compulsion to procure and take an opioid for mind-altering purposes for recreational, nonmedical reasons. The cancer patient in pain takes opioids for pain relief to restore a reasonably normal, functional life-style for the period of life remaining. Studies have shown that the number of individuals who become addicted to drugs by an introduction to them through medical use is extremely small (Portenoy and Payne, 1992).

It is unfortunate but common that physicians' unfamiliarity and discomfort with prescribing "strong" opioids chronically results in postponing their use far beyond the time indicated for good medical pain control practices. The global prejudice that opioid use is bad, no matter what the reason, inspires physicians when chronic use is contemplated or required to postpone treatment until a patient's survival is measured in only weeks or months. As a result, cancer patients often do not get adequate pain treatment until their agonal days because of this practice, although cancer pain may be severe for as long as years before death.

Knowledge Deficits

Information in modern pharmacology textbooks about the dosing of opioids is based on single-dose studies using a postoperative pain model (Twycross, 1988), and the pharmacodynamic action was studied in subjects who were not in pain. Dosing studies were also done in the only human pain model available at the time, which excluded cancer patients whose survival time was short and who had persistent complications that augmented their disease. Currently, cancer patients provide a new model for analgesic study, largely because their survival times have improved. Furthermore, cancer patients are suitable for meaningful pharmacodynamic studies because they represent a human model experiencing pain, in contrast to the earlier studies composed of a study population of volunteers who were former drug addicts and not experiencing pain.

Study results have demonstrated that pain itself alters the pharmacologic response to opiates by antagonizing the analgesic and respiratory depressant effects of the drugs (Hanks et al., 1981). Dose recommendations based on postoperative pain studies apply only to patients with this type of pain. Extrapolating these doses to patients with other types of pain, especially chronic cancer pain, is misleading. Postoperative pain rarely achieves the intensity of persistent, unrelieved cancer pain. Because of the antagonistic effects of pain on analgesia, doses of opioids must be tailored to whatever level is necessary to relieve the patient's pain. These doses almost always exceed recommended doses for postoperative pain in pharmacology textbooks. However, efficacious doses should not be viewed as "high," "large," or "excessive"; they are simply adequate to meet the patient's pain relief requirements.

ASSESSMENT OF PAIN IN THE CANCER PATIENT

Cancer patients with pain require a careful assessment to determine the nature of their pain and to design appropriate treatment. Painful manifestations of systemic cancer are often caused by damage to neurologic structures. The identification of neurologic dysfunction often helps to direct appropriate therapy. Gonzales et al. (1991), for example, after reviewing a large series of patients in a cancer referral center, found that neurologic consultation identified a previously undiagnosed etiology for pain in 64% of patients and resulted in adding antitumor therapies (radiotherapy, surgery, or chemotherapy) for 18% of patients evaluated. The importance of neurologic evaluation is underscored by the fact that pain is frequently the only manifestation of tumor involving critical neural structures. A complaint of back pain in a cancer patient, for example, may be the only apparent manifestation of epidural spinal cord compression and is, in fact, the only consistent sign or symptom (Byrne and Waxman, 1990). Similarly, pain was the only symptom of lumbosacral plexopathy in 24%

of patients in one series, and in 15% of these patients diagnosis resulted in the discovery of a primary pelvic tumor (Jaeckle et al., 1985).

In addition to the obvious difficulties of experiencing persistent pain, secondary consequences of unrelieved pain in the cancer patient include decreased functional activity and depressed appetite, which may negatively impact the course of the disease itself (Cleeland, 1984). Patients or families may also refuse palliative or potentially curative cancer treatment because of a perceived need to "end the suffering" of the patient (Foley, 1991). Despite our current level of sophistication in treating cancer pain, it is estimated that 29% of patients with cancer suffer from moderate to severe pain despite analgesic therapy (Ventafridda et al., 1987). This fact largely reflects errors in cancer pain treatment, such as inadequate dosing of analgesics in an attempt to avoid producing addiction (Hill and Fields, 1989; Foley, 1989).

The goal of the oncologist or any physician in evaluating and treating the painful manifestations of cancer is dual. The first and often understated task is diagnostic—to appropriately identify the source of pain. To accomplish this, knowledge of the natural history of specific cancer types as well as an appreciation of common pain syndromes occurring in the cancer patient are essential. The second task is therapeutic—to relieve or minimize pain using appropriate management techniques, thereby allowing the patient to be as active and pain-free as possible.

Mechanisms of Cancer Pain: Implications for Treatment

The majority of the pain in cancer is caused by direct tumor involvement of organic structures, notably neural structures. Pain associated with direct tumor involvement occurs in 65% to 85% of patients with advanced cancer (Foley, 1979). Cancer therapy accounts for pain in approximately 15% to 25% of patients receiving chemotherapy, surgery, or radiation therapy (Higginson, 1997). Between 3% and 10% of cancer patients have pain syndromes, which are most commonly observed in the general noncancer population (e.g., low back pain secondary to degenerative disc disease or diabetic neuropathy). Common clinical pain syndromes are listed in Table 23–1.

Cancer pain can occur after activation of peripheral nociceptors (somatic and visceral "nociceptive" pain) or as a result of direct injury to peripheral or central nervous structures (neuropathic or "deafferentation" pain). In addition, both nociceptive and neuropathic pain may be modified by involvement of

Table 23–1. Common Clinical Pain Syndromes and Their Causes

Pain due to tumor
Bone pain due to metastasis (somatic pain) from breast, prostate, and other cancers
Plexopathy pain (neuropathic pain) due to Pancoast's tumor/pelvic tumor
Abdominal pain (visceral pain) due to pancreatic cancer and liver metastasis
Chest wall pain due to mesothelioma (somatic and neuropathic pain)
Pain due to cancer treatment
Postchemotherapy pain syndromes
Peripheral neuropathy due to cisplatin and paclitaxol
Post-irradiation pain syndromes
Chronic throat pain due to radiation-induced mucositis
Chronic abdominal pain due to radiation-induced enteritis in fistulae
Radiation-induced plexopathy pain
Post-surgical pain syndromes
Post-mastectomy pain syndrome
Post-radical neck dissection pain syndrome
Phantom limb pain syndrome
Pain syndrome unrelated to cancer
Chronic low back pain due to degenerative process in the spine
Pain secondary to osteoarthritis and rheumatoid arthritis
Migraine headaches

the sympathetic nervous system (so-called reflex sympathetic dystrophy [RSD], currently called sympathetically maintained pain [SMP]. Each of these painful states has unique clinical characteristics, which may aid in identification and direct analgesic or antitumor therapies. A key step, therefore, in the evaluation of a cancer patient with pain is to elicit a careful history of the quality, nature, and location of perceived pain, which may provide valuable clues regarding the etiology of the complaint and may help direct investigative studies.

Somatic pain results from involvement of bone and muscle structures. Metastatic bone disease is the most common pain syndrome in patients with cancer. Myelinated and unmyelinated afferent fibers are present in bone, and their density is greatest in the periosteum. Prostaglandins (PGs) play a multifactorial role in the etiology of bone pain. Prostaglandin concentrations are increased at sites of bone metastasis (Galasko, 1976). In addition, PGs mediate osteolytic and osteoclastic metastatic bone changes. Prostaglandin E_2 sensitizes nociceptors and produces hyperalgesia. These observations have resulted in considerable interest in the use of steroidal and nonsteroidal anti-inflammatory medications as important therapies for metastatic bone pain (Stambaugh and Drew, 1988), although some have questioned their value in the treatment of bone pain (Mercadante, 1997).

Visceral pain is also common in the cancer patient and results from stretching or distending viscera or from the production of an inflammatory response and the release of analgesic substances in the vicinity of nociceptors. Visceral pain is commonly referred to cutaneous sites, which can mislead the examiner, particularly because those cutaneous sites may be tender to palpation. This phenomenon likely results from the convergence of visceral and somatic afferent information onto common neuronal pools in the dorsal horn of the spinal cord (Milne et al., 1981).

Neuropathic pain from neural injury, such as brachial plexus or lumbosacral plexus infiltration by tumor, is often severe. The hallmark of neuropathic pain is paroxysms of burning or electric shock sensations, which may result, at least in part, from spontaneous discharges in the peripheral and central nervous systems. By definition, the nervous system is not behaving normally in these painful states, and conventional analgesic therapies may not be efficacious. For example, Arner and Meyerson (1988) argued that opioids are ineffective for treating neuropathic pain. Although this view has been challenged (Portenoy et al., 1990), it was observed that larger doses of opioids were required to manage deafferentation pain compared with nociceptive pain. These clinical observations are consistent with recent experimental observations that report a fourfold decrease in the potency of morphine when primary afferent fibers are severed. However, recent studies support the use of opioids for severe neuropathic pain (Dellemijn, 1997; Cherny et al., 1994).

Somatic, visceral, and deafferentation pain may be modified by the sympathetic nervous system, as evidenced by the positive response of some patients to anesthetic and pharmacologic sympathetic blockade. Sympathetically maintained pain is often suspected when pain is severe in intensity (even after relatively trivial tissue insults) and is described as burning in quality, with associated features of allodynia, hyperpathia, brawny edema, and osteoporosis. Several mechanisms involving both the peripheral and central nervous systems have been postulated to explain SMP. One peripheral mechanism may be the development of ephaptic connections at sites of tissue injury whereby efferent sympathetic impulses produce activation of afferent nociceptive pathways. Other investigators have postulated that traumatic injury to peripheral tissues may produce sensitization of spinal cord nociceptive neurons, which may then be secondarily activated by efferent sympathetic activity. Despite debate concerning its physiological mechanisms, the clinical recognition of SMP is critical, as prompt sympathetic blockade and aggressive physical therapy and mobilization of the affected part(s) are vital for achieving a good clinical outcome.

It is common (indeed usual) for cancer patients to present with mixtures of the pain types, mandating initiation of multiple therapeutic approaches ("balanced analgesia") (Payne and Foley, 1984). Furthermore, the pattern of pain intensity is often not constant, but rather includes episodes of pain exacerbations, called *breakthrough pain,* which is defined as a "transitory exacerbation of pain that occurs on a background of otherwise stable persistent pain" (Reddy and Nguyen, 2000). Breakthrough pain is well recognized as the most intractable pain to manage and in some studies has been the reliable predictor of poor response to treatment with routine pharmacotherapy (Bruera et al., 1989c, 1995). This typical pattern suggests that continuous, or around-

the-clock analgesic therapies are appropriate for the vast majority of cancer patients and that strategies for treating incident and breakthrough pain (Portenoy and Hagen, 1990) should be implemented to ensure adequate pain relief during periods of exacerbation.

As has been emphasized, the clinical assessment of pain may be critical in defining its etiology, and several principles have been delineated that are essential to this assessment. Table 23–2 lists the parameters involved in the assessment of cancer pain.

SPECIFIC PAIN SYNDROMES IN PATIENTS WITH CANCER

Neurologists and oncologists when evaluating the cancer patient with pain encounter several specific pain syndromes that present difficult diagnostic and therapeutic problems (Kelly and Payne, 1991). Clinical data comprising these syndromes are summarized below and listed in Table 23–3.

Invasion of bone by either primary or metastatic tumor causes pain in most patients with cancer. Important pain syndromes are often misdiagnosed because physicians are unfamiliar with their characteristic signs and symptoms, and plain X-rays of the involved areas may be (falsely) negative. Some of these syndromes are considered below.

Tumor Infiltration of Bone

The pathophysiology of metastatic bone pain is poorly understood. Although most patients with bone metastasis report pain, some patients with well-established lesions do not. Occasional patients report bone pain when radiographic lesions are not evident. This phenomenon has been best studied in breast cancer (Front et al., 1979), but also occurs in patients with prostate cancer. Tumor growth in bone may produce pain through several mechanisms: *(1)* Relatively rapid growth causes expansion of the marrow space and increases interosseal pressure (beyond 50 mm Hg). In theory, this may activate mechanoreceptive nociceptors in bone. Elevation or invasion of the periosteum may also activate nociceptors, which innervate this structure. *(2)* Weakening of the bone causes fractures. *(3)* Edema and inflammation associated with tumor growth in bone may liberate chemical mediators that activate nociceptors. *(4)* Finally, data regarding mechanisms of bone destruction postulate that osteoclasts may be stimulated by humoral factors associated with tumors. For example, carcinomas

Table 23–2. Assessment of Cancer Pain

History

1. Ask patient about pain and use a self-report form
   a. Use simple scales (e.g., 0–10 numerical scale or visual analog scale)
   b. Pain when patient is at rest and when moving
   c. Pattern of pain (i.e., the presence of continuous and/or breakthrough pain)
2. Evaluate psychosocial dimensions of pain and cancer experience
   a. Coexisting depression, anxiety, and psychological distress
   b. Meaning of pain to patient and family
   c. Attitudes about pain and drug use (especially opioid use) with patient and family

Physical and neurologic examinations

1. Evaluate site of pain and examine possible sites of referral
2. Evaluate presence of secondary myofascial pains, trigger points, or muscle spasms
3. Evaluate motor, sensory, and autonomic findings (especially for neuropathic pain syndromes)

Neuroimaging studies

1. Review radiographic studies to ensure that appropriate body parts were imaged
2. Be aware of false-negative bone scans in areas of prior irradiation
3. Know the limitations of plain radiographs in C7–T1 and base of skull areas
4. Pain may precede "objective" radiographic evidence of tumor recurrence

Reassess pain

1. Evaluate at frequent intervals
2. Evaluate at transition points in patient's care

Table 23–3 Intractable Pain Syndromes*

Pain Syndromes	*Clinical Characteristics*
Tumor-related infiltration of bone	Acute and chronic nociceptive pain
Skull-base metastasis	Severe head pain (usually referred to vertex or occiput) with associated cranial nerve deficits
	Bone scan and plain films of the skull may be negative
Vertebral metastasis	Significant risk of associated spinal cord compression†
Pelvis and long bone	Risk of pathologic fracture with weight-bearing activities; orthopedic consultation helpful
Tumor-related infiltration of nerve	Acute and chronic neuropathic pain
Brachial/lumbosacral plexopathy	May occur by contiguous spread of tumor or by hematogenous dissemination; radiographic studies helpful to distinguish from radiation-induced plexopathy
Spinal cord compression	Neurologic emergency requiring prompt treatment with corticosteroids, radiation therapy, and/or surgery
Meningeal carcinomatosis	Headache and meningeal signs cause significant pain in about 15% of patients
Visceral tumor infiltration‡	Acute and chronic visceral pain that is poorly localized and widely referred
Therapy related; post-surgical pain	Chronic pain that persists well beyond healing of the incision and may or may not be associated with recurrent disease
After thoracotomy	May be associated with recurrent tumor or may occur as a chronic intercostal neuralgia
After mastectomy	Occurs in 5% of women; more common in women undergoing modified radical procedure with axillary dissection; intercostal-brachioradial neuralgia is one etiology
After radical neck surgery	Mechanisms unclear; chronic infection may play a role
After amputation	Stump pain and phantom phenomena are common; role of preventive analgesic and anesthetic therapies under investigation

*List excludes significant but short-lived pain syndromes such as mucositis that complicate chemotherapy and radiation therapy and the acute pain associated with diagnostic and therapeutic procedures such as bone marrow aspiration.

†30% of patients with back pain and vertebral body metastases will eventually develop epidural spinal cord compression, and pain alone may precede root or spinal cord signs by many months.

‡Common examples include pancreatic carcinoma, liver metastasis, and pleural effusion.

may secrete PG (Galasko, 1982), which would have the dual role of activating osteoclasts and sensitizing nociceptors. These observations have provided a rationale for the use of corticosteroids and nonsteroidal anti-inflammatory analgesics such as naprosyn for the management of metastatic bone pain (Levick et al., 1988). Lymphomas and myelomas may secrete another chemical, osteoclast-activating factor. However, the effects of osteoclast-activating factor on bone nociceptors are not yet known.

Metastatic bone pain is often associated with neurologic dysfunction because of the close anatomic relationships between the brain and cranial nerves with the skull vault and spinal cord with the vertebral column. Therefore, characteristic clinical syndromes may be identified by the site of bony involvement, the co-existence of mechanical instability secondary to fractures, and neurologic dysfunction caused by tumor infiltration of contiguous neurologic structures. Bone metastases to the hip and pelvis often produce local pain, which is exacerbated by movement, especially during weight bearing. In addition to palliative radiotherapy, this type of "incident pain" may require specific orthopedic interventions for satisfactory control of pain, such as pinning and other mechanisms of mechanical stabilization. In fact, true incident pain is notoriously difficult to manage with conventional analgesic therapy alone. Unilateral incident pain at or below the waist, which has failed management with hormonal and radiation therapy in addition to analgesics, may require cordotomy as the ultimate means of treatment (Foley, 1993).

Spread of cancer to the vertebral bodies and calvarium, especially the skull base, often produces dis-

tinctive neurologic syndromes. It is important to recognize these early because prompt initiation of antitumor treatments (especially radiation) may prevent neurologic impairment. For example, local and radicular back or neck pain is the predominant symptom in epidural spinal cord compression, complicating vertebral body metastasis in these locations. Pain may be the only symptom of impending spinal cord compression and often precedes motor weakness and bowel or bladder incontinence by days or weeks. The spinal cord is compromised by growth of tumor in an anterior direction from the vertebral body. Irreversible spinal cord injury may occur when the vascular supply is compromised as a result of severe compression. Thoracic spine vertebral body metastases often produce bilateral radicular pain and sensory symptoms (a "band-like" squeezing sensation across the upper abdomen or chest) because of the close proximity of the thoracic nerve roots to the vertebral body. On the other hand, metastasis to the cervical or lumbar spine may produce unilateral pain and sensory loss as the vertebral bodies are wider in these areas and lateral extension of the tumor may compress only one root at the time.

Cervical Spine Metastasis

Metastatic disease involving the odontoid process of the axis (C1 vertebral body) results in a pathologic fracture. Secondary subluxation occurs and results in spinal cord or brain stem compression. The symptoms are usually severe neck pain radiating over the posterior aspect of the skull to the vertex, which is exacerbated by movement. Diagnostic evaluation may require tomography or computed tomography (CT) scanning as plain X-rays and bone scans may be negative. Imaging procedures must be done carefully and with neurosurgical consultation to ensure spinal stability.

Pain localized to the adjacent paraspinal area is characterized by a constant dull aching pain radiating bilaterally to both shoulders with tenderness to percussion over the spinous process. Radicular pain in a C7–8 distribution occurs most commonly unilaterally in the posterior arm, elbow, and ulnar aspect of the hand. Paresthesias and numbness in the fourth and fifth fingers and progressive hand and triceps weakness are the neurologic signs. Horner's syndrome suggests paraspinal involvement. The diagnostic evaluation must be done carefully. Plain X-rays are often negative because they visualize this area poorly and CT, or preferably magnetic resonance imaging (MRI), scans are necessary to define metastatic disease.

Lumbar Spine and Sacral Metastasis

Dull and aching mid-back pain exacerbated by lying or sitting and relieved by standing is the usual presenting complaint of L1 metastasis: Pain may be referred to the hip. Radicular pain occurs anteriorly to both paraspinal lumbosacral areas, and referred pain affects the sacroiliac joint or superior iliac crest.

Aching pain in the lower back or coccygeal region exacerbated by lying or sitting and relieved by walking is the common complaint associated with sacral metastases. Symptoms include perianal sensory loss, bowel and bladder dysfunction, and impotence (see section on lumbosacral plexopathy for a more complete discussion).

The onset of back pain in association with band-like tightening across the chest or upper abdominal area, or radicular arm or leg pain, may be the first sign of impending spinal cord compression. Motor and sensory losses occur later, and autonomic disturbances producing bladder and bowel incontinence occur later still. Thus, evaluation of the patient should begin at the onset of pain for the best chance to preserve motor and sphincteric function and should include plain X-rays of the entire spine, focused on the symptomatic area, and an MRI or CT myelogram, which image the entire spine. This is a necessary diagnostic step because there is an approximately 15% incidence of another (clinically silent) epidural lesion being present (Byrne and Waxman, 1990).

Corticosteroid therapy should be started before radiologic evaluation, which may decrease pain and protect the spinal cord from further compression caused by edema from tumor or radiotherapy. If metastatic disease is found on plain spine films, MRI or CT myelogram should be done to define the extent of tumor invasion into the epidural space. This information influences the size of radiation therapy ports and determines the dose and duration of corticosteroid therapy.

If anterior vertebral body subluxation has occurred and there is bony compression of the spinal cord, surgical decompression is indicated if the patient's medical condition is stable enough to withstand the procedure. Surgical decompression is usually fol-

lowed by radiation therapy. Surgery is usually not attempted as the primary treatment modality because the results of radiation therapy and corticosteroid treatment together are usually equal to the results achieved from surgical decompression (Byrne and Waxman, 1990). This is especially true if a simple posterior decompressive laminectomy is performed. However, if patients have recurrent spinal cord compression in a previously irradiated port, then an anterior spinal approach with removal of tumor from the vertebral body, decompression of tumor from the spinal canal, and restructuring of the vertebral body with methylmethacrylate should be considered (Sundaresan et al., 1989). Recently vertebroplasty has gained popularity in vetebral metastasis causing pain due to fractures, without neurologic involvement (Cotten et al., 1996; Martin et al., 1999).

Local invasion of tumor from the pelvis into the sacrum may produce the syndrome of perineal pain, which is often difficult to manage. This syndrome is characterized by local pain in the buttocks and perirectal area, which is often accentuated by pressure on the perineal region such as that caused by sitting or lying prone. In its most extreme form, patients cannot sit to eat meals or lie flat to sleep and may spend much of their time standing. Because of the critical role of the parasympathetic sacral innervation to normal bladder and rectal sphincter function, continence is impaired early in the course of this syndrome (in distinction to spinal cord compression with more rostrally placed lesions), perhaps even before significant weakness can be discerned in the legs.

Skull Metastasis

Spread of tumor to the calvarium may produce neurologic symptoms via a number of mechanisms. Metastases to the skull vault, which compress the sagittal sinus, may produce a syndrome of severe headache with associated papilledema and seizures caused by elevated intracranial pressure. If untreated, focal neurologic deficits may occur secondary to (hemorrhagic) venous infarction of the brain. The cause of metastatic sagittal sinus occlusion is usually obvious and is easily confirmed by MRI imaging of the brain. Gadolinium-enhanced MRI demonstrates tumor metastasis as well as occlusion of the sagittal sinus. Nonmetastatic sagittal sinus occlusion may also occur as a complication of a hypercoagulable state induced by diethylstilbestrol treatment of prostate cancer or secondary to treatment with asparaginase for acute lymphoblastic leukemia.

Tumor metastasis to the base of the skull produces distinct neurologic syndromes (Greenberg et al., 1981). In general, bone metastasis to this portion of the skull often produces severe headache referred to the top of the head or occiput. Single or multiple cranial nerve palsies usually accompany basal skull metastasis. For example, clival metastases often compress the hypoglossal nerve, producing unilateral weakness of the tongue with deviation to the side of the lesion when protruded. Bone metastasis to the middle cranial fossa may compress and infiltrate the facial nerve, producing ipsilateral weakness of the upper and lower face. Tumor invasion of the jugular foramen will produce severe head pain with associated dysphagia, dysphonia, and hoarseness caused by dysfunction of the glossopharyngeal and vagal nerves that exit the skull base through this foramen.

Small lesions at the skull base may not be seen by plain films or bone scans of the skull. It is mandatory that CT scans with bone windows and 5 mm sections (so-called thin cuts) are done to demonstrate the tumor. It is sometimes desirable to image the base of the skull with MRI when CT scans are negative (Kelly and Payne, 1991). Radiation therapy directed to the base of the skull is the preferred treatment. Again, prompt recognition of these syndromes and aggressive treatment can prevent irreversible cranial nerve palsies, which often produce devastating neurologic impairments.

TUMOR INFILTRATION OR TRAUMA TO PERIPHERAL NERVE, PLEXUS, AND ROOT

These syndromes present with radicular pain in the neck, chest, or trunk. The differential diagnosis includes tumor infiltration of the peripheral nerves and surgical injury—either partial, complete, or secondary to direct surgical interruption or traction, nerve compression secondary to musculoskeletal imbalance, diabetic peripheral neuropathy, acute herpes zoster, and postherpetic neuralgia.

Managing pain in these syndromes is hindered in general by the lack of any well-established approach to treat neuropathic pain, characterized by constant burning pain with hypesthesias and dysesthesias in an

area of sensory loss. The most common causes are tumor compression in the paravertebral or retroperitoneal area or metastatic tumor in the rib, which causes intercostal nerve infiltration.

Pain, either local, radicular, or referred, is usually the first sign that tumor has infiltrated nerve. Local and radicular pain occur when tumor infiltrates or compresses nerves peripheral to the paraspinal region, whereas referred pain with or without a radicular component occurs when tumor infiltrates the paraspinal region and more proximal areas. Associated autonomic dysfunction (i.e., loss of sweating and of axonal flair response to pin scratch) can help define the site of nerve compression or infiltration. Pain is initially characterized as a dull, aching sensation with tenderness to percussion in the distribution of the nerve. Mild paresthesiae or dysesthesiae may be the next sensory symptom, followed by the late appearance of motor symptoms and signs. As tumor invades the perineurium or compresses nerve externally, the nature of the pain changes to a burning, dysesthetic sensation. A careful neurologic examination followed by a CT scan to define the site of nerve compression are the diagnostic procedures of choice. Electromyography can help to define the site of nerve involvement, but is not diagnostic. Rib erosion and retroperitoneal and paraspinal soft tissue masses are the most common associated findings. For patients with paraspinal tumor, myelography (and/or MRI scanning) is often necessary to exclude epidural extension. Antitumor therapy is the first-line therapy when possible, but interim pain management with analgesics is almost always necessary.

Steroids may provide a useful diagnostic test while providing both anti-inflammatory and antitumor effects or may reduce local swelling and, secondarily, relieve pain. However, they are not an option for long-term management because of their toxicity. The sequelae of long-term steroid use are peripheral edema, weight gain, hyperglycemia, cataracts, osteoporosis with compression fractures, and an increased risk of infection from immunosuppression.

Brachial Plexopathy

In patients with cancer, brachial plexopathy may occur via

1. Metastatic spread of tumor to the plexus
2. Radiation injury producing transient sensory and motor symptoms and more prolonged neurologic dysfunction resulting from previous radiation therapy (RT) to a port that has included the plexus
3. Involvement of the plexus by radiation-induced tumor such as malignant schwannoma or fibrosarcoma
4. Trauma to the plexus during surgery and anesthesia

Tumor infiltration and radiation injury are the most common causes (Kori et al., 1981). A review of 100 cases suggested that reliable clinical signs and symptoms distinguish metastatic plexopathy from radiation injury. The characteristics of the pain are quite different from each cause and create useful distinguishing clinical signs.

Computed tomography is useful in diagnosing brachial plexus region pain, as described in the studies by Cascino et al. (1983). However, recently MRI scanning has been advocated as the optimal imaging technique for the brachial plexus region (Blair et al., 1987) and may be useful for diagnosing metastatic brachial plexopathy. Median nerve somatosensory evoked potentials (MSEP) is a useful neurodiagnostic tool to detect the site of nerve involvement in patients with pain of the upper extremity. This modality may detect brachial plexus lesions earlier than radiologic studies. Electrodiagnostic studies (electromyography [EMG]) are useful in distinguishing tumor infiltration of the brachial plexus from radiation injury. When present, myokymia is almost always associated with radiation injury of the plexus. However, in patients who present with neurologic symptoms in a C8–Tl distribution in a port of previous radiation, the presence of myokymia does not exclude tumor infiltration of the plexus. In fact, the authors have seen several patients with both radiation fibrosis and tumor occurring simultaneously in whom myokymia was present.

Rarely, biopsy of the brachial plexus may be necessary to distinguish (recurrent) tumor infiltration from radiation fibrosis or the occurrence of a new primary tumor (Payne and Foley, 1986). Biopsy is not, however, always definitive.

Metastases to the brachial plexus most commonly involve the lower cords of the brachial plexus, giving rise to neurologic signs and symptoms in the distribution of the C8, T1 roots. In contrast, radiation plexopathy most commonly involves the upper cords of the plexus, predominantly in the distribution of the

C5, C6, and C7 roots. Severe pain is most often associated with metastatic plexopathy, and Horner's syndrome is more frequently associated with metastatic plexopathy than with radiation plexopathy. A significant number of patients with metastatic plexopathy demonstrated epidural extension of disease. A primary tumor of the lung, the presence of Horner's syndrome, and involvement of the whole plexus should alert the physician to the possibility of epidural extension and warrants an immediate myelogram (or MRI scan). Neither a negative surgical biopsy nor observation for several years for other metastases rules out recurrence of tumor or a new primary tumor (Payne and Foley, 1986).

Brachial Plexopathy in Pancoast Tumors

Brachial plexopathy in Pancoast tumors, as described by Kanner et al. (1981), is an integral part of the disease. Pain in the distribution of C8–Tl is an early sign and is one aspect of the clinical diagnosis of Pancoast syndrome. Pain is the most reliable sign to follow as it closely reflects the progression of disease and may be the only sign of epidural cord compression. Plain X-rays and bone scans are not reliable diagnostic tests in assessing this disorder, whereas CT scans and myelograms yield the most important diagnostic information. As many as 50% of patients develop epidural cord compression, with pain being the earliest and most consistent clinical symptom. In patients who present with a Pancoast syndrome and involvement of the brachial plexus, the initial diagnostic work-up should include a CT scan, tomograms of the vertebral bodies, and myelography to determine the extent of tumor infiltration. Initial antitumor surgery should be directed at radial removal of all local tumor. Secondary treatment is composed of external radiation therapy and brachytherapy (Sundaresan et al., 1987).

The Pancoast syndrome is commonly misdiagnosed and confused with cervical disc disease, which appears in less than 5% of patients in a C8–Tl distribution. Early diagnosis of tumor is crucial to curative therapy, and neurologists often play an important role in the initial evaluation of these patients.

Lumbosacral Plexopathy

Lumbosacral plexus tumor infiltration most commonly occurs in genitourinary, gynecologic, and colonic cancers (Jaeckle et al., 1985). Pain varies with the site of plexus involvement. Radicular pain occurs in an L1 through L3 distribution (i.e., anterior thigh and groin) or down the posterior aspect of the leg to the heel with an L5/S1 distribution. In some instances, there is only referred pain without local pain over the plexus. Common referred points are the anterior thigh, knee, and lateral aspect of the calf. These areas are commonly painful, but the origin of the pain is in the plexus. Pain is the earliest symptom, followed later by complaints of paresthesiae, numbness, and dysesthesiae leading to motor and sensory loss.

The clinical symptoms and natural history of this disorder have been described by Jaeckle et al. (1985) in a review of 85 patients with lumbosacral plexopathy. Pain was noted to be of three types: local in 72 of 85 patients, radicular in 72 of 85 patients, and referred in 37 of 85 patients. Local pain in the sacrum or sciatic notch occurred in 59% of patients, followed by low back pain in 27% and pain in the groin or lower abdominal quadrant in 21%. Pain referred to the hip or flank occurred in patients who had upper plexus lesions, whereas pain in the ankle or the foot occurred in patients with a lower plexopathy. Typically, the pain precedes objective sensory, motor, and autonomic signs for weeks to months (mean of 3 months), and initially the CT scan may be negative. Unilateral and bilateral plexopathy with significant motor weakness is commonly associated with epidural extension, and both CT scan and myelography are necessary to define the extent of tumor infiltration and/or epidural compression. Plain X-rays are not often helpful because the lumbosacral plexus lies within the substance of the psoas muscle and is not radiodense. Specific antitumor therapy depends on the tumor type, and relief of pain symptomatology is directly related to tumor responsiveness. Patients with colorectal and cervical cancers and sarcomas have persistent pain and progressive plexopathy. Pain management for these patients is particularly difficult because selective analgesia cannot be provided without interfering with motor, sensory, and autonomic functions.

Overall, management of painful plexopathies is currently unsatisfactory, but a series of approaches have been tried with varying success. All patients should be managed with nonopioid and opioid analgesics. Steroids are helpful for those patients who have significant local swelling because they have anti-

inflammatory and antitumor effects and provide additive analgesia. For patients with acute lancinating pain superimposed on dysesthetic pain, carbamazepine is sometimes helpful, as are tricyclic antidepressants (Wiffen et al., 2000; Swerdlow, 1984). Newer anticonvulsants like gabapentin, lamotrigine, and oxcarbazepine may offer advantages as far as their side effect profiles are concerned (Zakrzewska et al., 1997; McCleane, 2000; Remillard, 1994).

Specific anesthetic and neurosurgical pain management approaches vary with the site of tumor involvement. Epidural local anesthetics can provide local pain relief for lumbosacral plexopathy and can be appropriately titrated to provide only sensory loss. However, they cannot be maintained for long periods of time because a tolerance develops to their analgesic effects, along with infection of the catheter track and epidural space. Epidural or intrathecal phenol or alcohol are used to produce chemical neurolysis and can be titrated to produce predominant sensory changes. Recently, psoas compartment neurolysis has been shown to treat upper plexus pain (Calava et al., 1996). However, loss of motor function and in some cases bladder incontinence are limitations of these procedures. The patient's terminal status and the intractability of these pain syndromes may, however, provide a favorable risk/benefit ratio for taking these measures.

Subarachnoid administration of phenol and alcohol to block the cauda equina can produce bowel and bladder dysfunction with associated motor loss. No patient should undergo a subarachnoid lumbar block (or spinal opioid administration) with such agents until MRI has demonstrated the patency of the subarachnoid space (Cherry et al., 1986). The patient must understand the consequences of undergoing these procedures, which may involve loss of autonomic function and (mild) bilateral leg weakness.

Percutaneous or open cordotomy may be helpful for patients with unilateral lumbosacral plexopathy. However, for those with brachial plexopathy, the results are much less impressive because pain radiating to the neck and ears often escapes the cordotomy level. Bilateral pain from a bilateral lumbosacral plexopathy requires a bilateral cordotomy for effective pain control with a consequent risk to bowel and bladder function as well as bilateral corticospinal tract involvement. Epidural and intrathecal morphine infusions can provide analgesia that is selective without interfering with motor, sensory, and autonomic function (Payne, 1987). However, this technique is limited by the fact that escalation of drug doses as tolerance to the drug develops limits its usefulness for patients who have far advanced disease and a prior exposure to opioids. Epidural and intrathecal infusions are each associated with significant systemic uptake of the drugs and do not completely obviate the side effects of systemic drug administration (Max et al., 1987). Recently, epidural clonidine has been approved for cancer pain management and has been used successfully for neuropathic cancer pain (Eisenach et al., 1995). Neuronal-specific calcium channel blockers administered intrathecally may be used to treat such intractable neuropathic pain syndromes in the future (Bowersox et al., 1996). Although these techniques provide useful alternatives, they are not the sole techniques for treating these pain syndromes. In most cases, a multipronged approach provides optimal control of pain and other symptoms resulting from cancer.

Both dorsal column stimulation and periventricular brain stimulation have been of limited usefulness in this patient population. Behavioral techniques help patients cope with pain and control the associated symptoms of anxiety and depression, which occur with chronic pain and neurologic disability. These syndromes are particularly difficult to manage, and the effectiveness of the approaches used depends on the expertise available to the patient and his or her physician as well as a willingness on the part of the patient to undergo novel procedures in return for only partial relief.

Leptomeningeal Neoplasia

Pain occurs in 40% of patients with leptomeningeal metastases (Wasserstrom et al., 1982) and is of two types: headache with or without neck stiffness or back pain localized to the low back and buttocks. There may be associated confusion, delirium, cranial nerve palsies, radiculopathy, and myelopathy. Diagnostic work-up should include an MRI (with contrast) to determine enhancement in the basal subarachnoid cisterns and to rule out hydrocephalus. Magnetic resonance imaging can also rule out bulk disease on the nerve roots, which might require focal radiation therapy. A lumbar puncture should be performed to determine cerebrospinal fluid glucose, protein, cell count, cytology and biochemical markers (e.g., α-microglobulin, CEA, and LDH).

PAIN SYNDROMES ASSOCIATED WITH CANCER THERAPY

This category includes clinical pain syndromes that occur in the course of or subsequent to treatment of cancer patients with the common modalities of surgery, chemotherapy, or radiation therapy.

Post-Surgical Pain—Surgical Injury to Peripheral Nerves

Four distinct pain syndromes involving the peripheral nerves occur following surgery in patients who have cancer. These are outlined in the following sections.

Post-Thoracotomy Pain

Post-thoracotomy pain occurs in the distribution of an intercostal nerve following surgical interruption or injury. The intercostal neurovascular bundle (vein, artery, and nerve) courses along a groove in the inferior border of the rib. Traction on the ribs and rib resection are the common causes of nerve injury during a surgical procedure on the chest. Kanner et al. (1981) prospectively evaluated 126 consecutive patients undergoing thoracotomy and defined several groups of patients. In most (79 patients,) immediate postoperative pain was reduced at approximately 2 months, but 13 of the 79 patients had a recurrence of pain caused by recurrence of tumor in the distribution of the intercostal nerves. Immediate postoperative pain is characterized by an aching sensation in the distribution of the incision and sensory loss, with or without autonomic changes. There is often an exquisite point of tenderness at the most medial and apical point of the scar with a specific trigger point. In another group of patients, pain persisted in 16% (20/126) after thoracotomy and increased in intensity during the follow-up period. Local recurrences of disease and/or infection were the most common cause of increasing pain in this group of patients. In the third group, 14% (18/l26) of patients had stable or decreasing pain, which resolved over time and did not represent a difficult management problem. Therefore, persistent or recurrent pain in the distribution of the thoracotomy scar in patients with cancer is commonly associated with recurrent tumor. The one caveat to this conclusion is that a small number of patients will have a traumatic neuroma at the site of a previous thoracotomy scar, but this should not be the initial consideration in their evaluation.

Chest X-rays are insufficient for evaluating recurrent disease. A CT scan (or MRI) through the chest with bone and soft tissue windows is the diagnostic procedure of choice. These imaging studies are also necessary before consideration of intercostal nerve blocks for pain management of these syndromes. If pain management is inadequate or the patient is not actively rehabilitated following surgery, a frozen shoulder and secondary reflex sympathetic dystrophy involving the arm can occur. This complication requires early and active mobilization of the arm and active physical therapy combined with analgesics, occasionally steroids, and occasionally sympathetic blocks of the stellate ganglion. The nature of the pain in patients with traumatic neuroma in contrast to tumor infiltration of the nerve is not sufficiently distinct clinically, and the ability to localize a specific trigger point and to provide dramatic pain relief with a local anesthetic blockade are strong indications to suggest traumatic neuroma as a possible etiology. Cryoprobes to freeze the peripheral nerve have also been used in the management of patients with post-thoracotomy pain (Katz et al., 1980) and may be useful in the other syndromes. The management of tumor infiltration depends on the type of cancer and the specific antitumor therapy available.

Post-Mastectomy Pain

Post-mastectomy pain occurs in the posterior arm, axilla, and anterior chest wall following any surgical procedure on the breast whether lumpectomy or radical mastectomy (Watson et al., 1989). It is especially likely to occur after axillary and lymph node dissection (Vecht et al., 1989). The marked anatomic variation in size and distribution of the intercostal brachial nerve accounts for the variable appearance of this syndrome in patients who are undergoing mastectomy. Pain results from interruption of the intercostal brachial nerve, a cutaneous sensory branch of Tl–T2. The pain may occur immediately after surgery and as long as 6 months later. It is characterized as a tight, constricting, burning pain in the posterior aspect of the arm and axilla radiating across the anterior chest wall. The pain is exacerbated by movement of the arm and relieved by its immobilization.

Patients often posture their arm in a flexed position close to the chest wall, placing them at risk of

developing a frozen shoulder syndrome if adequate pain and post-surgical rehabilitation are not implemented early on. Approximately 5% of women undergoing surgical procedures on the breast develop this syndrome. The nature of the pain and the clinical symptomatology should readily distinguish it from tumor infiltration of the brachial plexus. The syndrome appears to occur most commonly in patients with postoperative complications who are at risk for local fibrosis in and about the nerve following surgery (e.g., following wound infection or seroma). Typically a trigger point in the axilla or on the anterior chest wall may be found, which is usually the site of the traumatic neuroma. Breast reconstruction does not alter the tight, constricting sensation in the anterior chest wall that is associated with this syndrome. The management of pain in this syndrome is similar to the management of pain for any patient with peripheral nerve injury and pain.

Post-Radical Neck Surgery

Prospective studies of post-radical neck dissection pain are lacking. In any patient in whom the pain occurs late (i.e., several months after the surgical procedure) and particularly any pain occurring several years following the surgical procedure, re-evaluation is necessary to exclude the recurrence of tumor. This is particularly true of adenocystic tumors involving the head and neck, which typically invade and metastasize locally along peripheral nerve, giving rise to sensory loss and several qualities of painful sensations, including burning dysesthesia and shock-like shooting and lancinating pains.

Post-Amputation Phenomena

Loss of a body part is often followed by a psychological adjustment period that may include a grief reaction (Bradway et al., 1984). The physiologic phenomena of nonpainful and painful phantom sensations (referred to the missing part), pain in the scar region (called a stump after limb amputation), and involuntary motor activity also occur.

Phantom sensations may be divided into three types. Kinetic sensations, the perception of movement, may be spontaneous or willed. Kinesthetic perceptions, those of size, shape, and position of the body part, may be normal or distorted. Exteroceptive perceptions of touch, temperature, pressure, itch, and vibration are frequently reported. Patients readily distinguish unpleasant or annoying sensations from those labeled as painful. Many patients note most sensations in the distal phantom limb or in the nipple of the phantom breast. A phantom visceral organ may be associated with functional sensations (e.g., the urge to urinate or defecate).

Phantom pains may be described as intense versions of normal exteroceptive sensations. Patients offer bizarre descriptors, such as "my foot is being crushed by a bar rolling over it, and my toes are twisted." The intensity, frequency, and duration of pain, as well as provocative and palliative factors, differ among individuals.

Stump pain may be associated with or occur independently of phantom pain. The usual postoperative wound pain is expected to resolve as healing takes place. Persistent stump pain may be due to a local pathologic process, for example, circulatory disturbance, infection, and tumor, or other lesions of skin, soft tissue, or bone. Neuromas, which develop at the severed end of peripheral nerve, may act as a trigger for phantom pain and contribute to stump pain (see "Pathophysiology", below).

The natural history of phantom limb pain has been best studied in trauma patients and those undergoing surgical amputation for nonmalignant conditions (Sherman et al., 1984). There is wide variation in the reported incidence of severe persistent phantom pain due to many factors. Many investigators fail to distinguish painful from nonpainful phantom sensations and phantom from stump pain. It is also known that patients may be reluctant to report their phantom sensations and pain. A thorough review of the literature supports the conclusion that virtually all patients have nonpainful phantom sensations and that the majority have unpleasant or painful phantoms even if only briefly (Jensen et al., 1984).

Painful and nonpainful phantoms change in character and location. Patients often describe "telescoping" or shortening of the phantom limb over time. They may perceive only the distal portion of the limb attached to the stump. Others have reported gradual fading of the phantom. A common course would be gradual reduction in the frequency and duration of painful episodes, generally over several weeks to 2 years. Late-appearing phantom pain has been reported, although most patients note the onset of phantom pain soon after amputation.

Although persistent phantom pain is unusual before age 8 years, patients as young as 4 years old have reported phantom limb pain (Simmel, 1962). Verbal children describe feelings in a limb that is no longer present and can distinguish phantom from stump pain.

The value of preoperative pain for predicting post-amputation pain is not well established. Some data support a positive predictive value of preoperative pain as a harbinger for postoperative pain (Wall et al., 1985; Jensen et al., 1985). One study has shown that preoperative pain predicted immediate postoperative pain that resembled preoperative pain in character and location. This implies a persistence of preoperative nociceptive paths, or memory of pain, which usually resolves in the subacute period (Katz and Melzack, 1990). Patients with significant preoperative pain have a similar risk as patients without preoperative pain of developing chronic phantom pain (different from their preoperative pain).

A few reports chart the course of post-amputation pain in malignant disease. In a study of 17 cancer patients who underwent forequarter amputation, after an average of 69 months follow up none of the 7 survivors experienced pain that required the use of analgesics (Steinke et al., 1991). Larger surveys of post-mastectomy patients reveal that at least 10% experience chronic phantom breast pain, a greater percentage than is generally believed (Kroner et al., 1989). Increasing pain in the cancer amputee may signify disease progression or recurrence (Sugarbaker et al., 1984; Boas et al., 1993).

Treatment Approaches for Phantom Limb Pain

Many treatment approaches have been tried to alleviate phantom pain, including medications, neurostimulation, ablation of peripheral and central nervous system structures, physical therapy, and psychological and behavioral methods. In 1984, Sherman reviewed phantom pain treatment methods in the United States. He noted that of the 68 treatment methods reported, none was uniformly successful. Subsequent reviews by Davis (1993) concluded similarly.

As for many other types of neuropathic pain, the efficacy of pharmacologic interventions varies between individuals. Thus, patients should be given sequential pharmacologic interventions, including opiates (Foley, 1993). The administration of intrathecal fentanyl reduced phantom limb pain and induced painless phantoms in a few cases of chronic phantom pain. Analgesia was not improved with concurrent administration of lidocaine (Jacobson et al., 1989, 1990). Anecdotal reports suggest that some patients benefit from carbamazepine (Patterson, 1988) and other anticonvulsants (Backonja, 2000). Amitriptyline may be efficacious for phantom pain in children (Rogers, 1989). In one randomized trial of topical application of capsaicin for general post-mastectomy pain, 62% of 13 patients reported 50% or better pain relief (Watson and Evans, 1992). Capsaicin has also been reported to relieve chronic stump pain (Rayner et al., 1989).

Physical stimulation of the stump by mechanical, thermal, and electrical means provides relief for some patients. In a randomized trial of 51 patients (Finsen, 1988), transcutaneous electrical nerve stimulation (TENS) resulted in faster stump healing, but did not affect postoperative pain or chronic phantom pain. Auricular TENS resulted in small but significant differences in painful and painless phantoms in a crossover study of 28 amputees (Katz and Melzack, 1991).

No specific recommendations can be offered to identify the operative procedures that are most likely to reduce the incidence of post-amputation pain. Postoperative compression bandaging or hard casting to reduce stump edema may facilitate rehabilitation. It is not certain if this contributes to pain relief.

In a small series of patients undergoing amputation for nonmalignant disease, a threefold reduction in the incidence of phantom pain 1 year after amputation was demonstrated after preoperative ("preemptive") treatment with an epidural infusion of opioid and local anesthetic (Bach, 1988).

Chemotherapy-Related Pain Syndromes

Painful dysesthesias follow treatment with several chemotherapeutic agents, in particular the Vinca alkaloid drugs (i.e., vincristine and vinblastine). Cisplatin and taxol are also toxic to peripheral nerve (Young and Posner, 1985; Asbury and Bird, 1992). These agents produce a symmetric polyneuropathy as a result of a subacute chronic axonopathy. Pain is usually localized to the hands and feet and is characterized as burning pain exacerbated by superficial stimuli, which improves as the drug is withdrawn.

Steroid pseudorheumatism (Rotstein and Good, 1957) is characterized by diffuse myalgias and arthralgias, with muscle and joint tenderness on palpation. It occurs from both rapid and slow withdrawal of steroid medication in patients taking these drugs for either short or long periods of time. The signs and symptoms revert with reconstitution of the steroid medication.

Aseptic necrosis of the humeral and, more commonly, femoral head is a known complication of chronic steroid therapy (Ihde and DeVita, 1975). Pain in the shoulder and knee or leg is the common presenting complaint, with X-ray changes occurring several weeks to months after the onset of pain. A bone scan and MRI scan are the most useful diagnostic procedures.

Post-herpetic neuralgia (Loeser, 1986) can be thought of as a postchemotherapy pain syndrome because immunocompromised patients are at risk for acute herpes zoster infection or a recurrence of latent zoster. Persisting pain after healing of the cutaneous eruption of herpes zoster infection usually has three components: *(1)* a continuous burning pain in the area of sensory loss, *(2)* painful dysesthesias, and *(3)* intermittent shock-like pain. Elderly patients are at greatest risk for developing this complication (Watson, 1982). Many anesthetic, surgical, and drug therapies have been proposed. The most consistently effective treatment is administration of tricyclic antidepressants such as amitriptyline and desipramine. Randomized controlled trials of substance P-depleting agents such as topical capsaicin are effective in some patients. Recently, a Japanese study suggested that intrathecal steroids might be used to effectively treat post-herpetic neuralgia (Kotani et al., 2000).

Post-Radiation Therapy Pain

Post-radiation therapy pain syndromes are occurring less frequently because of the increased sophistication by which radiation therapy portals are planned. Developments in this area have decreased radiation overdose to tissues, sparing the surrounding normal tissues. Nonetheless, radiation fibrosis of peripheral neural structures such as the brachial and lumbar plexus still occur, and radionecrosis of bone is occasionally seen.

Radiation fibrosis of the brachial plexus is discussed earlier in this chapter. Pain in the leg from radiation fibrosis of the lumbar plexus is characterized by its onset late in the course of progressive motor and sensory changes in the leg (Thomas et al., 1985). Lymphedema, a previous history of radiation therapy, myokymia on EMG, and X-ray changes demonstrating radiation necrosis of bone may help establish this diagnosis.

Pain is an early symptom in 15% of patients with radiation myelopathy (Jellinger and Sturm, 1971; Palmer, 1972). Some patients may demonstrate Lhermitte's sign, signifying transient demyelination in the posterior columns, which does not necessarily predict the development of myelopathy. Pain may be localized to the area of spinal cord damage or may be referred pain with dysesthesias below the level of injury. The neurologic symptoms and signs are often initially manifested as the Brown-Séquard syndrome (lateral hemi-"section" of the cord) whereby pain and temperature sensation are lost contralaterally to the side of weakness. Position and vibration sensation are lost ipsilaterally to the side of weakness. The incidence of myelopathy increases with increasing radiation exposure and approaches 50% with 1500 ret exposure. The latency from completion of radiation to the onset of symptoms of myelopathy ranges from 5 to 30 months, with an average of 14 months reported in most series.

A painful enlarging mass in an area of previous irradiation suggests the presence of a radiation-induced peripheral nerve tumor (Foley et al., 1980; Ducatman and Scheithauer, 1983; Thomas et al., 1983; Powers et al., 1983). In one study, seven of nine patients who developed radiation-induced nerve tumors presented with pain and progressive neurologic deficit with a palpable mass involving the brachial or lumbar plexus; these nine patients developed their tumors 4 to 20 years following radiation therapy. Neurofibromatosis is associated with an increased risk for radiation-induced peripheral nerve tumors (Foley et al, 1980).

MANAGEMENT OF CANCER PAIN

General Principles

Numerous approaches can be used to manage pain in cancer patients (Foley, 1993). These encompass multiple modalities of therapy, including pharmacologic, anesthetic, physical, behavioral/psychological, and neurosurgical approaches. In the mid-1990s, a

comprehensive approach to the assessment of and guidelines for the management of pain in the patient with cancer was formulated by the Agency for Health Care Policy and Research (AHCPR) (Jacox et al., 1994). The guidelines emphasized the need to evaluate the extent of disease and use of appropriate antitumor therapies to treat the cancer whenever possible. Apart from humanistic considerations, treating cancer pain may be necessary for obtaining appropriate diagnostic studies to define the extent of disease or to allow the patient to complete radiotherapy or other treatments for cancer. For example, adequate titration of analgesics is often necessary to provide enough comfort for the patient to lie quietly so that CT or MR imaging may be completed to evaluate spinal cord compression or lumbosacral plexopathy. Guidelines established by the World Health Organization suggest using a three-step ladder approach, with titration of analgesic therapy following a continuum from mild pain, for which nonsteroidal anti-inflammatory analgesics and analgesic adjuvants are utilized, to moderate and severe pain, for which opioid drugs are added.

These and other guidelines regarding the appropriate use of opioid drugs for acute and chronic cancer pain advocate a basic knowledge of the clinical pharmacology of opioid analgesics, including the concepts of relative potency and dose titration to effect. Knowledge of these concepts permits selection of appropriate starting doses of opioids and provides a method for titration of the drugs. If unacceptable side effects intervene before pain relief is obtained (despite the use of adjuvant drugs to augment analgesia or to counteract side effects), another opioid drug should be used, or another route of administration or an alternative surgical or anesthetic approach should be considered. Although chronic opioid administration may produce physical dependence and tolerance, the need to augment opioid doses for a given patient is usually caused by increasing pain associated with progressive disease as opposed to tolerance caused by a change in opioid receptor responsiveness (Payne, 1989). Clearly, physical dependence and tolerance must be distinguished from psychological dependence. Fortunately, the occurrence of psychological dependence is rare in cancer patients who have not had a substance abuse disorder before the diagnosis of cancer. The fear of iatrogenic addiction should never be used as an excuse to withhold opioids for the treatment of pain.

Special Considerations in Bone Pain

As noted above, bone pain is a major cause of pain in many patients with cancer. Standard approaches for the treatment of bone pain include the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in combination with opioids. NSAIDs are said to be uniquely efficacious for treating bone pain (Portenoy and Hagen, 1990). Several lines of data suggest that in lytic bone metastasis, as is typical of breast and lung cancer, NSAIDs may decrease pain and aid in the inhibition of bone destruction because they inhibit PG synthesis. It is now known that PGs enhance osteoclast function and activate and sensitize nociceptors. Several of the newer NSAID drugs such as ketoprofen (Stambaugh and Drew, 1988) and ketorolac (Buckley and Brogden, 1990) have analgesic potencies that are much greater than aspirin and that approach the effectiveness of 10 to 12 mg intramuscular morphine. It should be noted that NSAIDs appear to be as effective in treating osteoblastic metastasis from prostate cancer as they are for osteolytic metastasis. COX-2 inhibitors, recently approved by the FDA, offer the advantages of causing less gastric dyspepsia and a lesser incidence of peptic ulcer disease and inhibition of platelets (Hawkey, 1999), benefiting cancer patients in particular. Even the most potent, newer NSAIDs should not, however, be viewed as substitutes for morphine or other opioids in managing severe pain, as all drugs in this class have a ceiling to their analgesic efficacy.

The role of radiation and hormonal therapies in managing bone pain in prostate and other cancers is important. During the past 10 years or so, interest has focused on the role of intravenous administration of radiopharmaceuticals such as ^{32}Phosphorus, ^{90}Ytterium, and ^{89}Strontium to manage metastatic bone disease. Of the three nuclides, ^{89}Strontium may be less myelotoxic than the others by virtue of its relative selectivity for bone. Overall response rates for pain relief are reported to be as high as 80% (mean, 68%) (Bryne and Waxman, 1990). While these agents have been considered useful in treating bone pain from prostate metastases, in general all three agents have generally fallen out of use because they are myelosuppressive and frequently necessitate the postponement of cytotoxic chemotherapy.

Drugs in the bisphosphonate class are used to manage hypercalcemia associated with malignancy (Coleman, 1991) and may secondarily influence bone

pain. Bisphosphonates such as etidronate and pamidronate have potent inhibitory effects on osteoclasts, thereby decreasing bone resorption. They are useful treatments for hypercalcemia and to promulgate bone remodeling in osteolytic metastasis. They do not appear, however, to be effective against bone pain in osteoblastic metastasis from prostate cancer (Smith, 1989). Bisphosphonates have been shown to reduce the incidence of fractures in breast cancer patients with bony metastasis and are administered monthly to breast cancer and multiple myeloma patients to reduce pain and osseous incidence (Hortobagyi et al., 1996; Berenson et al., 1996; Lahtinen et al., 1992).

Calcitonin also inhibits osteoclast function and is a treatment for hypercalcemia, as well as exerting antinociceptive effects in the central nervous system (Fraioli et al., 1984). Limited clinical trials have demonstrated analgesia when calcitonin is given intraspinally. Currently, this should be considered as experimental therapy for pain, as the FDA has not approved its use for this indication and the neurotoxicity of intrathecal calcitonin has not been fully studied. However, this therapy for bone pain is attractive for patients who do not obtain satisfactory relief from opioids because calcitonin provides a potential means of analgesia through nonopioid mechanisms. Thus, in theory, it provides a way to achieve pain relief in opioid tolerant or opioid nonresponsive patients. Conclusions await the results from future clinical trials.

Hypophysectomy has been used to manage generalized bone pain that has failed hormonal and systemic analgesic therapies (Waldman et al., 1987). Hypophysectomy is accomplished by alcohol injection and may produce immediate pain relief in 35% of patients, lasting as long as 20 weeks. Success rates as high as 90% have also been reported. The use of levodopa as a predictor of response to hypophysectomy and as a treatment in itself for metastatic bone pain is controversial. Earlier reports by Minton (1974) noted a 33% response rate in metastatic bone pain from breast cancer, but a more recent study reported a response rate in only 7% (1 of 14) of patients treated with levodopa-carbidopa for bone metastasis (Sjolin and Trykker, 1985).

Nonopioid Analgesics

Nonopioid analgesics (Table 23–4) constitute a heterogeneous group of substances differing in chemi-

Table 23–4. NSAIDs and COX-2 Inhibitors

NSAIDs		
Drug	*Usual Dosage*	
Acetaminophen (Tylenol and others)	500–1000 mg orally every 4–6 hours	
Acetylsalicylic acid (aspirin)	500–1000 mg orally every 4–6 hours	
Diflunisal (Dolobid)	1000 mg (initially)	
Naproxen (Naprosyn)	500 mg (initially); 250 mg orally every 6–8 hours	
Ibuprofen (Motrin and others)	200–400 mg orally every 4–6 hours	
Ketoprofen (Orudis)	25–50 mg orally every 4–8 hours	
Flurbiprofen (Ansaid)	50 mg orally every 4–6 hours	
Indomethacin (Indocin)	25 mg orally two or three times daily	
Diclofenac sodium (Voltaren)	25–50 mg orally every 6–8 hours	
Piroxicam (Feldene)	20 mg orally daily	
Ketorolac (Toradol)	60 mg (initially) intramuscularly, then 30 mg intramuscularly every 6 hours; then 10 mg orally every 6 hours (limit 5 days)	
COX-2 Inhibitors		
Drug	*Selectivity*	*Dose*
Celecoxib (SC 58635 Celebrix)	Specific	200–400 mg every 12 hours
Rofecoxib (MK 0966 Vioxx)	Specific	25–50 mg daily
Nimesulide (Mesulid)	Preferential	?
Meloxicam (Mobic)	Preferential	7.5–15 mg daily

cal structure and pharmacologic actions. With the probable exception of acetaminophen, these drugs vary in their roles as analgesic, anti-inflammatory, and antipyretic agents. Aspirin is the prototype of the group and is the most commonly used agent. As a group, these drugs are usually administered orally and are used to treat mild to moderate pain. In contrast to opioid analgesics, tolerance or physical dependence does not develop with these drugs. However, nonopioid analgesics have a ceiling to their effectiveness, and escalation of the dose of drug given beyond a certain level does not produce additive analgesic effects.

Increasing evidence suggests that nonopioid analgesics play a unique role in the management of pain for patients who have bone metastases. Because many of the nonopioid analgesics act as potent PG synthetase inhibitors, they appear to have specific analgesic, anti-inflammatory, and, in some instances, antitumor effects in cancer patients with bony disease.

The choice and use of nonopioid analgesic drugs must be individualized for each patient. Patients must be given an adequate trial of one drug before switching to an alternative agent. Such a trial should include administration of the drug to maximum levels at regular intervals. These drugs should be used judiciously because they may produce significant adverse effects in cancer patients—gastrointestinal (GI) hemorrhage, masking of fever in an immunocompromised host, and platelet dysfunction—that can each be a serious and potentially fatal complication of therapy.

This category is essentially limited to inhibitors of the enzyme cyclooxygenase (COX), thus inhibiting the synthesis of PGs and pain and inflammation mediators. The NSAIDs can be divided into COX-2–selective and COX-2–nonselective NSAID subgroups. These medications are only useful as step 1 drugs or adjuncts to opioid therapy in the most advanced cases. They have the advantage of a very low short-term side effect profile that does not affect the patient's lifestyle. In general, their use for cancer pain is limited due to a ceiling effect as well as a deleterious long-term side effect profile. Except for COX-2 inhibitors and nonacidic subgroups, they are contraindicated or, at best, controversial for all patients with thrombocytopenia, which constitutes a large sector of those receiving antineoplastic therapy.

Gastric and duodenal ulceration is another potential problem that could result from long-term use of aspirin and other nonselective NSAIDS. Several techniques used to limit this consequence include the concurrent administration of an H2-blocker or misoprostol, each of which has its own particular limitations. This is less of a problem with newer COX-2 inhibitors. It should be mentioned that, when appropriate, ketorolac offers the advantage of parenteral administration (including subcutaneous), making this agent unique. This advantage, however, does not affect concerns over maintaining the integrity of the gastric mucosa.

Finally, acetaminophen, with none of the above side effects, is used more often than other step 1 drugs, especially in combined preparations with opioids. The downside of acetaminophen use is a dose limitation at 3000 mg/day to avoid potential hepatotoxicity and its lack of peripheral anti-inflammatory properties.

The New Selective COX-2 Enzyme Inhibitors

COX-2 remains the predominant source of PGs in the human GI tract and platelets, the reason this group of drugs was developed. In preliminary trials, these agents exhibited a safety profile comparable with placebo in contrast with the non-selective group; however, they affect the kidney similarly. COX-2 inhibitors (Table 23–4) are equally as efficacious as the older agents so the promise they carry is mainly due to safety and elimination of the major NSAID contraindications, thus benefiting more cancer (and rheumatoid) patients. Celecoxib (Celebrex) with a recommended dose of 200 mg qd or 100 mg bid, and Rofecoxib (Vioxx) with a recommended dose of 25 to 50 mg qd, are commonly used. Other COX-2 inhibitors are in clinical trials.

Opioid Analgesics

Opioid analgesics are the mainstay of treatment for moderate to severe cancer-related pain. These drugs (Table 23–5) produce analgesia through binding to specific opiate receptors in the brain and spinal cord (Yaksh and Rudy, 1976) and are categorized by how they interact with the receptors: *(1)* opioid agonists (e.g., morphine) interact with the receptor to produce analgesia and *(2)* opioid antagonists reverse or block receptor effects but have analgesic properties. Opioid antagonists are divided into two drug classes and are distinguished as being either morphine-like or nalorphine-like on the basis of their pharmacologic effects and the character of their abstinence syndromes.

Table 23–5. Opioid Analgesics

Drug	*Usual Starting Dosages*
Full opioid agonists	
Morphine*	15 to 30 mg orally every 3 to 4 hours
	30 to 60 mg orally every 8 to 12 hours
Hydromorphone (Dilaudid)	2 to 4 mg orally every 4 to 6 hours
Levorphanol (Levo-Dromoran)	2 to 4 mg orally every 4 to 6 hours
Fentanyl (Duragesic)	25 to 50 μg/hr transdermally every 3 days
Codeine	15 to 30 mg orally every 3 to 4 hours
Oxycodone (Percodan and others)	5 to 10 mg orally every 3 to 4 hours
Meperedine (Demerol Hydrochloride)	75 to 100 mg intramuscularly every 3 to 4 hours
Methadone hydrochloride (Dolophine)	5 to 10 mg orally every 3 to 4 hours
Propoxyphene (Darvon and others)	100 mg orally every 4 to 6 hours
Partial agonists and mixed agonists/antagonists†	
Nalbuphine (Nubain)	10 mg intravenously every 3 to 4 hours
Butorphanol (Stadol)	0.5 to 2 mg intravenously every 3 to 4 hours
	1 to 2 mg sublingually three times a day
Dezocine (Dalgan)	10 mg intravenously every 3 to 4 hours
Pentazocine (Talwin)	50 mg orally every 4 to 6 hours

*Morphine can be given as an immediate-release formulation or as a sustained-release preparation. It is recommended that a relatively rapid onset, short-acting opioid preparation (such as immediate-release morphine) be available to patients who take sustained-release morphine to provide rescue medication for breakthrough pain.

†This class of drugs is *not* recommended for the management of chronic cancer pain because the drugs will reverse analgesia when co-administered with full opioid agonists and precipitate withdrawal in physically dependent individuals.

Opioids produce pharmacologic effects through binding to activated opioid receptors. Opioids that bind to receptors are classified as agonists (e.g., morphine) if they produce analgesia. Opioid antagonists (e.g., naloxone) block the action of an agonist: They have an affinity for opioid receptors but cannot activate the receptors to produce analgesia. Agonist–antagonist drugs (e.g., pentazocine and butorphanol) produce analgesia through their interaction with a specific receptor (e.g., kappa) but also bind to other receptors (e.g., mu) where they can block the action of an agonist. Partial agonists (e.g, buprenorphine) are opioid drugs that bind to receptors and produce analgesia, but, unlike morphine, they exhibit a ceiling effect: Increases in doses do not parallel increases in analgesia. The clinical use of mixed agonist–antagonists is limited by their ability to produce dysphoria and hallucinations; these effects are mediated by kappa receptors and possibly nonopioid sigma receptors. Mixed agonist–antagonists and partial agonists will each cause withdrawal syndromes when administered to a patient taking opiates chronically. Antagonists are used as an antidote for opiate overdose; they should be used judiciously because they will cause acute withdrawal in patients on chronic opioid therapy. Opioid overdose is an uncommon cause of encephalopathy in patients with cancer. Common causes of altered mental status changes should be sought before naloxone is administered. Sepsis in particular should be excluded, as this is one of the most common causes of delirium in cancer.

"Weak" Opioids: The Second Rung of the Analgesic Ladder

It is clinically useful to classify opioids as weak or strong, depending on their relative efficacy. Weak opioids are the second rung of the "analgesic ladder"

and are used for less severe pain; their efficacy is limited by an increased incidence of side effects at higher doses (e.g., nausea and constipation with codeine, central nervous system excitation with propoxyphene). When weak opioids are given at a fixed oral dose mixed with a nonopioid analgesic their efficacy is limited by the maximal safe dose for nonopioid analgesics such as acetaminophen or aspirin. Strong opioids are used for more severe pain: They have a wide therapeutic window and no ceiling effect for analgesia. Higher doses produce an increasing level of analgesia; they are the third rung of the analgesic ladder. This is a simplistic but clinically useful approach once the decision to start opioid therapy has been made.

Codeine, an alkaloid of opium, is the prototype of the weak analgesics. Although a parenteral preparation is available, it is nearly always given by mouth, often in a fixed mixture with a nonopioid analgesic. A 200 mg dose is equipotent to 30 mg of morphine. The affinity of codeine for mu receptors is several thousand-fold less than morphine (Pasternak, 1993). The half-life of codeine is 2.5 to 3 hours; approximately 10% of orally administered codeine is demethylated to morphine; free and conjugated morphine can be found in the urine. The analgesic action of codeine may be due to its conversion to morphine (Millan, 1990), although analgesic structure–activity studies do not support this hypothesis (Beaver et al., 1978a,b). Constipation is the main side effect at the usual therapeutic doses (30 to 60 mg every 4 hours) and is thus used for some patients with chronic diarrhea.

Hydrocodone is a codeine derivative available in the United States only and is found in combination with acetaminophen or aspirin in doses of 2.5, 5, 7.5, and 10 mg. It is thought to be more potent than codeine, although convincing data are lacking. At the above doses its analgesic effect is very weak and probably only slightly superior to acetaminophen alone. Some pharmacists have started to formulate hydrocodone without acetaminophen.

Propoxyphene is a synthetic analgesic structurally related to methadone. It is approximately equipotent to codeine as an analgesic but lacks its antitussive properties; it binds to mu receptors. Its analgesic activity lasts 3 to 5 hours, and its half-life is 6 to 12 hours. Its major metabolite is norpropoxyphene, which has a half-life of 30 to 36 hours, which may be responsible for some of the toxicity observed (Chan and Matzke, 1987). Norpropoxyphene has local anesthetic effects similar to lidocaine, and high doses may cause arrhythmias. Seizures occur more often with propoxyphene intoxication than with opiate intoxication. Naloxone antagonizes the toxic effects of propoxyphene (Inturrisi and Foley, 1984), which is very irritating to vessels and soft tissues when used parenterally. Inadvertent injection into the brachial artery has resulted in amputation of digits. Because it is more difficult to manage and offers no advantage over other opioids, its usefulness is limited.

Meperidine, a synthetic phenylpiperidine derivative mu agonist with anticholinergic properties, is the analgesic most commonly prescribed for acute pain and is also widely used for chronic pain. The reasons for this enthusiasm are unclear and are likely irrational. A lesser rise in pressure in the common bile duct compared with morphine (Jaffe and Martin, 1990) has not been shown to be clinically advantageous. In contrast, the central nervous system (CNS) excitatory effects that appear after chronic use are instead well substantiated. The accumulation of its metabolite, normeperidine, causes multifocal myoclonus and grand mal seizures (Kaiko et al., 1983; Szeto et al., 1977), which are not reversed by naloxone. In this context dilated pupils and hyperactive reflexes are characteristic. The half-life of meperidine is 3 hours. It is, in part, demethylated to normeperidine, the only active metabolite, which has a half-life of 15 to 30 hours. Normeperidine accumulates only after chronic treatment, particularly in patients with renal dysfunction. Short-term treatment with meperidine has been associated with mild negative alterations in various elements of mood (Kaiko et al., 1983). When meperidine is given to patients being treated with monoamine oxidase inhibitors, two different patterns of toxicity have been observed: severe respiratory depression or excitation, delirium, hyperpyrexia, and convulsions. The dose equianalgesic to 10 mg of parenteral morphine is 75 to 100 mg. The oral to parenteral ratio is 1:4. Its use by either route is rarely justified.

Oxycodone is a semisynthetic derivative of the opium alkaloid thebaine. Because of its high bioavailability (>50%) it is suitable for oral administration and by this route is equipotent to morphine and 10-fold more potent than codeine (Beaver et al., 1978a,b) Parenterally, intensity and duration of analgesia are 25% less than morphine (Beaver et al., 1978b). It has a half-life of 2 to 3 hours and dura-

tion of action of 4 to 5 hours. It is metabolized like codeine: demethylated and conjugated in the liver and excreted in the urine (Beaver et al., 1978b). Its analgesic action is partially mediated by active metabolites. Oxycodone is considered a weak analgesic because of its use in a fixed combination with acetaminophen and aspirin. These combinations limit its dose to 10 mg every 4 hours. However, oxycodone is now available as a 5 mg tablet as well as 20 mg/ml liquid and should be classified as a strong opioid. Soon, even higher strength oxycodone tablets will be available. When oxycodone is used alone, like other opioid agonists it has no ceiling effect for analgesia. It has been reported to have fewer side effects than morphine (Kalso and Vainio, 1988, 1990). Its availability in 5 mg tablets permits careful titration for patients with a narrow therapeutic margin. Oxycodone is a versatile and flexible drug that can be used to treat pain of any intensity requiring an opiate analgesic (Beaver et al., 1978b; Glare and Walsh, 1993; Poyhia et al., 1993).

"Strong" Opioids: The Third "Rung" of the Analgesic Ladder

Morphine, a phenanthrene derivative, is the prototype opiate agonist. All other opiates are compared with morphine when determining their relative analgesic potency. It is the drug of choice for severe pain associated with cancer (World Health Organization, 1986). Like other "strong" opiates, there is no ceiling to morphine's analgesic effect, although side effects, particularly sedation and confusion, may intervene before optimal analgesia can be achieved. It is metabolized in the liver where it undergoes glucuronidation at positions 3 and 6.

Morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) accumulate with chronic administration of morphine (Sawe et al., 1983). M6G binds to mu receptors with an affinity similar to morphine (Pasternak et al., 1987), but also binds to delta receptors; this may account for its higher analgesic potency (Oguri et al., 1987). M6G is 3.7-fold more potent than morphine when administered subcutaneously and 45-fold more potent when administered in the cerebral ventricles (Pasternak et al., 1987); only 0.077% of this metabolite crosses the intact blood–cerebrospinal fluid barrier (Portenoy et al., 1991).

In single-dose morphine studies the relative parenteral/oral potency ratio has been shown to be 1:6 (Houde et al., 1966). After chronic use the ratio changes to 1:3 (Twycross, 1975); this is likely due to accumulation of active metabolites. There is experimental (Labella et al., 1979) and clinical (Morley et al., 1992) evidence that M3G, which has a negligible affinity for opioid receptors and does not produce analgesia, has an excitatory effect on neurons and can cause myoclonus and, rarely, a hyperalgesic state. These effects of M3G may be mediated by different receptor mechanisms (Smith et al., 1990). The half-life of morphine is about 2 hours; the half-life of M6G is somewhat longer (Jaffe and Martin, 1990). The duration of analgesia is 4 hours. Slow-release preparations, which permit a twice a day regimen, are safe and effective (Kaiko, 1990); they are generally best used after dose titration with morphine sulfate. Because morphine metabolites are eliminated by glomerular filtration and can accumulate in renal failure leading to an increased incidence of side effects (Osborne et al., 1986), morphine should be used with caution in renal failure. A useful strategy for patients with compromised renal function is to increase the interval of time between doses or use an alternative opioid.

Hydromorphone is another semisynthetic phenanthrene derivative opioid agonist commercially available as a highly water-soluble salt. When administered parenterally 1.3 mg of hydromorphone is equipotent to 10 mg of morphine; it is somewhat shorter acting but has a greater peak effect. Its bioavailability is 30% to 40% with an oral to parenteral ratio of 5:1 (Houde et al., 1986) and a half-life of 1.5 to 2 hours. Because of its high potency and water solubility, hydromorphone is the drug of choice via a subcutaneous route.

Levorphanol is a synthetic opioid agonist structurally related to the phenanthrene-derivative opiates. A potent mu agonist, it also binds to delta and kappa receptors (Pasternak, 1993; Tive et al., 1992). When administered parenterally, 2 mg of levorphanol is equianalgesic to 10 mg of morphine (Kaiko et al., 1981). The drug also has good oral efficacy with an intramuscular/oral ratio of 0.5. It has a half-life of 12 to 30 hours (Dixon, 1986), and its duration of analgesia is 4 to 6 hours. Therefore, repeated administration is associated with accumulation; a dose reduction may be required 2 to 4 days after starting the drug to avoid side effects from overdosage. For the

same reason, it is best avoided by patients with impaired renal function or encephalopathy. It is sometimes useful as second-line drug for patients who cannot tolerate morphine.

Methadone is a synthetic diphenylheptane opioid mu agonist (Jaffee and Martin, 1990). The equianalgesic dose of 1 mg of methadone ranges from 4 to 10 mg of morphine sulfate (MSO6) (Ripamonte et al., 1998). An inexpensive and effective analgesic, its use is limited by the need for carefully individualized dosing and interval titration. Methadone is rapidly absorbed within 30 minutes of oral dosing, with bioavailability ranging from 41% to 99% (Meresaar et al., 1981). Plasma levels decline in a biexponential manner with a half-life of 2 to 3 hours during the initial phase and 15 to 60 hours during the terminal phase (Sawe, 1986); this biexponential decline accounts for its relatively short analgesic action of 4 to 6 hours (Beaver et al., 1967) and the tendency for drug accumulation with repeated dosing. A reduction of dose and interval of frequency are often needed during the first days of treatment to prevent side effects from overdosage. In addition, when urine pH exceeds 6, renal clearance of methadone is significantly decreased (Inturrisi and Foley, 1984); patients with cancer and patients 65 years of age or older have a decreased clearance; and plasma protein binding and rate of hepatic extraction also influence the highly variable half-life of this substance (Inturrisi et al., 1987).

Despite these and other factors that determine the need for a careful individual titration, it is an extremely effective second-line drug for patients who experience unrelieved pain and intolerable side effects with the use of morphine (Morley et al., 1992). Because of its low cost it could be excellent for use in developing countries or for patients requiring very high doses of opioids. The rare patient allergic to morphine might benefit from methadone because it has a different chemical structure (Morley et al., 1993). Methadone is excreted almost exclusively in the feces and has been proposed as a safe and effective analgesic for patients with chronic renal failure (Kreek et al., 1980). A possible mechanism for the action of methadone is the prevention of monoamine reuptake in the periaqueductal gray matter and presynaptic inhibition of *N*-methyl-D-aspartate (NMDA) receptors. Hence, methadone may offer advantages for patients with opioid tolerance and also for intractable neuropathic pain states (Gorman et al., 1997; Codd et al., 1995; Ebert et al., 1995; Davis and Inturrisi, 1999). Guidelines for methadone usage are now available (Davis and Walsh, 2001).

Fentanyl is a synthetic phenylpiperidine-derivative opioid agonist that interacts primarily with mu receptors (Jaffe and Martin, 1990). It is 80-fold more potent than morphine and is highly lipophilic; these properties render it as a suitable candidate when a transdermal route for opiate analgesia is desirable. Following results from the first clinical study in patients with cancer pain (Miser et al., 1989), the use of transdermal fentanyl became popular. Its use, however, should be limited to patients with chronic pain who are unable to take drugs by mouth and who do not require a rapid titration. The transdermal fentanyl therapeutic system delivers drug continuously to the systemic circulation for as long as 72 hours. The skin permeability constant of fentanyl is approximately 0.0021 ml/min/cm^2 (Michaels et al., 1975), a figure that is 60- to 120-fold lower than regional blood flow to the skin of the chest (Hwang et al., 1991). A special rate-controlling membrane provides additional control of drug release; only extreme conditions, such as the cutaneous blood supply being completely cut off, would therefore influence absorption.

The transdermal absorption of fentanyl is the same from chest, abdomen, and thigh (Roy and Flynn, 1990). A skin reaction at the application site occurs in 4% of patients (Hwang et al., 1991), although there is no skin sensitization. After application of the transdermal patch, systemic absorption is very low in a 0 to 4 hour period, increases in the 4 to 8 hour period, and remains relatively constant, with a coefficient of variation of 28%, from 8 to 24 hours (Varvel et al., 1989). The initial delay is likely due to the time required to establish a reservoir of fentanyl in the stratum corneum. Patients reach steady-state concentrations within 12 to 24 hours from application; adjustments in efficacy and toxicity can, therefore, be made on a daily basis. Following removal of the transdermal patch, serum fentanyl concentration falls about 50% in approximately 16 hours. This apparently long half-life is probably caused by the slow wash out of the cutaneous reservoir. These considerations translate clinically into a several hour delay in the onset of analgesia after an initial application and a persistence of analgesia and eventual side effects long after removal of the transdermal system. For patients with chronic pain, after a variable period of titration, it is possible to obtain relatively constant

serum fentanyl concentrations comparable with continuous intravenous or subcutaneous infusions (Southam et al., 1991).

Fentanyl also has an important role via epidural and intrathecal routes. A more recent use of oral transmucosal fentanyl, which has been approved by the FDA, is for the treatment of breakthrough pain; initial pain relief was noted within a few minutes, with maximum effect occurring in 20 to 30 minutes (Fine et al., 1991).

Sufentanil, a synthetic derivative of fentanyl, is 5 to 10 times more potent, and it is generally reserved for anesthesia. As clinical familiarity with this agent increases and other routes of administration besides injection become available, it is expected that the use of sufentanil will increase for patients with cancer pain, especially those who are highly tolerant to opioids. Good results have been reported from intravenous use (including patient-controlled analgesia [PCA]) and in subcutaneous infusions in the context of palliative care (Paix et al., 1995). According to one report, sufentanil can be used successfully for breakthrough pain when applied sublingually (Paix et al., 1995; Kunz et al., 1993). In addition, neuraxial application is occasionally used for some patients.

ROUTES OF ANALGESIC DELIVERY

The onset, peak, and duration of analgesia vary with the drug used, the route of administration, and the individual patient. Recognition of this variability allows the appropriate choice of drug, route, and scheduling. When undertaking sequential trials of different opiates one-half of the calculated equianalgesic dose is recommended for initial titration (Foley, 1984).

For patients with acute severe pain, parenteral morphine is the opioid of choice. The drug should be titrated to effect, with boluses repeated every 15 minutes, if necessary, until either analgesia or intolerable side effects develop. The concomitant use of an anti-inflammatory drug is often warranted. An antiemetic might be needed. When the intensity of pain decreases to a bearable level, a continuous infusion of morphine should be started; the initial hourly dose can be obtained by dividing the total loading dose by three to four (the duration of analgesia after single morphine doses is 3 to 4 hours). Patients receiving chronic opioid therapy may require very high doses to control acute exacerbations of pain. An infusion pump with a device for self-administration of extra doses of medication every few minutes (PCA) should be used if available (Citron et al., 1986). The PCA dose can be as high as the hourly rate during the titration phase and when incident pain is a concern. The continuous basal rate should be adjusted frequently on the basis of the patient's self-reporting and the PCA usage.

When venous access is problematic the subcutaneous route should be used. It is good practice to avoid the intramuscular route. Once the exacerbation of the patient's acute pain abates, an oral route should be used. If the oral route is impractical, a transdermal system is available (Miser et al., 1989). An oral transmucosal route may be effective for rescue doses, but absorption is usually inadequate for more sustained relief; the same is true of the rectal route, which, in addition, is often uncomfortable for the patient and caregiver. Long-term intravenous opioid administration can be used for patients with central venous access who cannot take oral drugs (Portenoy et al., 1986). Long-term subcutaneous administration is a very effective alternative (Bruera et al., 1985).

For patients with mild to moderate pain, oral analgesics such as oxycodone or codeine are appropriate choices (World Health Organization, 1986). Fixed combinations with nonopioid analgesics are generally not advisable because they might limit the carefully individualized titration, which is the basis for therapeutic success.

Adjuvant analgesics (Table 23–6) should be given early in the pain treatment course (World Health Organization, 1986); like the opioids, they should be administered at regular intervals. Acetaminophen or NSAID medications should always be given unless contraindicated. Steroids can be highly effective in treating pain from direct tumor invasion of neural and somatic structures (Bruera et al., 1985); their side effects are numerous and well known but often without consequence in the terminal stages of life. Anticonvulsants are used for lancinating, paroxysmal pain. Antidepressants are used for dysesthetic pain, although no controlled studies of them in a cancer population are available. Neuroleptics and benzodiazepines are useful for some patients. Ketamine has been reported to be effective when the patient's pain does not respond to massive doses of opiates (Jaffe and Martin, 1990; Kanamaru et al., 1990). A putative mechanism is through reversing tolerance.

Table 23–6. Adjuvant Medications for Cancer Pain

Drug	*Therapeutic Effects*	*Comments*	*Dosage*
Antidepressants			
Amitriptyline	Analgesic, elevates mood, induces sleep	Effective for neuropathic pain	Start with 10–25 mg HS; increase gradually to 75–100 mg HS
Desipramine (Norpramin)	Analgesic, elevates mood	Effective for neuropathic pain	25–150 mg/day, orally
Doxepin	Analgesic, elevates mood, induces sleep	Effective for neuropathic pain	Start with 10–20 mg HS; increase gradually to 75–100 mg HS
Imipramine	Analgesic, elevates mood	Effective for neuropathic pain	200 mg HS for severe depression
Nortriptyline	Analgesic, elevates mood	Effective for neuropathic pain	Start with 10–25 mg HS; increase gradually to 75–100 mg HS
Venlafaxine	Analgesic, elevates mood	Effective for neuropathic pain	—
Anticonvulsants			
Carbamazepine	Anticonvulsant, decreases abnormal CNS neuronal activity	Useful for neuropathic pain; hematologic monitoring suggested	Start with 100 mg daily; increase by 100 mg q4d to 500–800 mg/d
Phenytoin	Anticonvulsant, decreases abnormal CNS neuronal activity	Useful for neuropathic pain; hematologic monitoring suggested	Start with 100 mg/d; increase by 25–50 mg q4d to 250–300 mg/day
Gabapentin	Anticonvulsant, decreases abnormal CNS neuronal activity	Useful for neuropathic pain; better toxicity profile	300 mg to 900 mg tid
Lamotrigine	Treatment of trigeminal neuralgia, migraine headaches, diabetic neuropathy	Inhibitor of voltage gated Na+ channels; suppresses glutamate release and inhibits serotonin reuptake	25–50 mg/day, increased by 50 mg/week, until max 900 mg bid or tid
Topirimate	Treatment of cluster headaches, diabetic neuropathy	Increases CNS GABA levels, blocks AMPA kainate excitatory receptors	200–400 mg/d with bid dosing. Start at 25 mg bid increasing 50 mg each week
Oxcarbazepine	Treatment of trigeminal neuralgia, neuropathic pain states	Blockade of voltage-gated Na^+ channels	300–600 mg/day, up to a max 1200–2400 mg/day
Zonisamide	Trials ongoing	Na^+ channel blockade; T-type Ca^{2+} channel blockade	
Tigabine	Neuropathic pain	GABA reuptake inhibitor	—
Corticosteroids			
Prednisolone	Potentiates analgesia, elevates mood	Effective for pain caused by compression of nerves, spinal cord, or intracranial contents; risk of GI bleeding	10 mg tid PO

(*Continued*)

Table 23–6. Adjuvant Medications for Cancer Pain (*Continued*)

Drug	*Therapeutic Effects*	*Comments*	*Dosage*
Dexamethasone	Improves appetite		≥4 mg PO q6h
Phenothiazines			
Methotrimeprazine	Produces moderate analgesia without risk of tolerance or physical dependence	Used as an alternative to narcotics if they are contraindicated	10–20 mg IM or 20–30 mg PO
Chlorpromazine	Reduces anxiety and psychotic behavior	Risk of orthostatic hypotension; rarely causes jaundice and neurologic reaction	10–25 mg q4–8h
Prochlorperazine	Antiemetic, no analgesic effect		5–10 mg q4–8h
Amphetamines			
Dextroamphetamine	Potentiates narcotic analgesia; elevates mood	For terminally ill patients with pain, depression, and lethargy	2.5 mg tid or 5 mg/day PO in morning
Methamphetamine	Potentiates narcotic analgesia; elevates mood	For terminally ill patients with pain, depression, and lethargy	5 mg in morning
Methylphenidate	Potentiates narcotic analgesia; elevates mood	For terminally ill patients with pain, depression, and lethargy	5–10 mg bid; AM and midday
Anxiolytics			
Hydroxyzine	Potentiates opioid analgesia; reduces anxiety; antiemetic; sedative	Convulsions occur >500 mg/day	Start with 25 mg tid PO; increase to 50–100 mg q4–6h
Diazepam	Relieves acute anxiety and panic; antiemetic; sedative	More antiemetic and fewer sedative effects than chlorpromazine; risk of orthostatic hypotension and hypotonia	5–10 mg PO, IV, or rectally bid or tid

HS, at bedtime.

The epidural, intrathecal, and intracerebroventricular routes are reserved for the patient who fails a careful and sequential trial of different opiates and adjuvants.

GUIDELINES FOR THE USE OF OPIOID ANALGESICS

This section details a practical approach for individualizing treatment for each patient so as to provide optimal control of pain.

Start with a Specific Drug for a Specific Type of Pain

Parenteral morphine is the drug of choice for patients with acute severe pain. Oral analgesics such as codeine or hydrocodone are appropriate choices for patients with mild to moderate pain. Although meperidine is also used for this level of pain, its relatively poor oral potency and the stimulatory CNS effects of its metabolite normeperidine makes this a poor choice for chronic administration for most cancer patients (Kaiko et al., 1983).

Know the Pharmacology of the Drug Prescribed

Type of Drug

The opioid antagonist drugs produce psychotomimetic effects with increasing doses. Patients previously exposed to an opioid agonist are exquisitely sensitive to opioid antagonists. Administering an opioid antagonist such as pentazocine (Talwin) may precipitate an acute withdrawal state in such patients.

Duration of Analgesic Effects

The onset, peak, and duration of analgesic effect vary with each drug and its route of administration. Each drug has a specific time course of effectiveness. For example, methadone and levorphanol act for only 5 to 6 hours, whereas morphine (immediate release) and hydromorphone are effective for 3 to 4 hours. Sustained-release morphine may be active for 8 to 12 hours. In general, drugs administered by mouth have a slower onset of action and longer duration of effect, whereas drugs given parenterally have a rapid onset of action but a shorter duration of effect.

Pharmacokinetics of the Drug

Plasma levels of opioid analgesics do not correlate directly with their analgesic effect. More importantly, the plasma half-life of the drug, which reflects its route of elimination, does not correlate with its analgesic properties. Opioids such as methadone (half-life 17 to 50 hours) and levorphanol (half-life 12 to 16 hours) produce analgesic effects for only 5 to 6 hours and must be given at 4 to 6 hour intervals to maintain adequate analgesia. However, because of their long half-life, these drugs accumulate in plasma, which may account for their side effects with repeated administration. Adjustment of dose and dosing interval may be necessary during the initial use of these drugs. For this reason, they are generally not considered to be first-line agents for cancer pain management.

Equianalgesic Doses for the Opioid and its Route of Administration

Table 23–7 lists the equianalgesic doses of the commonly used opioid analgesics. These doses have been derived from double-blind relative potency studies by Houde and colleagues (1966) and provide a useful reference when switching from one opioid drug to another and from one route of administration to another. Unfamiliarity with these doses is one of the most common causes of undermedicating patients with pain. Special care should be exercised when switching to methadone, which is more potent, with a conversion ratio varying between 4 and 10 (Bruera et al., 1996; Lawlor et al., 1998; Ripamonti et al., 1998).

Administer Analgesics Regularly

Medication should be administered on an around-the-clock basis. This approach will keep pain at a tolerable level and limit the patient's anxiety about medication. It may also allow for a reduction in the total amount of drug given during a 24 hour period. Studies by Fordyce (1983) suggest that such an approach reduces abnormal pain behavior in hospitalized patients. The pharmacologic effect is to maintain plasma

Table 23–7. Equianalgesic Dosing and Conversion Table*

Opioid	*Parenteral Opioid to Parenteral Morphine*	*Parenteral Opioid to Oral Opioid*	*Oral Opioid to Oral Morphine*	*Oral Morphine to Oral Opioid*
Morphine	1	2.5	1	1
Hydromorphone	5	2	5	0.2
Meperidine	0.13	4	0.1	10
Levorphanol	5	2	5	0.2
Codeine	NA	NA	0.15	7
Oxycodone	NA	NA	1.5	0.7
Hydrocodone	NA	NA	0.15	7

NA, not applicable.

*Steps to use the table: *(1)* Take the total amount of opioid that effectively controls pain in 24 hours; *(2)* multiply by the conversion factor in the table and give 30% less of the new opioid to avoid partial cross tolerance; and *(3)* divide by the number of doses/day.

levels of the circulating drug in an effective dose range.

Use a Combination of Drugs

The additive effects of aspirin and acetaminophen when combined with morphine have been well demonstrated in clinical studies. Practically speaking, the addition on a regular basis of 650 mg of aspirin or acetaminophen to the standard opioid dose will often enhance analgesia without requiring escalation of the opioid drug dose. Antiemetic agents such as metoclopramide may be useful for suppressing nausea and vomiting, which can be caused by an opioid drug or underlying (GI or CNS) pathology. In special instances, the use of muscle relaxants and antianxiety drugs may be helpful, but these drugs often produce sedation. Both diazepam (Valium) and chlorpromazine (Thorazine) have been reported to have antianalgesic effects. The sedating effects of these drugs may limit the amount of opioid analgesic used. This practice is often a disservice to the patient who is oversedated with drugs that are not primarily analgesics. Appropriate treatment of pain will often lead to a marked reduction in anxiety, making the usefulness of antianxiety drugs specious. Amitriptyline used as a hypnotic drug for patients with pain may enhance analgesia, especially for neuropathic pain (Watson et al., 1982). In bedtime doses as low as 25 to 50 mg, it can be a useful adjunctive medication.

Gear the Route of Administration to the Patient's Needs

Oral administration has a slower onset of action than parenteral administration. Parenteral administration is the route of choice for patients who require immediate relief. For patients who cannot take oral drugs or for whom parenteral administration is contraindicated, the rectal route should be considered. Oxymorphone (Numorphan) and hydromorphone (Dilaudid) suppositories are available. Intravenous administration of an opioid produces the most rapid onset of action, with analgesia occurring 10 to 15 minutes following its administration. However, the duration of analgesia is also markedly reduced, requiring frequent dosing at 1 to 2 hour intervals. Continuous intravenous infusion of drugs is important for some hospitalized patients (Portenoy et al., 1986; Miser et al., 1980). Infusions can maintain therapeutic plasma levels and obviate difficulties inherent to erratic absorption. The starting intravenous dose is usually one-half the parenteral dose, but must be adjusted to the needs of the patient. Subcutaneous infusions using portable pumps have also been effective (Bruera et al., 1985).

Side Effects of Opioids

Diminution or elimination of side effects is an important aspect of effective opioid therapy. With few

exceptions, dose readjustment should be the first measure taken to manage adverse reactions.

Constipation. Constipation is one of the most common side effects and tends to be refractory to treatment. Because tolerance develops very slowly if it develops, patients will likely require regular laxative treatment for the duration of opioid therapy. A bowel stimulant (e.g., Senna) and a softening agent (e.g., Docusate) is the combination most commonly used. Single-agent prophylaxis with gradual increments may be necessary to reach the desired effect, which is assessed by the patient's subjective reports as well as by clinical examination, sometimes necessitating imaging of the abdomen. Resorting to an osmotic laxative such as lactulose or bowel preparations is reserved for severe cases and might produce diarrhea. As a back-up measure, bowel lavage can be used in refractory cases until regular bowel movements are restored. Caution should be exercised with patients in whom constipation could be due to ileus or intestinal obstruction, which is not uncommon in cases of abdominal and pelvic malignancies. Occasionally, oral naloxone or methylnaltrexone has been tried to manage particularly severe cases of constipation (Chater et al., 1998; Ellison et al., 1997).

Nausea and Vomiting. Nausea and vomiting are the second most common side effects. Tolerance usually occurs within the first few days of opioid administration. It is useful to attempt to determine the dominant mechanism (central versus peripheral) to guide therapy with neuroleptics versus motility agents, respectively. Metoclopramide is frequently used because of its multiple mechanisms of action that antagonize opioids both at the chemoreceptor trigger zone and in the GI tract. Other agents include prochlorperazine, diphenhydramine, butyrophenones, serotonin antagonists such as ondansetron, benzodiazepines, and steroids. A more aggressive approach should be taken for patients who are also receiving a chemotherapy regimen.

Sedation. Sedation is a commonly encountered side effect often signifying excessive dosing. Downward titration of the dose to the level of analgesia is recommended. Drug combinations of opioids and other adjuvant medications create an opioid sparing effect, thereby minimizing a sedative side effect. If the sedation tends to be refractory, the addition of a CNS stimulant (e.g., methylphenidate or dextroamphetamine) with upward titration might help (Bruera et al., 1989a). Methylphenidate is started with an initial dose of 5 mg on awakening and 5 mg at noon and can be titrated up until a response is achieved.

Cognitive Impairment. Patients who undergo a significant increase in the dose of intermittent narcotics experience significant cognitive impairment for approximately 1 week after dose escalation (Bruera et al., 1989b). At other times, alternative sources for cognitive impairment should be aggressively sought before opioid medications are implicated as the cause. Delirium, hallucinations, agitation, or somnolence can occur with sepsis, leptomeningeal disease, brain metastases, metabolic derangements (especially hypercalcemia), ifosfamide therapy (Merimsky et al., 1992), radiation-induced encephalopathy (Crossen et al., 1994), and hepatic encephalopathy.

Cancer patients often take a variety of psychotropic medications for depression and other conditions. Alone or in conjunction with opioids, these may produce mental status changes. Benzodiazepines, in combination with opioids and other psychotropic drugs, tend to produce sedation, dizziness, and cognitive impairment. If opioids are causing cognitive impairment, the initial step should be to lower the dose, the results of which can also be diagnostic. It is highly recommended that other medications to treat agitation or other symptoms should not be added. If manipulation of the analgesic regimen, including rotation of the opioids used, is not effective, haloperidol or a drug from the same class may be considered.

Respiratory Depression. Respiratory depression is a rare occurrence in patients receiving chronic opioid therapy as tolerance to this action of opioid drugs usually develops after a short period of time. However, this adverse effect has been known to result from accidental administration of a very large dose of drugs due to miscommunication about the concentration and unit set on the PCA pumps. As long as respiratory function is not significantly impaired, temporary discontinuation and recommencement at a lower dose when recovery becomes evident are recommended. Opioids taken in combination with benzodiapines is a common cause of respiratory problems. When respiration is compromised and causes derangements in blood gas values, the opioid antagonist naloxone should be titrated to response in 40 μg

increments. This action can help avoid inducing a withdrawal syndrome. Cases of tachyarrhythmias leading to myocardial compromise as well as pulmonary edema have been observed with a bolus dose of 400 μg of naloxone, as commonly recommended in most major textbooks on pain management. Occasionally, a continuous infusion of naloxone is required to prevent recurrence of respiratory depression because of its short half-life.

Myoclonus. Myoclonus is a dose-dependent phenomenon presumably related to opioid metabolites, mainly those of meperidine, which cause central motor excitability and might indicate that the patient's level of tolerance is being overwhelmed. A simple dose adjustment may abate the symptoms, but occasionally rotation of opioids or addition of a benzodiazepine, specifically clonazepam, becomes necessary.

Urinary Retention. Urinary retention is a relatively rare adverse reaction usually observed in very old and very young patients and is most likely to occur when concomitantly administered with medications having anticholinergic properties. Tolerance occurs rapidly and occasionally requires temporary catheterization.

Watch for the Development of Tolerance

Tolerance occurs in all patients taking opioids chronically. "Tolerance" describes the inevitable resistance to the analgesic effect of a drug, necessitating increasing doses of the drug to maintain analgesia. Tolerance develops to all of the effects of opioid drugs, but at varying rates. The earliest sign of developing tolerance is the patient's complaint that the duration of effective analgesia has decreased so that increasing the frequency of administration or the amount of drug at each dose is necessary to overcome tolerance. Cross-tolerance among the opioid drugs occurs, but it is not complete, and, therefore, switching from one opioid drug to another in an individual patient can provide more adequate pain control. This is best accomplished by switching to an alternative opioid drug but using a dose one-half the equianalgesic dose as the starting dose and slowly escalating the dose.

Withdraw the Medication Slowly

Abrupt withdrawal of opioid analgesics after their chronic use produces agitation, tremors, insomnia, fever, and marked autonomic nervous system hyperexcitability. Slowly tapering the dose prevents such symptomatology. The appearance of abstinence symptoms after drug withdrawal is related to the elimination curve of the particular drug. The nature of abstinence symptoms similarly varies with the individual drug; for example, with morphine, withdrawal symptoms will occur within 6 to 12 hours following cessation. Reinstituting administration of the drug in doses of approximately 25% of the previous daily dose suppresses these symptoms.

Respect Individual Differences Among Patients

The metabolism of opioid drugs is variable. Individual variations in analgesia and side effects commonly have a pharmacologic basis rather than being caused by the "psychological" state of the patient. All attempts should be made to optimize therapy for each patient.

Do Not Use Placebos to Assess the Nature of the Pain

The placebo response is a potent phenomenon in clinical medicine, but its appropriate use is not widely recognized (Lasagna et al., 1954; Goodwin et al., 1979). For a patient with pain, a positive analgesic effect from intramuscular saline suggests that the patient is a placebo responder. It does not suggest that the patient's pain is "unreal" or less severe than reported. Such misuse of placebos tends to create mistrust between patient and physician, which can interfere with adequate pain control.

COMPLICATIONS OF OPIOID ANALGESICS

In general, there are no demonstrable long-term effects on intellectual function of the chronic use of opioids; no definable deterioration in personality testing; and no important long-term metabolic derangements (although transient endocrine abnormalities occur with disruption of the normal hypothalamic-pituitary axis, which reverts to normal with continued use of the drug). Chronic opioid use may produce sustained elevation of albumin with increased albumin synthesis, although this is almost never clinically significant. The major complications of the opioid analgesics are as follows.

Tolerance

The development of tolerance results in escalation of the dose of drug necessary to provide adequate analgesia, which has been previously discussed. For the cancer patient, a rapid escalation of opioid requirements is often associated with increased pain from progressive tumor growth.

Physical Dependence

"Physical dependence" describes the phenomenon of withdrawal with acute discontinuance of the opioid drug or with administration of an opioid antagonist.

Addiction

Tolerance and physical dependence are both predictable pharmacologic effects of chronic opioid administration. These states are distinct from psychological dependence (addiction) in which there is a concomitant behavioral pattern of drug abuse by an individual who craves a drug for other than pain relief. Fear of addiction limits the use of opioid analgesics in clinical practice; however, there are few available published data that delineate the degree of addiction in patients receiving opioid analgesics for cancer and pain.

Many of the studies before 1954 present a biased view by using opioid addicts admitted to a treatment facility as the subjects of their studies. In another prospective study, Porter and Jick (1980) monitored the incidence of opioid addiction in 11,882 hospitalized medical patients who received at least one opioid preparation. There were only four cases of reasonably well-documented addiction in patients who had no history of addiction. Analysis of the patterns of drug intake in a series of cancer patients receiving opioid analgesics chronically suggests that drug abuse and psychological dependence did not occur in the population of patients with cancer (Kanner et al., 1981). The dearth of clinical studies offers limited support to the belief that chronic opioid use for analgesia is associated with a high risk of addiction.

Overdose

Escalating the dose of a drug to maintain adequate analgesia may lead to excessive sedation and respiratory depression. Respiratory depression in patients receiving opioids on a chronic basis is rare, however. Use of naloxone to reverse the effect of sedation and respiratory depression should be undertaken with extreme caution. Thorough evaluation of respiratory status, which involves respiratory rate, oxygen saturation, and sedation intensity, should be assessed before routinely giving an ampoule of naloxone. Generally, only close observation is required while the effects of the opioids slowly subside.

For patients chronically receiving opioids, diluted doses of naloxone (0.4 mg in 10 cc saline) should be titrated carefully to prevent severe withdrawal symptoms while reversing respiratory depression. For the comatose patient, an endotracheal tube should be placed before naloxone administration to prevent aspiration-associated respiratory compromise with excessive salivation and bronchial spasm. For patients with cancer who take opioid analgesics chronically and who develop the side effects of excessive sedation or respiratory depression, excessive drug intake is rarely the cause of stupor. More commonly, the cause is medical deterioration of the patient with a superimposed metabolic encephalopathy. Reducing the dose of the opioid drug with careful assessment of the patient's metabolic status will usually provide the diagnosis.

Inappropriate Antidiuretic Hormone Syndrome

Inappropriate antidiuretic hormone syndrome occurs rarely and is usually transient. It occurs most commonly with morphine and methadone.

Drug Interactions Involving Opioids

Examples of drug interactions with meperidine, methadone, and propoxyphene are as follows (Inturrisi and Foley, 1984).

1. Meperidine with phenobarbital: Phenobarbital enhances *N*-demethylation of meperidine. Increasing the metabolite normeperidine produces CNS toxic effects without added analgesia.
2. Meperidine with monoamine oxidase inhibitors: This combination may produce malignant hyperthermia, which may be fatal.
3. Methadone with rifampin: Rifampin induces opioid withdrawal by lowering plasma concentrations of the drugs and increasing urinary excretion of its major metabolite.

4. Propoxyphene with phenytoin: Propoxyphene interferes with Dilantin metabolism by inhibiting hydroxylating enzymes.

ANALGESIC ADJUVANT DRUGS

Clinical interest in the use of analgesic adjuvant drugs (Table 23–6) in pain management has developed from understanding the neuropharmacology of pain. Recognition of the important role of neurotransmitters in central pain modulation and the ability of these analgesic adjuvant drugs to enhance or block neurotransmitter function has led to clinical trials in painful states.

The analgesic effects of some of these drugs have been well established in controlled clinical trials (i.e., phenytoin or carbamazepine for trigeminal neuralgia; methotrimeprazine for postoperative pain. [Swerdlow, 1984; Lasagna and Kornfield, 1961]), but anecdotal data or clinical surveys provide the rationale for the use of others. Recently, gabapentin in diabetic neuropathy and post-herpetic neuralgia (Backonja et al., 1998; Rowbotham et al., 1998) has been shown to be effective. A number of anecdotal reports show gabapentin to be safe and effective for neuropathic pain. Newer generation anticonvulsants may offer a better side-effect profile (Backonja et al., 1998; Rowbotham et al., 1998).

The clinical use of these drugs to manage cancer pain has not been well established. They have been used primarily as "co-analgesics," intended to increase the analgesic effects of the opioid analgesics either additively or synergistically or to counteract the undesirable side effects of these agents. Therefore, any attempt to develop guidelines for the use of adjuvant drugs in clinical cancer pain management must be prefaced with certain caveats:

1. Appropriate use of the drugs to enhance analgesia or to treat side effects depends on careful assessment of clinical signs and symptoms.
2. The drugs have been developed and released for clinical indications other than analgesia. A partial list of these indications includes nausea, vomiting, anxiety, mania, depression, psychosis, delirium, and epilepsy.
3. The drugs are not as effective in relieving pain as the opioid analgesics, except in certain instances such as methotrimeprazine and amitriptyline (Lasagna and De Kornfield, 1961).
4. There are no efficacy studies for their co-analgesic properties in cancer patients.
5. The choice of adjuvants should be individualized, using the simplest and most potent combination of drugs.

These caveats notwithstanding, attention to and inclusion of these drugs in the management of pain must be at least considered, but caution must be used when designing guidelines based on anecdotal information.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are the main group of antidepressants currently being used for the purpose of treating neuropathic pain syndromes. Several theories have been suggested to explain their analgesic properties, yet none has yet been proved (Magni, 1991). They probably act by inhibiting serotonin and norepinephrine reuptake by nerve endings in the spinal cord and brain. Their pharmacologic action is independent of their mood-altering effects, and they either exert an inherent influence over the nervous system or modulate opioid pathways by an unknown mechanism (Haddox, 1992). These agents, because of their nonanalgesic properties, are particularly useful for patients who are depressed or have insomnia, conditions that are frequently encountered in the cancer pain patient population.

Tricyclic antidepressants are not universally tolerated especially at the initiation of therapy and often have to be discontinued or decreased due to dose-limiting side effects, most commonly anticholinergic and sedative effects. Amitriptyline and nortriptyline (lower cardiovascular side-effect profile) are thought to be the most efficacious agents and are the most often used. The dose should be gradually escalated from 10 mg, and patients should be told that the full benefit does not occur until after the first week or two of therapy.

Anticonvulsants

Anticonvulsants have been traditionally used with good results to treat diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, and similar

syndromes (Kloke et al., 1991), which has encouraged researchers to conduct trials of these drugs with other types of pain with variable outcomes. Although the conditions listed above can co-exist in cancer patients, space-occupying lesions cause the most significant pain secondary to brachial and lumbosacral plexopathies. Phantom pain is also commonly seen in our practice and can be treated with anticonvulsants.

Phenytoin, valproate, carbamazepine, and clonazepam have been used. Because of issues regarding their safety and side effects, their use has been strictly limited to pain control to situations when they are most needed, namely, neuropathic pain.

Gabapentin can be considered a breakthrough drug in this regard. Despite its lack of domination in the field of seizure control, the opposite can be said for its place in pain management. With its wide therapeutic window and similar (or better) efficacy compared with other anticonvulsants, gabapentin was very beneficial for clinicians prescribing anticonvulsants because there is no need to monitor blood levels or perform other clinical testing during its administration. Sedation is a side effect, which can be reduced by starting therapy at 100 mg tid and adding 100 mg to each dose every second or third day until the desired effect is acquired. If necessary, dose escalation up to 3600 mg/day is recommended.

Lidocaine

Analgesia from the sodium channel blocking activity of lidocaine can be derived from systemic administration, as evidenced by several case reports. Like gabapentin, the greatest benefit is acquired in neuropathic pain syndromes and in phantom pain with mainly central features (Nagaro et al., 1995; Brose and Cousins, 1991). Slow-rate infusions have been used as a third or fourth line of treatment, especially for opioid-tolerant patients. Incremental rate infusions over 20 to 30 minutes can, on the other hand, be used as a therapeutic test before starting the oral form of mexiletine in patients where anticonvulsants are not effective. Cardiac monitoring is mandatory.

Ketamine

The analgesic properties of ketamine, an anesthetic agent (NMDA receptor antagonist), have been well documented. Over the past 10 years, a large series of reports of its use as an analgesic in subanesthetic doses, mainly in cancer patients, have been published (Mercadante et al., 1995; Clark and Kalan, 1995; Yang et al., 1996). Ketamine can be used in cases of extreme opioid tolerance and for long-term palliative care. Starting doses of 150 mg/day by subcutaneous infusion or 1 mg every 12 hours intrathecally have been suggested (Yang et al., 1996). It is also available in oral and rectal forms. In the authors' experience, ketamine is particularly beneficial for counteracting opioid tolerance in patients taking chronic high-dose opioids and undergoing surgery. Additional investigations and clinical trials are needed before ketamine is used routinely.

Capsaicin

Due to its high toxicity profile, capsaicin is used only as a topical cream to treat neuropathic pain (Ellison et al., 1997). It acts by inhibiting substance P formation at the skin. It is effective in only 50% to 60% of patients.

Miscellaneous Drugs

In refractory pain situations, drugs from other classes have been tried, some with potentially good responses and others with only a minimal response. They include psychotropic drugs (Breitbart, 1998; Patt et al., 1994), benzodiazepines (Reddy and Patt, 1994), bisphosphonates (Bruera et al., 1996), steroids, radiopharmaceuticals (^{89}Strontium, Sumarium), antibiotics in infection, and occasionally in head and neck cancer patients (Bruera et al., 1996). Recent studies have concluded that pamidronate or a drug from that class can be used routinely for metastatic bone disease, especially in breast cancer.

PHYSICAL MEDICINE APPROACHES: NONPHARMACOLOGIC, NONINVASIVE TREATMENTS

There has been only limited scientific research into the analgesic benefits of many commonly used treatments, especially in the cancer population. A random survey of American adults was reported in the *New England Journal of Medicine* (Eisenberg et al., 1993) and confirmed that one out of three American adults pays out of pocket to obtain treatment from

"alternative" healthcare providers. The two most commonly used therapies were chiropractic manipulation and massage therapy. The leading medical diagnosis for which such treatments were obtained was chronic back pain. Chiropractic bony adjustments of the skeleton and massage therapy (soft-tissue manipulation) are part of a spectrum of manipulative interventions that also includes orthopedic and osteopathic manipulation and physical treatment modalities usually delivered by physical therapists.

Physical Therapy

The true incidence of musculoskeletal conditions in cancer patients is unknown. Major deforming surgical procedures of the neck, trunk, and extremities may result in musculoskeletal imbalances. Physical treatments such as massage, ultrasound, hydrotherapy, electroacupuncture, and trigger point injection are clinically indicated for musculoskeletal pain. Skillful soft tissue manipulation is probably underutilized in the traditional medical setting. Exercises for strength, general conditioning, and ambulation training are necessary components of an overall rehabilitation program (see Chapter 22).

The use of "passive" modalities of treatment has been criticized in the setting of chronic nonmalignant pain, due to the potential reinforcement of dependency on caregivers. However, cancer patients often feel stigmatized and socially isolated. A physical demonstration of caring through a "hands-on" method, if it alleviates this, might offset the possible negative outcome of reinforced dependency.

Physiologic and Psychological Effects of Massage

Massage may be studied in terms of the physiologic basis of its effects; the psychological effects; the effects of different techniques; effects on tissue, organ or system; or its application as a treatment for a specific condition. Massage therapy has been shown to reduce pain intensity in nonmalignant chronic pain and headache (Konrad et al., 1992; Koes et al., 1992; Jensen et al., 1990; Puustjarvi et al., 1990). Limited data suggest that massage might serve as a useful adjunctive therapy for cancer pain. One study has demonstrated that patient acceptance of this type of treatment is high (Engel et al., 1987); complications are unusual (Tachi et al., 1990).

Other Physical Therapy Modalities

The application of thermal agents produces analgesia through the physiologic responses of the tissues treated. Heat may be applied superficially or deeply. Counterirritation with topical salves may act through the depletion of analgesic mediators such as substance P.

Electrical stimulation of surface tissues may produce analgesia via amplification of non-noxious inputs that interfere with nociceptive transmission of sensation at the level of the dorsal horn. Stimulation of spinal cord or brain stem structures is thought to activate segmental or descending modulating influences, which inhibit ascending nociceptive transmission.

Traction may be applied manually by a therapist or with various devices. This is effective for stretching soft tissue contractures and mobilizing stiff joints and may be useful when these conditions contribute to painful limitation of motion.

Psychological Interventions

Providing analgesia through pharmacologic methods helps to mitigate the stress of ongoing pain. Many patients would also like to utilize methods that enhance their sense of personal control and thus assist them in regaining a sense of personal integrity. Psychological strategies are widely employed in the treatment of chronic pain of nonmalignant origin. The psychological treatment of cancer patients has been reviewed elsewhere (Trijsburg et al., 1992). New cognitive strategies for coping may need to be learned. Supportive psychotherapy is indicated at times of particular psychological stress on coping mechanisms (Breitbart, 1989) (see Chapter 26.)

Simple relaxation methods can be used for acute and chronic pain. More complex relaxation techniques, such as those that utilize music, imagery, or biofeedback, have also been shown to be effective analgesic methods (ACHPR Acute Pain Guidelines).

NEUROSURGICAL AND ANESTHETIC APPROACHES

A major challenge to the oncologist in managing the patient with intractable pain relates to the timing and selection of alternative therapies. The alternative ther-

apies are often costly and invasive, thereby posing a significant risk of morbidity to the patient, and often are not as convincingly efficacious as first-line treatments.

Standard analgesic therapies such as oral morphine in combination with NSAIDs and adjuvant drugs used in accordance with World Health Organization guidelines should almost always be exhausted before alternative approaches are tried. In addition, the decision to initiate alternative analgesic therapies also implies that no further antitumor treatments will be effective for the management of the primary tumor. As stated before and repeated for emphasis here, treatment failure with conventional analgesic therapies implies titration of all drug therapies to maximum doses, such that the patient reaches dose-limiting side effects, until adequate pain relief is achieved. For most patients with cancer pain, this also means that alternative routes of opioid administration, such as subcutaneous or intravenous infusion and patient-controlled administration (PCA), have been tried and failed.

Both neurosurgical and anesthetic procedures play a small but significant role in the management of cancer pain. According to the AHCPR guidelines, approximately 10% of all cancer patients could benefit from some of these procedures. They are, however, best regarded as complimentary to other therapies, which include primary treatment for cancer, pharmacotherapy, and behavioral and psychiatric approaches.

Principles of anesthetic procedures are as follows:

1. They are useful and/or needed in 10% to 15% of patients.
2. They are not a panacea, but useful when complimentary to other therapies.
3. They are usually reserved for patients with intractable pain, experiencing dose-limiting side effects.
4. Local anesthetic blocks have limited value, but can act as diagnostic tools.
5. Neurolytic blocks have a favorable risk/benefit ratio when given in terminal situations, except for sympathetic blocks like celiac and hypogastric, which some physicians believe are best administered early in the course of treatment.
6. Intrathecal therapy is reserved for pain of the lower body and for patients with a prognosis of at least 6 months or more. Clonidine may help patients with neuropathic pain syndromes.
7. Epidural therapy is preferable for patients with thoracic and lower body pain, especially neuropathic, and for patients with a prognosis of 1 to 3 months. Infection and cost are the limiting factors.
8. Neurosurgical procedures have a limited role secondary to complications and the wider use of pharmacotherapy. Useful neurosurgical procedures include cordotomy and myelotomy.

Types of Anesthetic Nerve Blocks

Somatic Nerve Blocks

Somatic nerve blocks (Table 23–8) may be diagnostic (i.e., to determine an indication for permanent neurolysis of somatic nerves), facilitative, prophylactic, or therapeutic and are indicated for pain that is well characterized, well localized, and somatic in origin. Somatic nerve blocks include paravertebral block for localized chest pain and brachial plexus block for upper extremity pain. Unless a neurolytic agent is used to neurolyze somatic nerves, the local anesthetic block lasts for the duration of local anesthetic effect. However, the neurolytic blocks, which are aimed at chemical destruction of the nerve, may be limited in use secondary to neurologic deficits that may result from the block. Somatic neurolytic blocks may also result in post-block dysesthesias, pain that can be worse than the original pain being treated.

Sympathetic Nerve Blocks

Sympathetic nerve blocks (Table 23–8) are indicated for SMP as well as for visceral pain (e.g., complex regional pain syndrome type 1), or reflex sympathetic dystrophy, visceral pain as in pancreatic cancer, and pelvic pain. A stellate ganglion block is indicated for SMP of the upper extremity (Warfield, 1984). Celiac ganglion blocks are used for pancreatic cancer pain (Bridenbaugh et al, 1964) and hypogastric blocks for pelvic pain (Plancarte et al., 1990). The effects from blocks used with local anesthesia are short lived and are used only for diagnostic and prognostic purposes. If a block with local anesthetic is successful, a neurolytic block with either alcohol or phenol is given to achieve longer lasting relief.

Table 23–8. Anesthetic Approaches for Cancer Pain

*Procedures**	*Usual Indication(s)*	*Examples*
Local anesthetic blocks with or without steroids	Diagnostic blocks. Used to diagnose source of pain and to diagnose type of pain	Stellate ganglion blocks
	Prognostic blocks. Used as a prelude to paravertebral block or neurolytic block	Celiac plexus block
		Epidural steroid injection
		Brachial plexus and lumbar plexus block
Neurolytic blocks† (with alcohol or phenol)	Localized refractory pain that is expected to persist, usually in the presence of a short life expectancy; pain localized to a region that is associated with a low risk of neurologic complications	Alcohol celiac plexus block
		Phenol intercostals saddle block
Thoracic subarachnoid neurolysis	Focal chest wall pain	
Intercostal neurolysis	Focal chest wall pain	
Lumbar subarachnoid neurolysis	Unilateral leg pain in bed-bound patients	
Psoas compartment block	Unilateral pain in upper lumbar dermatomes	
Celiac plexus/splanchnic/neurolysis	Abdominal pain, back pain	
Superior hypogastric plexus neurolysis	Pelvic pain	
Phenol saddle block	Perineal pain with urinary diversion	
Gasserian ganglion	Facial pain	Trigeminal nerve block branches
Spinal analgesics‡	Refractory pain, usually in lower body, but may be widespread or diffuse	Externalized epidural catheter (useful when large volume infusion is needed, e.g., local anesthesia)
		Intrathecal catheter with fully implanted pump (useful when prognosis is expected to be >6 months)

*These blocks are temporary and usually last for the duration of local anesthetic.

†These blocks can cause temporary or permanent neurologic deficits. Hence, they are done if the risk/benefit ratio is favorable (e.g., in terminal cancer situation and localized pain).

‡These procedures are useful if pain is intractable and refractory to other modalities. They offer better risk/benefit ratio versus neurolytic procedures; most helpful for patients with a prognosis of 3 months or more.

Intrathecal/Epidural Analgesia

Administration of opioids and other medications into the neural axis is well documented and widely practiced (Bennett et al., 2000). It is a routine practice in acute pain management as well as for labor pain. However, long-term use of these medications requires special expertise in patient selection and techniques for implantation of devices. The principle underlying this therapy is that a drug can be administered at close proximity to opioid and other receptors, requiring minute quantities while achieving superior analgesia. This assumption has been recently questioned, but for a selected patient population this method may prove to be quite effective. The CNS can be accessed by an epidural, intrathecal, or intraventricular route.

Epidurals are useful for patients who have intractable neuropathic pain that has not responded to either oral or parenteral therapy, and who most likely need a moderate amount of local anesthetic in the epidural space, e.g., lumbosacral plexopathy resulting from a pelvic tumor. But their long-term use is associated with tolerance, infection, and expense. Hence, epidural use is limited to patients whose prog-

nosis is likely to be from 1 to 3 months (Bedder et al., 1991; Hassenbusch et al., 1992).

Intrathecal opioids are indicated for patients with diffuse somatic pain syndromes that do not respond to either oral or parenteral opioid therapy or for patients with dose-limiting side effects from other routes. Intrathecal administration is useful for patients who have bilateral or midline pain below the level of the midthorax (Payne, 1987). However, the pharmacokinetics of spinally administered morphine are such that supraspinal effects such as sedation and nausea/vomiting might not be avoided (Max et al., 1987). Of interest, one study showed that epidural morphine was indistinguishable from systemic morphine in its effect on cognitive function (Sjogren and Banning, 1989). Therefore, spinal morphine administration should not be considered as a first line of therapy for most patients with intractable cancer pain

Administration of opioids by this route requires implantation of a special pump that delivers opioid continuously into the cerebrospinal fluid. Minor surgery is required for implantation. The infection rate is low compared with epidurals because of internalization of the delivery system. In addition to opioids, other medications like clonidine, local anesthetic, and neuronal-specific calcium channel blockers (ziconotide) may be used. Cost is an issue, but may be justified if the pain control provided is stable and the patient's prognosis is expected to be more than 6 months (Bedder et al., 1991; Hassenbusch et al., 1992). This method is best suited for cancer survivors who have intractable chronic pain syndromes resulting from treatment of cancer (e.g., peripheral neuropathy from chemotherapy, post-surgical pain syndromes, and radiation-induced pain).

Neurosurgical Procedures

Neurosurgical procedures (Table 23–9) are infrequently used because of their lack of efficacy, high complication rate, and the wide availability and effective use of opioids and adjuvant medications. Moreover, intrathecal techniques and infusion of various opioids and nonopioids have resulted in a decreased need for neuroablative procedures. Some of the neurosurgical procedures that are still used effectively include pituitary adenolysis (Levin, 1980), percutaneous cordotomy for unilateral lower extremity pain (Rosomoff et al., 1965; Sanders and Zuurmond, 1995), and myelotomy for midline pain (Hassenbusch et al., 1997). Surgical ablation may also be accomplished by rhizotomy (section of nerve root) (Broager, 1974) or dorsal root entry-zone lesions (Nashold and Nashold, 1996). Spinal anterolateral tractotomy, mesencephalotomy, medullary tractotomy, and cingulotomy are rarely performed and should be reserved for carefully selected patients.

Cordotomy may be an alternative for patients with midline sacral or perineal pain who have failed systemic and spinal opioid therapy. This can be accomplished safely by an experienced neurosurgeon using a percutaneous approach to produce a destructive lesion in the spinothalamic tract in the cervical cord. Most patients obtain immediate pain relief, and as

Table 23–9. Neurosurgical Procedures for the Control of Cancer Pain

Operation	*Target Site*	*Method*
Peripheral neurotomy	Sensory or mixed nerve, greater occipital nerve, glossopharyngeal nerves, intercostal nerves, trigeminal divisions, trigeminal spinal	Radiofrequency—thermal, chemical, surgical
Rhizotomy		Radiofrequency—thermal, chemical, surgical
Stereotactic thalamotomy	VPM/VPL basal thalamus	Radiofrequency—thermal
DREZ lesion	Spinal	Radiofrequency—thermal
Cordotomy	C1–2, T2, lower cervical	Radiofrequency—thermal, microsurgical; anterior approach to low cervical
Commisural myelotomy	Segmental, conus medullaris	Microsurgical ± laser
Trigeminal glycerol rhizolysis	Gasserian ganglion	Radiofrequency—thermal, chemical
Hypophysectomy	Pituitary	Open or stereotactic radiofrequency—thermal, chemical, or radiosurgery

many as 60% maintain pain relief for 6 months. Transient urinary retention and ipsilateral paralysis are the most common side effects. Fewer than 1% of patients develop uncomfortable post-cordotomy paresthesia, generally occurring more than 18 months after the procedure. Percutaneous cordotomy should be considered early in the course for a patient with incident pain because the rapid increase in pain with movement does not usually allow adequate treatment with opioids, even when PCA is attempted. However, new pain sites are unmasked in many patients after a unilateral cordotomy, and bilateral procedures are required for the management of midline or bilateral pain.

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