Cancer Pain and Analgesia

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Pain ranges in prevalence from 14–100% among cancer patients and occurs in 50–70% of those in active treatment. Cancer pain may result from direct invasion of tumor into nerves, bones, soft tissue, ligaments, and fascia, and may induce visceral pain through distension and obstruction. Cancer pain is multifaceted. Clinicians may describe cancer pain as acute, chronic, nociceptive (somatic), visceral, or neuropathic. Despite implementation of the WHO guidelines, reports of undertreatment of cancer pain persist in various clinical settings and in spite of decades of work to reduce unnecessary discomfort. Substantial obstacles to adequate pain relief with opioids include specific concerns of patients themselves, their family members, physicians, nurses, and the healthcare system. The WHO analgesic ladder serves as the mainstay of treatment for the relief of cancer pain in concert with tumoricidal, surgical, interventional, radiotherapeutic, psychological, and rehabilitative modalities. This multidimensional approach offers the greatest potential for maximizing analgesia and minimizing adverse effects. Primary therapies are directed at the source of the cancer pain and may enhance a patient's function, longevity, and comfort. Adjuvant therapies include nonopioids that confer analgesic effects in certain medical conditions but primarily treat conditions that do not involve pain. Nonopioid medications (over-the-counter agents) are useful in the management of mild to moderate pain, and their continuation through step 3 of the WHO ladder is an option after weighing a drug's risks and benefits in individual patients. Symptomatic treatment of severe cancer pain should begin with an opioid, regardless of the mechanism of the pain. They are very effective analgesics, titrate easily, and offer a favorable risk/benefit ratio. Cancer pain remains inadequately controlled despite the diagnostic and therapeutic means of ensuring that patients feel comfortable during their illness. Therefore, all practitioners need to make control of cancer pain a professional duty, even if they can only use the most basic and least expensive analgesic medications, such as morphine, codeine, and acetaminophen, to reduce human suffering.

Key words: **cancer; pain; analgesia; opioids; addiction; barriers to pain relief; cancer pain; adjuvant therapies; nonopioid therapies; co-analgesics; malignancy; therapies; WHO 3-step analgesic ladder**

Scope of the Problem

Pain ranges in prevalence from 14–100% among cancer patients[1] and occurs in 50–70% of those in active treatment.[2] The literature reports pain figures as high as 60–90% for patients with advanced stages of cancer.[2–4] Two-thirds of this pain in advanced disease is due to tumor infiltration, and almost one-fourth is a consequence of cancer treatments. No cures exist for many patients with advanced systemic cancers; yet, pain therapies do exist that can ease the suffering related to an individual's course of illness. This knowledge is critically important to communicate given that patients with advanced cancer commonly experience and fear pain. The World Health Organization (WHO) recognized the global need

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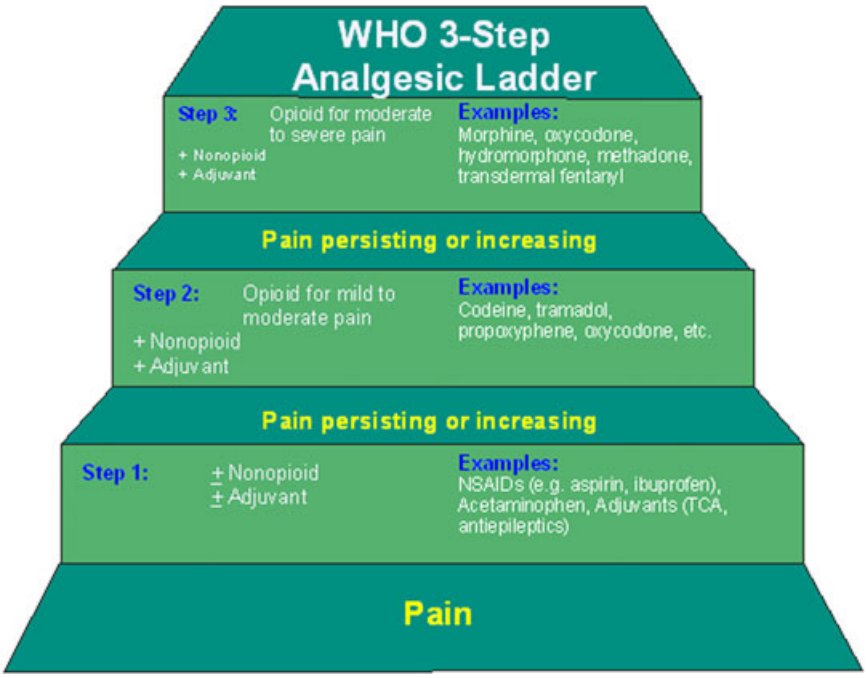

Figure 1. World Health Organization 3-Step Analgesic Ladder with examples of analgesics. Adapted from Management of Cancer Pain: Clinical Practice Guideline Number 9. Rockville, MD: U.S. Department of Health and Human Services; 1994, AHCPR Pub No. 94-0592.

to establish guidelines for basic pain control in cancer patients and thereby developed an elemental "3-step analgesic ladder" in 1986 for use among practitioners.[5] The WHO made an important step in disseminating critical concepts of pain management through education and opioid availability. Increasingly, patients, healthcare providers, and healthcare accreditation bodies are demanding greater attention to the burden of pain and, in particular, cancer-related pain. However, despite application of the WHO "3-step analgesic ladder" (Fig. 1), advancing pain research, and expansive interventional modalities, as many as 50% of cancer patients with pain may remain undertreated.[6] In response to the significant problem of unrelieved pain in cancer and other disease states, the Joint Commission on Accreditation of Health Organizations, an independent, nonprofit organization that evaluates and accredits healthcare organizations in the United States, created comprehensive standards for pain management in 1999. Healthcare institutions must fulfill these standards in order to meet the requirements for reaccreditation. Perhaps this initiative will move clinicians closer to the overarching goal that, "no cancer patient should live or die with unrelieved pain."[7]

The following review will discuss important principles of managing pain in malignant disease. Concepts relating to the sources of pain in cancer, types of pain in cancer, barriers to effective pain control, measuring pain in cancer patients, and pharmacotherapeutic approaches to pain control will be discussed.

Sources of Cancer Pain

Cancer pain may result from direct invasion of tumor into nerves, bones, soft tissue, ligaments, and fascia, and may induce visceral pain through distension and obstruction (Table 1). While over two-thirds of cancer pain usually results from the tumor burden, a quarter of pain experienced by cancer

TABLE 1. Sources of Cancer Pain

Direct invasion
Bone
Soft tissue
Nerves
Ligaments
Fascia
Metastases
Treatment side effects
Surgery
Radiation
Chemotherapy

TABLE 2. Types of Cancer Pain

Examples of neuropathic pain
Tumor compression of plexi
Tumor invasion into nerves
Tumor invasion into spinal cord
Chemotherapy-induced neuritis
Radiation-induced nerve injury
Examples of somatic/nociceptive pain
Tumor invasion into bone
Pathologic fracture
Postsurgical pain
Examples of visceral pain
Tumor invasion into organs
Obstruction (e.g., biliary, intestinal)
Organ rupture (e.g., bowel, bladder)

patients can be attributed to the cancer-related treatments.[3] For instance, surgery, radiation, and chemotherapeutics may all elicit acute pain that diminishes in time, while other therapies may cause chronic pain conditions.[8] Radiation treatment frequently causes acute muscle stiffness and aching, but carries the risk of chronic pain secondary to nerve injury, chronic inflammation, osteoradionecrosis, or myofascial injury. Surgery-associated pain may result from direct nerve injury, inflammation, postamputation phantom pain conditions, and even the development of Complex Regional Pain Syndrome. Many chemotherapeutic agents are known to cause pain. Several classes, such as the alkaloids, platinum-based compounds, and the antimitotics, are known to contribute to peripheral neuropathies.

Types of Pain

Cancer pain is multifaceted, as illustrated in Table 2. Clinicians may describe cancer pain as acute, chronic, nociceptive (somatic), visceral, or neuropathic. Alternatively, some have proposed just three prime categories of cancer pain: nociceptive, neuropathic, and psychogenic.[9] Furthermore, multiple taxonomies of pain exist including a research-oriented and treatment-oriented classification of pain that groups together patients with similar pain mechanisms.[10] Clearly, no individual classification is optimal in truly capturing the multidimensional phenomenon of cancer pain. Clinically, patients experience pain with varying degrees of intensity, frequency, anatomic location, duration, and body system involvement. Further, they may describe features of both nociceptive and neuropathic pain rather than distinctive elements of a single process. It is instructive, nevertheless to understand common terminology often applied to cancer pain. For instance, nociceptive pain arises from activation of nociceptors (free nerve terminals of primary afferent fibers that respond to painful stimuli) that are located in all tissues except the central nervous system. Neuropathic pain results from a primary lesion or dysfunction in the central or peripheral nervous system.[11] The following terms help distinguish varying physiological types of cancer pain.[12]

Nociceptive pain—associated with tissue injury from surgery, trauma, inflammation, or tumor. The pain is caused by stimulation of pain receptors in cutaneous and deeper musculoskeletal structures. It is often proportional to the degree of nociceptor activation. Both somatic and visceral pain conditions may be characterized as nociceptive.

Somatic pain—arising from direct injury to bones, tissue, or tendons. Some consider somatic and nociceptive pain to be synonymous. Somatic pain is described as aching or dull and sometimes stabbing.

It tends to be very focal. This category often includes metastatic bone pain, postsurgical incisional pain, and musculoskeletal inflammation and spasm.

Visceral pain—arising from organ damage or tumor infiltration, compression, or distortion of organs within the pelvis, abdomen, or thorax. It is described as a pressure-like sensation, internal squeezing, or crampiness. It tends to be vague and diffuse and may be associated with distension/stretching of organs, nausea, vomiting, and sweating. The pain may be referred to superficial locations that are distant from the affected organ.

Neuropathic pain—may be directly related to the malignant disease, such as tumor infiltration of peripheral nerves, plexi, roots, or spinal cord. It may arise from efforts to treat the disease, such as surgery, chemotherapy, or other drug-induced neuropathy or neuritis, and even from radiation-induced injury to peripheral nerves and the spinal cord. This type of pain is invariably associated with sensory changes caused by injury to the central or peripheral nervous system and may be incompletely responsive to opioid therapy. Patients typically describe this pain as burning, shooting, pins/needles, electrical, or numbness, and it tends to radiate over dermatomal distributions.

Barriers to Treating Pain

Despite implementation of the WHO guidelines and in spite of decades of work to reduce unnecessary discomfort, reports of undertreatment of cancer pain persist in various clinical settings.[13] Substantial obstacles to adequate pain relief with opioids include specific concerns of patients themselves, their family members, physicians, nurses, and the healthcare system.[14–17] Many of these barriers focus on psychosocial factors related to the fear of opioid addiction and physical dependence, concerns about adverse effects of medications, and patient fears of disappointing their physician by reporting pain.[18–20] Healthcare providers, patients, and their families report distinct but sometimes overlapping concerns.

Healthcare Providers as Barriers to Pain Relief

Physicians are often reluctant to prescribe opioids and nurses may express concern about administering opioids to patients. Physicians tend to feel that managing pain with opioids and other controlled substances leads to documentation woes, entails frequent prescription refills, requires onerous telephone calls, and exposes themselves to intense regulatory scrutiny.[21] Moreover, many healthcare professionals still lack appropriate knowledge of analgesic (primarily opioid) pharmacology with respect to dosing, timing, alternative routes of administration (such as rectal, subcutaneous, epidural, intrathecal), and converting from intravenous to oral therapies. Coupled with an over-exuberant fear of respiratory compromise and a pervasive fear of addiction, physicians and other healthcare providers leave many patients inadequately treated.

While understandable, fears of opioid adverse effects and complications related to respiratory depression need not paralyze practitioners from prescribing opioids. Opioids do affect both the rate and depth of respiration. Data from studies on mice indicate that both the analgesic and respiratory depressive features of morphine are linked to the mu opioid receptor[22,23] in a dose-dependent fashion (that is, increasing the dose produces greater analgesia and greater depression of respiration). A recent acute-pain study in healthy human volunteers shows similar effects and notes that respiratory depression is possible irrespective of concomitant severe pain.[24] In contrast, many clinicians find that respiratory depression rarely precedes analgesia when administering opioids to relieve chronic pain. That is, physicians treating chronic pain patients with opioids report that

patients typically feel comfortable before experiencing respiratory compromise. This clinical phenomenon provides some comfort in escalating doses of opioids in patients who continue to experience pain. Further, cancer pain may in fact more accurately mimic chronic rather than acute pain models, thereby attenuating the risk of respiratory depression in this population. Nonetheless, serious adverse effects can be mitigated by attention to dosing, frequency of dosing, duration of pain (periodic or constant), co-administration of psychoactive substances (such as benzodiazepines, barbiturates, alcohol, other opioids), and proper supervision of patients on chronic opioid therapy. Practitioners can safely tailor opioid therapy in cancer patients by considering the delicate balance between depression of respiration (from factors such as opioid therapy, sleep deprivation, and sedation from co-administered sedatives) and stimulation of respiration (from pain, arousal, stress, anxiety, inflammation, and other causes).

A myriad of healthcare providers use the risk of opioid addiction as justification for minimizing or withholding appropriate opioid therapy. Three medical societies (The American Society of Addiction Medicine, The American Pain Society, and The American Academy of Pain Medicine) define addiction as "a primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing the development and manifestations. It is characterized by behaviors that include one of more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving."[25] In the context of treating patients in chronic pain with opioids, addiction may be viewed as a combination of observations that suggest maladaptive behaviors rather than pharmacologic phenomena, such as tolerance, physical dependence, and dose escalation. These latter conditions are expected to occur during the course of pain treatment. Accordingly, addiction may be more specifically defined in patients on chronic opioid therapy as a series of behavioral observations that suggest: adverse consequences due to the use of drugs, loss of control over drug use, preoccupation with obtaining opioids despite the presence of adequate analgesia, evidence of psychological dependence, and demonstration of aberrant drug-related behaviors, such as obtaining additional drug by manipulating the treating physician or medical system, procuring drugs from other medical or nonmedical sources, and use of unsanctioned drugs during opioid therapy (see Table 3).[26,27]

TABLE 3. Warning Signs of Addiction among Patients Treated with Opioids

Apathy to adverse consequences
Loss of control
Preoccupation with opioids despite psychological dependence
Aberrant drug-related behaviors
Manipulation of healthcare provider
Seeking drugs from other providers
Use of unsanctioned drugs

Regrettably, overestimation of addiction in cancer patients treated with opioids has led to widespread undertreatment of pain in this population.[28] Unfortunately, some countries have even enacted laws and regulations that impede the availability of opioids for medical purposes because of this excessive fear of addiction.[29] It is difficult to interpret the results of many studies designed to estimate prevalence of addiction in cancer patients on long-term opioid therapy because few studies exist and many fail to clearly define the terms used to evaluate addiction. However, the evidence thus far suggests that addiction or related problematic opioid use ranges in prevalence from 0–7.7% in cancer patients.[30–33] One of these studies found an addiction rate as low as 0.2%.[33] These rates suggest that cancer-pain patients should receive sufficient opioid treatment to relieve their discomfort without an undue fear of addiction. In chronic, nonmalignant-pain patients, the risk of addiction requires continuous monitoring during the course of treatment with opioids. As the longevity of cancer patients grows due to improvements in chemotherapy and other antineoplastic agents, their pain conditions will

become longer-lasting and in fact may mimic those of the chronic, nonmalignant-pain population receiving opioid therapy. Therefore, rational use of opioids in cancer patients who receive opioids for chronic treatment demands continual monitoring for addictive behaviors, notwithstanding the low rates of addiction in this group.

Other barriers to effective pain control in cancer patients include insufficient education of adjuvant analgesics, such as tricyclic antidepressants (TCAs) and anticonvulsants. Both of these classes of agents may be may be useful at many stages of disease and especially in easing the symptoms associated with neuropathic pain. Finally, educational efforts that expose the entire healthcare team (including physicians, nurses, social workers, and pharmacists) to the array of targeted interventional therapies for cancer pain would help to deconstruct another barrier to pain relief in patients suffering from cancer.

Patients and Families as Barriers to Pain Relief

Patients and their families may also present obstacles to proper pain control (Table 4). For instance, patients worry that alerting physicians to their pain may divert attention away from their cancer treatment, and that "good" patients do not complain of pain. Furthermore, some patients and their families share a mistaken belief that neither medications nor interventions can alleviate their discomfort.

More specific evidence of these beliefs comes from work by Ward and colleagues in their survey of 270 patients with cancer. This investigation focused on reasons that patients may be to reluctant to report pain or use pain-relieving medications.[20] Almost 80% of patients cited fear of addiction with pain medications as a prime concern, and up to 85% reported believing that side effects of pain medications can not be controlled. Approximately 60% of patients stated that a choice needed to be made between treating the pain and treating the disease. An equally high percentage felt that pain medication should be reserved for severe pain; otherwise, it might be ineffective when needed. Finally, nearly half of the patients feared annoyance from the physician if they complained of pain. Clearly, healthcare providers must address the need to dispel these myths. Educating both patients and families on the proper use of pain medications and communicating the truth about their risks should be the duty of all clinical practitioners. Addiction concerns can be addressed with patients and their families in a way that reflects the known risk and describes methods of minimizing that risk through assessment, evaluation, and monitoring. Likewise, clinicians can share treatment options (including pharmacologic and holistic) for possible side effects of pain medications with patients and their families.

TABLE 4. Patient Barriers to Pain Control

Fear of addiction
Fear of developing tolerance
Fear of masking disease progression
Fear of physician fatigue or annoyance

Treatment of Cancer Pain with Medications

Advances in Past Decades

Prior to the discovery of opioid receptors in the central nervous system in 1973, only theories of their existence permeated the literature. Physicians inconsistently incorporated opioids into pain therapy for cancer patients and rarely in patients with noncancer pain. Unfortunately, many cancer patients died in severe pain despite a developing scientific base and improvements in therapeutic approaches. New methods of drug delivery were introduced in the 1980s, such as continuous subcutaneous, intravenous, epidural, and intrathecal infusions of opioids. The latter two techniques permitted more precise placement of opioids to their receptors and offered alternative means of

analgesia. Computerized tomography imaging gave physicians the ability to more clearly inspect cancerous lesions that may be a source of pain.[34] The introduction of the WHO 3-step analgesic ladder in 1986 provided a concrete tool for physicians worldwide to use in combating cancer pain with oral medications ranging from acetaminophen to morphine. Progress in opioid delivery systems has led to a variety of sustained-release preparations that permit transdermal dosing every 3 days or oral dosing twice daily or even once daily. This has produced more stable blood levels of medication, thereby enabling better pain control and increased compliance with therapy. Other routes of opioid delivery including patient-controlled analgesic pumps, epidural catheters, and intrathecal (implantable) pumps have dramatically improved our ability to achieve better pain control in patients with cancer pain.

WHO Cancer Pain "Ladder"

The WHO analgesic ladder serves as the mainstay of treatment for the relief of cancer pain in concert with tumoricidal, surgical, interventional, radiotherapeutic, psychological, and rehabilitative modalities. This multidimensional approach offers the greatest potential for maximizing analgesia and minimizing adverse effects. In fact, it is estimated that 70–90% of cancer pain is relieved when clinicians apply the WHO ladder appropriately.[5] Although several studies have validated the effectiveness of this tool in managing cancer pain,[5,35–37] few controlled clinical trials have been performed to support its effectiveness 20 years after its initial release.[37] Given the imperative for high-quality, evidence-based guidelines in medicine, it is important to analyze the effectiveness of analgesics and adjuvants recommended by the WHO pain relief ladder. Only in this way, can clinicians draw the most accurate conclusions about the value of each step of the ladder and compare the steps to other analgesic treatments. Until controlled, clinical trials suggest more effective analgesic therapies for cancer pain, clinicians must continue to implement the WHO analgesic ladder in order to meet the basic, global need for treating cancer pain adequately.

This stepwise approach to using pain-relieving medications suggests that clinicians begin with a nonopioid (such as acetaminophen or ibuprofen) and progress from weaker to stronger opioids for incremental pain states (Fig. 1). It is commonly recommended to consider adjuvant medications (that is, drugs that are primarily indicated for nonpainful conditions that can produce analgesia in certain painful conditions) at any step of the ladder. WHO advises that clinicians use acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) for mild pain (step 1); combination products, such as acetaminophen or aspirin plus codeine, hydrocodone, propoxyphene, or oxycodone, for moderate pain (step 2); and morphine, hydromorphone, oxycodone, methadone, or transdermal fentanyl for severe pain (step 3). In practice, new opioid formulations that include sustained-release preparations of codeine, oxycodone, morphine, tramadol, fentanyl, buprenorphine, or oxymorphone are given to patients at appropriate doses for moderate to severe pain. Generally, pain is more effectively controlled if the clinician evaluates the correct analgesic agent, dose, and timing while simultaneously assessing and managing side effects.[38,39] Some practitioners have moved to algorithm-based approaches for treating cancer pain,[40] and others have incorporated an interventional/procedural "fourth step" to the ladder because cancer pain rarely progresses in a stepwise fashion as indicated by the WHO ladder. Irrespective of the specific strategy employed, an overview of typical therapies to consider for the treatment of cancer pain is essential for clinical practitioners.

Primary Therapies

These treatments are directed at the source of the cancer pain and may enhance a patient's

function, longevity, and comfort. Analgesic agents are often needed in conjunction with these primary therapies.

Vertebroplasty: This procedure involves the injection of methylmethacrylate into a pain-sensitive vertebral body under radiographic guidance. The active agent stabilizes bony metastasis by solidifying the lesion and can achieve rapid resolution of pain with restoration of spine stability in 1–3 days.[41] Physicians trained in this technique treat cancer patients with osteolytic lesions of the vertebral body who do not have disruption of the posterior body wall, may or may not have vertebral body collapse, and suffer from severe pain.

Radiofrequency tumor ablation: This therapy may produce significant pain relief from certain cancerous conditions, such as liver cancer, pelvic tumor recurrences, pancreatic cancer, vertebral metastases, and renal and adrenal tumors. The anecdotal literature mostly supports this approach, and several thousand case reports demonstrate its promise in hepatic cancer therapy.[42]

Surgery: Surgery can be invaluable in relieving painful symptoms from hollow organ obstruction, neural compression, and unstable bony structures.[43,44] When cancerous conditions induce pain from obstruction of the esophagus, colon, biliary tract, or ureters, stenting of these structures may offer needed relief.[45,46]

Radiotherapy: Substantial data support the effectiveness of radiotherapy in reducing the pain associated with bone metastases, epidural neoplasm, and headaches caused by cerebral metastases.[47]

Chemotherapy: There is a strong clinical belief that an inverse relationship exists between cancer shrinkage from chemotherapy and analgesia, though there are virtually no data to illustrate the specific analgesic benefits of chemotherapy.[48] There are reports of pain reduction without tumor shrinkage,[49] but most clinicians relate pain relief to the likelihood of tumor response to chemotherapy.

Antibiotics: When pain is a manifestation of infection, antibiotics can serve an analgesic role. For instance, antibiotics are essential in treating pelvic abscess, chronic sinus infections, and cellulitis. Pain may also dissipate when empiric treatment of occult infections is initiated with antibiotic therapy.

Adjuvant Therapies (Co-analgesics)

These medications include nonopioids that confer analgesic effects in certain medical conditions, but primarily treat conditions that do not involve pain. Clinicians typically prescribe adjuvants for the treatment of neuropathic pain like postherpetic neuralgia or painful diabetic neuropathy. The evidence for their effectiveness derives from studies in the nonmalignant pain population rather than the cancer pain population. However, the pathologic processes of neuropathic pain are assumed to be similar in both groups of patients; therefore, these agents are successfully used in treating neuropathic pain in cancer patients. Medications, such as corticosteroids, topical local anesthetics, antidepressants, anticonvulsants, bisphosphonates, and radiopharmaceuticals, are included among the group of agents viewed as adjuvants.

Corticosteroids: These medications inhibit prostaglandin synthesis and reduce neural tissue edema.[50,51] They represent a widely used group of adjuvant therapies for cancer pain[52] and commonly treat the following conditions: increased intracranial pressure headache, superior vena cava syndrome, acute spinal cord compression, neuropathic pain due to nerve compression or infiltration, metastatic bone pain, hepatic capsular

distention from metastasis, painful cancer plexopathies, and symptomatic lymphedema. Dexamethasone is the drug of choice given its low mineralocorticoid effect and consequent reduction in risk of Cushing's syndrome. Doses range from 1–2 mg twice daily to 100 mg daily followed by tapered doses in cases of acute and severe pain.[52] The standard dose of dexamathesone is 16–24 mg per day and can be administered once daily because of its extended half-life.[53]

Topical local anesthetics: Painful lesions of the mucosa and skin may respond to lidocaine preparations. For instance, patients find that viscous lidocaine eases the discomfort associated with oropharyngeal ulcerations, though the risk of aspiration and dysphagia from anesthesia should be considered since the numbing effect can inhibit airway protective reflexes.

Antidepressants: Antidepressant medications can help treat neuropathic pain and offer analgesic effects independent of their antidepressant effects.[54,55] The strongest level of evidence for analgesic efficacy exists for the TCAs and specifically, the tertiary amines (including doxepin and amitriptyline).[54] The secondary amines (such as nortryptyline and desipramine) produce analgesia and a more favorable adverse effect profile, especially if there is concern about sedation, anticholinergic effects, and dysrhythmias. Clinicians tend to use TCAs in cancer patients for pain linked to surgery, chemotherapy, radiation therapy, or malignant nerve infiltration. The TCAs may also be useful adjunctively as anxiolytics and sedatives, and often promote sleep. The selective serotonin reuptake inhibitors (SSRIs) provide little analgesia based on clinical experience, and the literature demonstrates mixed results in randomized controlled trials (RCTs). Some clinicians do use the SSRIs in managing neuropathic pain in patients who fail TCAs because they have a lowered risk of adverse events.[56]

Anticonvulsants: Certain anticonvulsants may be effective for various types of neuropathic pain. They typically ease shooting, stabbing, burning, and electric-like sensations associated with a dysfunctional nervous system. Gabapentin, for instance, could be considered a first-line agent for treating neuropathic pain. High quality evidence from RCTs supports its analgesic effect, safety, good tolerability, and absence of drug–drug interactions.[57–59] Pregabalin may also be regarded as a principal anticonvulsant for use in neuropathic pain given strong evidence for its analgesic effect, rapid titration schedule, and tolerability.[60,61] Interestingly, small, open-label studies suggest that gabapentin may be effective in alleviating neuropathic pain induced by cancer treatment. Newer agents, such as topiramate, oxcarbazepine, and lamotrigine, hold promise in treating neuropathic pain as well.

Bisphosphonates: As a group, these substances inhibit osteoclast activity, adhere strongly to bone, demonstrate a long half-life, and can effectively reduce bone pain. For example, bisphosphonates, such as pamidronate and clodronate, have been shown in controlled trials to reduce bone pain in patients with advanced cancer.[62] Moreover, studies confirm their efficacy in treating bone pain from multiple myeloma and metastases from other cancers.[63,64]

Radiopharmaceuticals: Painful and diffuse metastatic bone disease can also be well treated with radiolabeled agents that areas of high bone turnover absorb. These agents deposit radiation directly to the affected region of the bone. The most commonly used and best-studied radiopharmaceutical is strontium-89.[65] Samarium-153 lexidronam, a

radiopharmaceutical linked to a bisphosphonate compound has produced a positive clinical response,[66] and both strontium and samarium can reduce pain for 6 months or more in 60–80% of patients with metastatic breast and prostate cancers.[67–69]

Nonopioid Therapy/ Over-the-Counter Agents

The WHO analgesic ladder recommends nonopioids beginning at step 1. These medications are useful in the management of mild to moderate pain and their continuation through step 3 is an option after weighing a drug's risks and benefits in individual patients. The two prime agents include the NSAIDS and acetaminophen. Both types have a "ceiling effect" or maximum therapeutic dose beyond which no further benefit is achieved and at which the risk of toxicity increases.

Acetaminophen: Acetaminophen produces analgesia and reduces fever (antipyretic activity) without clinically meaningful peripheral anti-inflammatory activity.[70] Clinicians often combine this agent with short-acting opioids if initial therapy is unsuccessful. Combining acetaminophen with opioids can offer a dose-sparing effect that not only may reduce the amount of opioid required for analgesia, but may limit opioid-induced adverse effects (examples include sedation, nausea and vomiting, constipation, dry mouth, and cognitive dysfunction). Healthcare providers must be mindful of the risk of acetaminophen hepatotoxicity at sustained doses of 4 g per day in adults[71,72] and note that a pending recommendation exists to limit the toxic dose to 3 g per day. Practitioners should also assess the number and dose of multi-ingredient products (such as cold/flu remedies and analgesics) containing acetaminophen that patients may be taking as treatment for pain or other conditions

NSAIDS: NSAIDS are commonly used to reduce inflammatory pain caused by cancer, such as metastatic bone pain and soft tissue infiltration. They have a well-established role in treating mild cancer pain as monotherapy and in conjunction with opioids in reducing moderate to severe pain.[73,74] Like acetaminophen, NSAIDS offer the benefit of an opioid-sparing effect.[75] In cancer patients, clinicians should consider the adverse effects of NSAIDS (mainly gastrointestinal and renal) and especially a patient's co-existing conditions (such as thrombocytopenia orneutropenia) when selecting a particular medication. NSAIDs inhibit the cyclooxygenase (COX) enzyme, which converts arachidonic acid to prostaglandins[76]; prostaglandins mediate renal plasma flow,[76] gastric mucosal protection,[76] platelet aggregation, and pain and inflammation. The COX-2 selective agents confer the same effectiveness as the nonselective agents with less risk of gastrointestinal damage and bleeding.[76] Care should be taken when using NSAIDS in the neutropenic population because the antipyretic and anti-inflammatory properties may mask signs and symptoms of infection.

Opioid Therapy

Symptomatic treatment of severe cancer pain should begin with an opioid, regardless of the mechanism of the pain. Opioids are very effective analgesics, titrate easily, and offer a favorable risk/benefit ratio. They reduce pain by binding to specific receptors located in the central and peripheral nervous system. Most of the commonly used opioids exert their effect through mu opioid receptors, though some bind to kappa or delta receptors. No compelling evidence supports the use of one opioid over another in managing cancer pain. The goal of

TABLE 5. Drug Enforcement Agency (DEA) Schedule of Controlled Substances

Schedule	Criteria	Examples
Schedule I	High potential for abuse No accepted medical use	Heroin Mescaline LSD
Schedule II	High potential for abuse Accepted medical use ± severe restrictions Abuse may lead to severe psychological or physical dependence	Codeine Morphine Fentanyl Hydromorphone Meperidine Methadone Oxycodone Oxymorphone Amphetamines Cocaine
Schedule III	Potential for abuse less than Schedules I and II Accepted medical use Abuse → moderate/low physical dependence or high psychological dependence	Combined codeine or hydrocodone w/ NSAID or acetaminophen Ketamine Buprenorphine
Schedule IV	Low potential for abuse Accepted medical use Abuse → limited physical dependence or psychological dependence	Propoxyphene Benzodiazepines Long-acting barbiturates
Schedule V	Lower potential for abuse than Schedule IV Accepted medical use Abuse → limited physical dependence or psychological dependence which is less than Schedule IV	Opioid preparations used to treat diarrhea or cough

Adapted from DEA, Title 21, Section 812 and Principles of Addiction Medicine, 3rd Edition.

minimizing adverse effects while maximizing analgesia remains paramount when selecting among opioids. Classification schemes include whether the opioid is a full agonist (morphine, oxycodone), partial agonist (buprenorphine), or mixed agonist-antagonist (nalbuphine, pentazocine); whether the opioid provides short- or long-term relief based on formulation (oxycodone versus sustained-release oxycodone); and where the opioid ranks on the federal schedule of controlled drugs (Table 5) according to their medical importance and abuse potential, from Schedule I (high abuse potential and no medical use) to Schedule V (low abuse potential and accepted medical use).

Tramadol: Tramadol is a centrally acting analgesic that shares properties of both opioids and TCAs. This agent binds weakly to the mu opioid receptor, inhibits the reuptake of serotonin and norepinephrine, and promotes neuronal serotonin release. The WHO places tramadol on step 2 of the ladder as an option for treating mild to moderate cancer pain. It is often used for its opioid-like analgesic effects in the cancer population, although it may be incorporated into the armamentarium of drugs considered for neuropathic pain. For instance, a recent RCT of tramadol compared to placebo demonstrated efficacy in controlling neuropathic

pain in patients with cancer.[77] Furthermore, high-quality studies in patients with nonmalignant neuropathic pain[78,79] confirm its efficacy in treating this painful condition. Clinicians feel comfortable using tramadol because it is not listed on the federal schedule of controlled drugs, has low abuse liability,[33] and is associated with low risk of respiratory depression.[80] Adverse effects resemble those of opioids and caution is advised when using tramadol with SSRIs, monoamine oxidase inhibitors, or TCAs given the potential for serotonin syndrome. Tramadol is available in immediate-release form or in combination with acetaminophen, and now in a controlled-release preparation.[81]

Morphine: Morphine remains the most commonly used opioid for treating severe cancer pain (step 3 of the WHO ladder). No other drug has demonstrated greater analgesic efficacy, though no controlled studies have proven morphine's superiority over other opioids. Morphine's wide availability, cost effectiveness, and multiple formulations (including oral, rectal, intravenous, intranasal, epidural, subcutaneous, intrathecal, and sustained-release) illustrate its preferred status for managing cancer pain. Oral administration is the preferred and simplest route. Morphine is metabolized in the liver, producing morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Although M3G is inactive, M6G is an active metabolite that exceeds morphine in potency and half-life. Both metabolites are excreted by the kidneys; however, patients with renal dysfunction may experience prolonged morphine effects, including respiratory depression from accumulation of M6G. Clinicians should consider small doses of immediate-release morphine and/or reducing the dosing frequency when prescribing morphine to patients with renal impairment. Some have advocated the avoidance of morphine altogether in patients with renal failure due to the risks of managing adverse effects of the metabolites.[82] A novel liposomal delivery system that carries morphine epidurally to targeted sites has been shown to provide 48 h of postoperative pain relief,[83] and this system holds exciting applications for future analgesic delivery in cancer patients.

Codeine: The WHO places codeine on step 2 of the analgesic ladder to be used for mild–moderate pain. Codeine is available as a combination product with acetaminophen or aspirin. The liver metabolizes codeine once absorbed and 90% of its metabolites are primarily excreted as inactive forms in the urine. Only about 10% of codeine is demethylated (converted) to morphine, which accounts for its analgesic properties as well as its recommendation for the control of only mild–moderate cancer pain. It is important to remember that genetic differences in the enzyme responsible for the conversion of codeine to morphine lead to the inability to produce morphine in about 10% of the Caucasian population.[84] Hence, codeine is rendered ineffective in these patients. Similarly, Chinese people convert less morphine from codeine and demonstrate less sensitivity to the effects of morphine.[85] Accordingly, clinicians should consider rotating to other opioids in the event that certain patients fail to experience adequate relief from codeine. Unique receptors that bind codeine exclusively may explain its significant antitussive effects.[86] Practitioners should avoid using codeine in patients with renal failure because its active metabolites accumulate[87] and can cause significant adverse effects.[88,89]

Hydromorphone: Hydromorphone (step 3 of the WHO ladder) is a semisynthetic derivative of morphine that is about 6 times more potent. It binds to both the mu and, to a lesser degree, the

delta opioid receptor.[90] Hydromorphone is available in oral (immediate-release and controlled-release [not available in the United States]), parenteral (intravenous, intramuscular, subcutaneous), and intraspinal preparations. RCTs support the drug's efficacy and tolerability in patients with cancer pain.[91,92] Therefore, it is included in clinical practice guidelines for the management of cancer pain.[53,93] Studies report that hydromorphone shares equivalency with morphine in analgesic efficacy and adverse effects.[92] Hydromorphone seems to have active, nonanalgesic metabolites which may cause neuroexcitatory effects (myoclonus, allodynia, seizures, confusion) at high doses or in the setting of renal failure.[94,95] Therefore, patients who present with increased pain, confusion, and myoclonus should rotate to another opioid or reduce the dose and frequency of administration.

Fentanyl: Initially used as an intraoperative anesthetic, fentanyl's use has evolved into a popular transdermal, controlled systemic delivery formulation. The data support the effectiveness of transdermal fentanyl (fentanyl patch) for treating cancer pain,[96–98] and most clinicians would place the drug on step 3 of the WHO analgesic ladder. The fentanyl patch serves as a viable alternative to oral opioids, especially when cancer or adverse treatment effects preclude the oral administration of analgesics. Fentanyl is 100 times more potent than morphine[99] and is very lipid soluble, which affords easy passage of the drug through the skin and mucous membranes en route to systemic circulation. As an opioid for patient-controlled analgesia infusions of short duration, fentanyl has a relatively short time to peak analgesic effect and a quick termination of effect after small bolus doses; it provides marked cardiovascular stability (fentanyl releases no histamine).[99] The transdermal system usually requires 12–24 h before serum levels stabilize when starting the patch or changing the dose.[100] Recommended dosing is every 72 h, though some patients report an attenuated analgesic response by the 3rd day and request a shortened dosing interval to every 48 h. Many clinicians prescribe the patch to patients who display stable pain symptomatology due to the longer time needed to increase the dose to therapeutic levels.[101] In addition to its transdermal formulation, fentanyl is administered intravenously, orally (lollipop, lozenge, buccal tablet), intravenously, epidurally, and intrathecally. An innovative delivery system called the fentanyl iontophoretic transdermal system shows promise in treating postoperative pain[102,103] and may have future value in treating breakthrough pain among chronic cancer pain sufferers. This system represents a noninvasive, transdermal method of drug delivery in which an electrical field drives small charged lipophilic particles across the skin.[104] The liver and to a lesser extent the duodenum metabolize fentanyl to inactive metabolites. Based on limited data, clinicians can use fentanyl in patients with renal failure, but should monitor patients for evidence of gradual accumulation of the opioid.[82]

Oxycodone: Oxycodone may be useful as a step 2 or step 3 analgesic on the cancer pain ladder. It binds to both the mu[105,106] and kappa[107] opioid receptors, and is often used in combination with acetaminophen, aspirin, or ibuprofen as a short-acting analgesic. Oxycodone is primarily used orally in both immediate-release (capsule, liquid, tablet) and controlled-release forms to manage pain. Several RCTs document oxycodone's ability in controlled-release preparation to provide effective pain relief in moderate to severe cancer pain compared to sustained-release morphine.[108–110] Further, patients in these

studies reported fewer hallucinations with oxycodone as well as less pruritus and nausea compared to morphine.[109,110] Controlled-release formulations of oxycodone and other opioids have greatly facilitated the provision of stable dosing and pain relief for patients with cancer pain. Controlled-release oxycodone, for example, provides sustained relief for 12 h and offers faster onset of relief than sustained-release morphine.[111] In the elderly, oxycodone may be a desirable alternative to morphine if patients are sensitive to morphine-induced sedation and mental status changes. The liver metabolizes oxycodone to small amounts of oxymorphone, the only active metabolite, and oxymorphone does accumulate in renal failure along with the parent drug.[112] Although the data are sparse, one case reports sedation and central nervous system toxicity in patients with renal failure given oxycodone.[113] Hence, clinicians should prescribe oxycodone cautiously and carefully monitor symptoms of toxicity in patients with renal compromise.

Meperidine: This opioid binds predominantly to the mu opioid receptor and is used most often as an intraoperative analgesic. Small, single doses are effective for postoperative shivering as well. The drug may produce an anticholinergic response in the form of tachycardia and acts as a weak local anesthetic. Oral and parenteral formulations are available for clinical use. Most clinicians avoid meperidine for the treatment of chronic pain and cancer pain due to its short duration of action and concerns over metabolic toxicity. In fact, The Agency for Health Care Policy and Research recommends its use for no longer than 48 h and in doses that do not exceed 600 mg per day.[114] Hence, this drug is rarely recommended as a therapeutic agent listed on the WHO analgesic ladder. Meperidine is metabolized to normeperidine which is eliminated by both the liver and the kidney; therefore, hepatic or renal dysfunction can lead to metabolite accumulation. Normeperidine toxicity manifests as shakiness, muscle twitches, myoclonus, dilated pupils, and seizures.[115] Renal failure greatly elevates the risk of normeperidine neurotoxicity, therefore clinicians should avoid its use in patients with kidney disease. Furthermore, co-administering monoamine oxidase inhibitors with meperidine can yield serious reactions, such as delusions, hyperpyrexia, respiratory depression or excitation, and convulsions.

Buprenorphine: Typically used as a step 3 agent for cancer pain, buprenorphine is a partial agonist at the mu opioid receptor and an antagonist at the kappa and delta receptors.[116–118] It has a high affinity for and slow dissociation from the mu receptor and may produce less analgesia than a full mu agonist. Aside from its analgesic properties, buprenorphine is approved for the treatment of opioid dependence disorders in a combination product with naloxone.[119] New data indicate that buprenorphine causes limited respiratory depression compared to fentanyl and probably other opioids.[120] In fact, buprenorphine may also have a ceiling effect for respiratory depression at high doses that is independent of its analgesic effect.[121] It is 25–50 times more potent than morphine, and is available in parenteral, sublingual, and transdermal formulations. A recent study of transdermal buprenorphine in cancer and noncancer patients showed that almost half of the patients reported satisfactory pain relief and over a one-third experienced good pain relief.[122] Evidence from other studies demonstrates that buprenorphine provides improvement in pain, enhanced quality of life, and stable dosing in cancer pain patients.[123–125] In addition, this opioid shows promise in treating neuropathic pain, which can often manifest

in cancer pain conditions.[40,126,127] Adverse effects, such as constipation and patch-related erythema and pruritis, appear at lower rates with buprenorphine than other opioids. For instance, constipation rates range from 0.97% to 6.7% in studies of transdermal buprenorphine.[128–130] In contrast, transdermal fentanyl produces constipation at rates between 9% and 28%.[131,132] Buprenorphine requires no dose adjustment in patients with renal failure, which confers substantial advantage to vulnerable populations like cancer patients and older adults.[122] The liver metabolizes buprenorphine to norbuprenorphine, which represents its major, weakly active metabolite. This metabolite, along with others, passes into the bile and then into the feces which bypasses any accumulation in patients with renal dysfunction. The safe administration of buprenorphine in patients with renal impairment[133,134] offers a unique alternative to many other opioids that may accumulate and cause severe adverse events.

Methadone: Methadone (step 3 agent on the WHO ladder) is a long-acting mu and delta opioid receptor agonist that shares similar efficacy and comparable adverse effect profile with morphine. It also causes monoamine reuptake inhibition. Further, methadone has N-methyl-D-aspartate (NMDA) antagonist properties based on animal studies.[135–137] This unique feature may make methadone a particularly useful choice for the treatment of neuropathic pain, though no trial evidence supports a role in alleviating neuropathic pain of malignant origin.[138] The available data suggest that methadone is an effective analgesic in patients with cancer pain.[138] However, it displays complex and erratic pharmacokinetics requiring extreme vigilance in initiation and dose titration—methadone's plasma half-life is about 24 h,[137,139] whereas its analgesic half-life if only 4–6 h.[140] Moreover, significant variability in plasma half-life between individuals has been observed in clinical practice.[141] Methadone firmly binds to extravascular binding sites and is released slowly back into plasma, resulting in a characteristically long half-life. Therefore, clinicians must be aware of the potential for delayed toxicity (including respiratory depression) from drug accumulation in tissues. Repeat administration ("by the clock" as proposed by the WHO) in treating cancer pain, coupled with a prolonged half-life, increases the risk of overdose in two vulnerable populations, those with cancer pain and older adults. Infrequent (two to three times daily), low, and slow dosing along with vigilant monitoring can lend a margin of safety to clinicians when prescribing methadone. Caution is advised when rotating to methadone, especially from high doses of a previous opioid given its variable conversion ratio.[142] Available formulations exist for oral, rectal, and parenteral administration. Patients taking monoamine oxidase inhibitors should not concurrently use methadone. Clinicians should be mindful of possible QT prolongation and torsades de pointes associated with higher doses of methadone (300 mg and above), and methadone use in concert with certain antidepressants, severe hypokalemia or hypomagnesemia, and congestive heart failure.[143,144] The liver transforms methadone to inactive metabolites[145] that are excreted in the urine and mainly in the bile (feces). Renal dysfunction does not seem to impair clearance of the drug, so clinicians may consider methadone in patients with renal failure.[146] Despite its hazards, methadone can serve as an ally in easing pain among gravely ill patients.[139,147,148] For example,

methadone produces a rapid onset of analgesic effect (about 30 min), has high oral bioavailability (85%), has a long half-life, induces tolerance slowly, produces no active metabolites, and costs little.

Oxymorphone: Oxymorphone, a metabolite of oxycodone, may reflect a new treatment option for cancer patients suffering from moderate-to-severe pain (step 3). Formerly available only as a parenteral or rectal agent, oxymorphone has recently been developed as immediate-release and sustained-release formulations. Its analgesic effects are mediated through mu and delta opioid receptors.[90] In a pilot study, Sloan and colleagues found that oxymorphone produced equivalent analgesia to extended-release morphine or extended-release oxycodone in patients with moderate-to-severe cancer pain.[149] In fact, patients taking sustained-release oxymorphone required less breakthrough medication than those taking extended-release morphine. The half-life of the immediate-release formulation of oxymorphone (approximately 7–9 h[150]) exceeds that of many short-acting formulations of opioids including morphine, oxycodone, and hydromorphone. Furthermore, a 6-h dosing interval is recommended, which is longer than most immediate-release opioids. Consequently, clinicians may find this shorter-acting form of oxymorphone an attractive option for limiting episodes of breakthrough pain. The liver biotransforms oxymorphone into oxymorphone 3-glucoronide and 6-hydroxyoxymorphone. The latter metabolite has been shown to have analgesic bioactivity in animals.[150] Oxymorphone is renally excreted and accumulates in renal failure,[112] so clinicians should consider increasing the dosing interval and/or lowering the dose in the setting of renal dysfunction.

Conclusion

Cancer pain remains inadequately controlled despite the diagnostic and therapeutic means of ensuring that patients feel comfortable during their illness. More effective methods of ensuring that physicians and healthcare providers apply the WHO cancer pain analgesic ladder must be developed. Further, educational tools that deconstruct the barriers to providing adequate pain care to cancer patients require initiation and implementation; otherwise, patterns of ignorance will prevail and patients will suffer in pain needlessly. Concerns about opioid compliance, diversion, abuse, and addiction all contribute to an inadequate level of interest in treating cancer patients with opioids. The available evidence suggests that rates of problematic opioid use in this population are low; therefore, patients should not be denied opioid therapy for fear of inducing substance abuse. Clinicians should consider the range of medical therapies (primary, adjuvant, nonopioid, and opioid) available for patients suffering from cancer pain, and incorporate them into a treatment strategy that maximizes analgesia and minimizes adverse effects. Importantly, an array of short- and long-acting opioids now exists and should be prescribed for cancer pain. Each opioid confers a unique set of analgesic properties and adverse effects which need to be considered before use in any cancer patient. Moreover, clinicians must pay special attention to active opioid metabolites in patients with renal disease. Uncontrolled pain is incompatible with a satisfactory quality of existence, and multiple studies highlight the deleterious impact of persistent pain on daily life and social interaction. Accordingly, all practitioners must make control of cancer pain a professional duty, even if they can use only the most basic and least expensive analgesic medications, such as

morphine, codeine, and acetaminophen, to reduce human suffering.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. NIH. 2002. NIH State of the Science Statement on symptom management in cancer: pain, depression, and fatigue. in NIH Con. *State of the Sci. Statm.* 1–29.
2. Keefe, F.A., AP Abernethy & CL Campbell. 2005. Psychological approaches to understanding and treating disease related pain. *Annual Rev. Psychol.* **56:** 1–22.
3. Bonica, J. 1990. *The Management of Pain*. Vol. 1. Lea & Febiger. Philadelphia.
4. ESMO. 2007. Management of cancer pain: ESMO Clinical Recommendations. *Annals of Oncology* **18**(Suppl 2): ii92–ii94.
5. Jadad, A.R. & G.P. Browman. 1995. The WHO analgesic ladder for cancer pain management. Stepping up the quality of its evaluation. *JAMA* **274:** 1870–1873.
6. Azevedo, S.L.F., M. Kimura & M. Jacobsen Teizeira. 2006. The WHO analgesic ladder for cancer pain control, twenty years of use. How much pain relief does one get from using it? *Support Care Cancer*.
7. Levy, M. 1999. Pain control in patients with cancer. *Oncology (Williston Park)* **13**(5 Suppl 2): 9–14.
8. Polomano, R.C. & J.T. Farrar. 2006. Pain and neuropathy in cancer survivors. *Am. J. Nurs.* **106**(3 Suppl): 39–47.
9. Portenoy, R.K. 1989. Mechanisms of clinical pain. Observations and speculations. *Neurol. Clin. North Am.* **7:** 205–230.
10. Loeser, J. 2001. *Bonica's Management of Pain*, 3rd edn.: 19–21. Lippincott, Williams & Wilkins. Philadelphia.
11. LeBel, A.A. 2002. *The Massachusetts General Hospital Handbook of Pain Management*, 2 edn. J.C. Ballantyne, Ed.: Lippincott Williams & Wilkins. Philadephia.
12. Foley, K. 1998. Pain assessment and cancer pain syndromes. In *Oxford Textbook of Palliative Medicine*. H.G. Doyle D & N. MacDonald, Eds.: 310–331. Oxford University Press. Oxford.
13. American Pain Society Quality of Care Committee. 1995. Quality improvement guidelines for the treatment of acute pain and cancer pain. *JAMA* **274:** 1874–1880.
14. Baltic, T.E., M.B. Whedon, T.A. Ahles & G. Fanciullo. 2002. Improving pain relief in a rural cancer center. *Cancer Pract.* **10**(Suppl 1): S39–S44.
15. Lasch, K. 2002. Why study pain? A qualitative analysis of medical and nursing faculty and students' knowledge of and attitudes to cancer pain management. *J. Palliat Med.* **5:** 57–71.
16. Payne, R. 2000. Chronic pain: challenges in the assessment and management of cancer pain. *J. Pain Symptom Manage.* **19**(1 Suppl): S12–S15.
17. Ward, S. 2001. Patient education in pain control. *Support Care Cancer* **9:** 148–155.
18. Gunnarsdottir, S. 2002. Patient-related barriers to pain management: the Barriers Questionnaire II (BQ-II). *Pain* **99:** 385–396.
19. Ward, S. & J. Gatwood. 1994. Concerns about reporting pain and using analgesics. A comparison of persons with and without cancer. *Cancer Nurs.* **17:** 200–206.
20. Ward, S.E., N. Goldberg, V. Miller-McCauley, *et al.* 1993. Patient-related barriers to management of cancer pain. *Pain* **52:** 319–324.
21. Phillips, D.M. 2000. JCAHO pain management standards are unveiled. Joint Commission on Accreditation of Healthcare Organizations. *JAMA* **284:** 428–429.
22. Dahan, A. 2001. Anesthetic potency and influence of morphine and sevoflurane on respiration in mu-opioid receptor knockout mice. *Anesthesiology* **94:** 824–832.
23. Romberg, R. 2003. Comparison of morphine-6-glucuronide and morphine on respiratory depressant and antinociceptive responses in wild type and mu-opioid receptor deficient mice. *Br J. Anaesth* **91:** 862–870.
24. Dahan, A. 2004. Simultaneous measurement and integrated analysis of analgesia and respiration after an intravenous morphine infusion. *Anesthesiology* **101:** 1201–1209.
25. American Society of Addiction Medicine. 1998. Public policy statement on definitions related to the use of opioids in pain treatment. *J. Addict. Dis.* **17:** 129–133.
26. Portenoy, R.K. 1990. Chronic opioid therapy in nonmalignant pain. *J. Pain Symptom Manage.* **5**(1 Suppl): S46–S62.
27. Sees, K.L. & H.W. Clark. 1993. Opioid use in the treatment of chronic pain: assessment of addiction. *J. Pain Symptom Manage.* **8:** 257–264.
28. McQuay, H. 1999. Opioids in pain management. *Lancet* **353:** 2229–2232.
29. *Cancer pain relief. With a guide to opioid availability*. 1996, World Health Organization.
30. Macaluso, C., D. Weinberg & K.M. Foley. 1988. Opioid abuse and misuse in a cancer pain population. *J. Pain Symptom Manage.* **3:** S24.

31. Passik, S.D., K.L. Kirsh, M.V. McDonald, S. Ahn, *et al*. 2000. A pilot survey of aberrant drug-taking attitudes and behaviors in samples of cancer and AIDS patients. *J. Pain Symptom Manage*. **19:** 274–286.
32. Passik, S.D., J. Schreiber & K.L. Kirsh. 2000. A chart review of the ordering of urine toxicology screen in a cancer center: do they influence on pain management. *J. Pain Symptom Manage*. **19:** 44.
33. Schug, S.A., D. Zech, S. Grond, *et al.* 1992. A long term survey of morphine in cancer pain patients. *J. Pain Symptom Manage*. **7:** 259–266.
34. Foley, K.M. & N. Sundaresan. 1985. Management of cancer pain. In *Cancer: Principles and Practice of Oncology*. Vol. 2. V.T. DeVita, Jr., S. Hellman & S.A. Rosenberg, Eds.: 1940–1962. JB Lippincott Company. Philadelphia.
35. Mercadante, S. 1999. Pain treatment and outcomes for patients with advanced cancer who receive follow-up care at home. *Cancer* **85:** 1849–1858.
36. Ventafridda, V. 1987. A validation study of the WHO method for cancer pain relief. *Cancer* **59:** 850–856.
37. Zech, D.F. 1995. Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study. *Pain* **63:** 65–76.
38. Quigley, C. 2005. The role of opioids in cancer pain. *BMJ* **331:** 825–829.
39. Twycross, R. & A. Wilcock 2001. *Symptom Management in Advanced Cancer*, 3rd edn. Radcliffe Medical Press. Oxford.
40. Miaskowski, C., J. Cleary, R. Burney, *et al.*, Eds. 2005. *Guideline for the Management of Cancer Pain in Adults and Children*, Vol. Clinical Practice Guidelines Series, No. 3. American Pain Society. Glenview, IL.
41. Fourney, D.R. 2003. Percutaneous vertebroplasty and kyphoplasty for painful vertebral body fractures in cancer patients. *J. Neurosurg.* **98**(1 Suppl): 21–30.
42. Neeman, Z. & B.J. Wood. 2002. Radiofrequency ablation beyond the liver. *Tech. Vasc. Interv. Radiol.* **5:** 156–163.
43. Krouse, R. 2004. Advances in palliative surgery for cancer patients. *J. Support Oncol.* **2:** 80–87.
44. McCahill, L. & B. Ferrell. 2002. Palliative surgery for cancer pain. *West J. Med.* **176:** 107–110.
45. Amersi, F., M.J. Stamos & C.Y. Ko. 2004. Palliative care for colorectal cancer. *Surg. Oncol. Clin. North Am.* **13:** 67–77.
46. Homs, M.Y. 2004. Quality of life after palliative treatment for oesophageal carcinoma—a prospective comparison between stent placement and single dose brachytherapy. *Eur. J. Cancer* **40:** 1862–1871.
47. Nielsen, O.S., S.M. Bentzen & E. Sandberg. 1998. Randomized trial of single dose versus fractionated palliative radiotherapy of bone metastases. *Radiother Oncol*. **47:** 233–240.
48. Bang, S.M. 2005. Changes in quality of life during palliative chemotherapy for solid cancer. *Support Care Cancer* **13:** 515–521.
49. Burris, H.A. 3rd. 1997. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J. Clin. Oncol.* **15:** 2403–2413.
50. Ettinger, A.B. & R.K. Portenoy. 1988. The use of corticosteroids in the treatment of symptoms associated with cancer. *J. Pain Symptom Manage.* **3:** 99–103.
51. Watanabe, S. & E. Bruera. 1994. Corticosteroids as adjuvant analgesics. *J. Pain Symptom Manage.* **9:** 442–445.
52. Rousseau, P. 2001. The palliative use of high-dose corticosteroids in three terminally ill patients with pain. *Am. J. Hosp. Palliat Care* **18:** 343–346.
53. Jacox, A., D.B. Carr & R. Payne. 1994. New clinical-practice guidelines for the management of pain in patients with cancer. *N. Engl. J. Med.* **330:** 651–655.
54. McQuay, H.J. 1996. A systematic review of antidepressants in neuropathic pain. *Pain* **68:** 217–227.
55. Sindrup, S.H. & T.S. Jensen. 1999. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain* **83:** 389–400.
56. Mattia, C. 2002. New antidepressants in the treatment of neuropathic pain. A review. *Minerva Anestesiol.* **68:** 105–114.
57. Backonja, M. 1998. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA* **280:** 1831–1836.
58. Bennett, M.I. & K.H. Simpson. 2004. Gabapentin in the treatment of neuropathic pain. A review. *Palliat Med*. **18:** 5–11.
59. Rice, A.S. & S. Maton. 2001. Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study. *Pain* **94:** 215–224.
60. Dworkin, R.H. 2003. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch. Neurol.* **60:** 1524–1534.
61. Freynhagen, R. 2005. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. *Pain* **115:** 254–263.
62. Wong, R & P.J. Wiffen. 2002. Bisphosphonates for the relief of pain secondary to bone metastases (Cochrane Review). *Cochrane Database Syst Rev* **2:** CD002068.

63. Berenson, J.R. 1996. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. *N. Engl. J. Med.* **334:** 488–493.
64. Bloomfield, D.J. 1998. Should bisphosphonates be part of the standard therapy of patients with multiple myeloma or bone metastases from other cancers? An evidence-based review. *J. Clin. Oncol.* **16:** 1218–1225.
65. Gunawardana, D.H. 2004. Results of strontium-89 therapy in patients with prostate cancer resistant to chemotherapy. *Clin. Nucl. Med.* **29:** 81–85.
66. Sartor, O. 2004. Samarium-153-Lexidronam complex for treatment of painful bone metastases in hormone-refractory prostate cancer. *Urology* **63:** 940–945.
67. Robinson, R.G., D.F. Preston, K.G. Baxter, R.W. Dusing & J.A. Spicer. 1993. Clinical experience with Strontium-89 in prostatic and breast cancer patients. *Seminars in Oncology* **20:** 44–48.
68. Rogers, C.L., B.L. Speiser & P.C. Ram. 1998. Efficacy and toxicity of intravenous strontium-89 for symptomatic osseous metastases. *J. of Brachytherapy International* **14:** 133–142.
69. Sciuto, R., C.L. Maini & A. Tofani. 1996. Radiosensitization with low-dose carboplatin enhances pain palliation in radioisotope therapy with strontium-89. *Nucl. Med. Commun.* **17:** 799–804.
70. Watson, A.C., S.T. Brookes, J.R. Kirwan & A. Faulkner. 2000. Non-aspirin, non-steroidal anti-inflammatory drugs for osteoarthritis of the knee. *Cochrane Database of Systematic Reviews* 2.
71. Makin, A.J., J. Wendon & R. Williams. 1995. A 7-year experience of severe acetaminophen-induced hepatotoxicity (1987-1993). *Gastroenterology* **109:** 1907–1916.
72. Schiodt, F.V. 1997. Acetaminophen toxicity in an urban county hospital. *N. Engl. J. Med.* **337:** 1112–1117.
73. Grond, S. 1991. The importance of non-opioid analgesics for cancer pain relief according to the guidelines of the World Health Organization. *Int. J. Clin. Pharmacol. Res.* **11:** 253–260.
74. McNicol, E. 2004. Nonsteroidal anti-inflammatory drugs, alone or combined with opioids, for cancer pain: a systematic review. *J. Clin. Oncol.* **22:** 1975–1992.
75. Mercadante, S., F. Fulfaro & A. Casuccio. 2002. A randomised controlled study on the use of anti-inflammatory drugs in patients with cancer pain on morphine therapy: effects on dose-escalation and a pharmacoeconomic analysis. *Eur. J. Cancer.* **38:** 1358–1363.
76. Simon, L., A. Lipman, A. Jacox, M. Caudill-Slosberg, *et al.* 2002. *Guideline for the management of pain in osteoarthritis, rheumatoid arthritis, and juvenile chronic arthritis*. American Pain Society. Glenview, IL.
77. Arbaiza, D. & O. Vidal. 2007. Tramadol in the treatment of neuropathic cancer pain: a double-blind, placebo-controlled study. *Clin. Drug. Investig.* **27:** 75–83.
78. Boureau, F., P. Legallicier & M. Kabir-Ahmadi. 2003. Tramadol in post-herpetic neuralgia: a randomized, double-blind, placebo-controlled trial. *Pain* **104:** 323–331.
79. Harati, Y. 1998. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology* **50:** 1842–1846.
80. Shipton, E.A. 2000. Tramadol—present and future. *Anaesth Intensive Care* **28:** 363–374.
81. Babul, N. 2004. Efficacy and safety of extended-release, once-daily tramadol in chronic pain: a randomized 12-week clinical trial in osteoarthritis of the knee. *J. Pain Symptom Manage.* **28:** 59–71.
82. Dean, M. 2004. Opioids in renal failure and dialysis patients. *J. Pain Symptom Manage.* **28:** 497–504.
83. Viscusi, E.R. 2005. Forty-eight hours of postoperative pain relief after total hip arthroplasty with a novel, extended-release epidural morphine formulation. *Anesthesiology* **102:** 1014–1022.
84. Eichelbaum, M. & B. Evert. 1996. Influence of pharmacogenetics on drug disposition and response. *Clin. Exp. Pharmacol. Physiol.* **23:** 983–985.
85. Caraco, Y., J. Sheller & A.J. Wood. 1999. Impact of ethnic origin and quinidine coadministration on codeine's disposition and pharmacodynamic effects. *J. Pharmacol. Exp. Ther.* **290:** 413–422.
86. Gutstein, H. & A. Huda. 2006. *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11 edn. Opioid Analgesics*. P. Laurence & L. Brunton, Eds.: 566. McGraw-Hill. New York, New York.
87. Guay, D.R.P., W.M. Awni & J.W.A. Findaly. 1988. Pharmacokinetics and pharmacodynamics of codeine in end-state renal disease. *Clin. Pharmacol. Ther.* **43:** 63–71.
88. Matzke, G.R., G.L.C. Chan & P.A. Abraham. 1986. Codeine dosage in renal failure. *Clinical Pharmacy* **5**(letter): 15–16.
89. Talbott, G.A. 1997. Respiratory arrest precipitated by codeine in a child with chronic renal failure. *Clin Pediatr (Phila)* **36:** 171–173.
90. Ananthan, S. 2004. Identification of opioid ligands possessing mixed micro agonist/delta antagonist activity among pyridomorphinans derived from naloxone, oxymorphone, and hydromorphone [correction of hydropmorphone]. *J. Med. Chem.* **47:** 1400–1412.
91. Junker, U. & V. Figge. 2005. Controlled-release hydromorphone in elderly patients with severe

pain of different etiologies. Results of an observational study. *MMW Fortschr. Med.* **147**(Suppl 3): 91–96.
92. Quigley, C. 2002. Hydromorphone for acute and chronic pain. *Cochrane Database of Systematic Reviews* **1**(CD003447).
93. World Health Organization. 1990. *Report on cancer pain relief and palliative care*. World Health Organization. Geneva.
94. Hagen, N.A. & R. Swanson. 1997. Strychnine-like multifocal myoclonus and seizures from extremely high dose opioids: treatment strategies. *J. Pain Symptom Manage.* **14:** 51–58.
95. Smith, M. 2000. Neuroexcitatory effects of morphine and hydromorphone: evidence implicating the 3-glucuronide metabolites. *Clin. Exp. Pharmacol. Physiol.* **27:** 524–528.
96. Ahmedzai, S. & D. Brooks. 1997. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. The TTS-Fentanyl Comparative Trial Group. *J. Pain Symptom Manage.* **13:** 254–261.
97. Donner, B. 1998. Long-term treatment of cancer pain with transdermal fentanyl. *J. Pain Symptom Manage.* **15:** 168–175.
98. Radbruch, L. 2001. Transdermal fentanyl for the management of cancer pain: a survey of 1005 patients. *Palliat Med.* **15:** 309–321.
99. Gutstein, H. & A. Huda. 2006. *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11 edn. Opioid Analgesics*. P. Laurence & L. Brunton, Eds.: 571. McGraw-Hill. New York, New York.
100. Muijsers, R.B. & A.J. Wagstaff. 2001. Transdermal fentanyl: an updated review of its pharmacological properties and therapeutic efficacy in chronic cancer pain control. *Drugs* **61:** 2289–2307.
101. Hanks, G.W. 2001. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br. J. Cancer* **84:** 587–593.
102. Hartrick, C.T. 2006. Fentanyl iontophoretic transdermal system for acute-pain management after orthopedic surgery: a comparative study with morphine intravenous patient-controlled analgesia. *Reg. Anesth. Pain Med.* **31:** 546–554.
103. Viscusi, E.R. 2004. Patient-controlled transdermal fentanyl hydrochloride vs intravenous morphine pump for postoperative pain: a randomized controlled trial. *JAMA* **291:** 1333–1341.
104. Viscusi, E.R. & T.A. Witkowski. 2005. Iontophoresis: the process behind noninvasive drug delivery. *Reg. Anesth. Pain Med.* **30:** 292–294.
105. Monory, K. 1999. Opioid binding profiles of new hydrazone, oxime, carbazone and semicarbazone derivatives of 14-alkoxymorphinans. *Life Sci.* **64:** 2011–2020.
106. Yoburn, B.C. 1995. Supersensitivity to opioid analgesics following chronic opioid antagonist treatment: relationship to receptor selectivity. *Pharmacol. Biochem. Behav.* **51:** 535–539.
107. Prommer, E. 2006. Oxymorphone: a review. *Support Care Cancer* **14:** 109–115.
108. Bruera, E. 1998. Randomized, double-blind, crossover trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain. *J. Clin. Oncol.* **16:** 3222–3229.
109. Heiskanen, T. & E. Kalso. 1997. Controlled-release oxycodone and morphine in cancer related pain. *Pain* **73:** 37–45.
110. Mucci-LoRusso, P. 1998. Controlled-release oxycodone compared with controlled-release morphine in the treatment of cancer pain: a randomized, double-blind, parallel-group study. *Eur. J. Pain.* **2:** 239–249.
111. Curtis, G.B., G.H. Johnson & P. Clark. 1999. Relative potency of controlled-release oxycodone and controlled-release morphine in a postoperative pain model. *Eur. J. Clin. Pharmacol.* **55:** 425–429.
112. Kirvela, M. 1996. The pharmacokinetics of oxycodone in uremic patients undergoing renal transplantation. *J. Clin. Anesth.* **8:** 13–18.
113. Fitzgerald, J. 1991. Narcotic analgesics in renal failure. *Conn. Med.* **55:** 701–704.
114. Acute Pain Management in Infants, Children, and Adolescents: Operative and Medical Procedures, in U.S. Dept. of Health and Human Services. 1992. Agency for Health Care Policy and Research. p. Rockville, MD.
115. Hershey, L. 1983. Meperidine and central neurotoxicity. *Ann. Intern. Med.* **98:** 548–549.
116. Cowan, A., J.W. Lewis & I.R. Macfarlane. 1977. Agonist and antagonist properties of buprenorphine, a new antinociceptive agent. *Br. J. Pharmacol.* **60:** 537–545.
117. Lee, K.O. *et al.* 1999. Differential binding properties of oripavines at cloned mu- and delta-opioid receptors. *Eur. J. Pharmacol.* **378:** 323–330.
118. Lewis, J.W. & S.M. Husbands. 2004. The orvinols and related opioids-high affinity ligands with diverse efficacy profiles. *Curr. Pharm. Des.* **10:** 717–732.
119. Gutstein, H. & A. Huda. 2006. *Goodman & Gilman's the Pharmacological Basis of Therapeutics, 11 edn. Opioid Anaglesics*. P. Laurence & L. Brunton, Eds.: 576. McGraw-Hill. New York, New York.
120. Dahan, A. 2006. Opioid-induced respiratory effects: new data on buprenorphine. *Palliat Med.* **20**(Suppl 1): s3–s8.
121. Cowan, A. 2003. Buprenorphine: new pharmacological aspects. *Int. J. Clin. Pract. Suppl.* 3–8; discussion 23–4.

122. Likar, R., H. Kayser & R. Sittl. 2006. Long-term management of chronic pain with transdermal buprenorphine: a multicenter, open-label, follow-up study in patients from three short-term clinical trials. *Clin. Ther.* **28:** 943–952.
123. Pace, M.C., M.B. Passavanti, E. Grella, *et al.* 2007. Buprenorphine in long term control of chronic pain in cancer patients. *Front Biosci.* **1:** 1291–1299.
124. Sittl, R., M. Nuijten & B.P. Nautrup. 2006. Patterns of dosage changes with transdermal buprenorphine and transdermal fentanyl for the treatment of non-cancer and cancer pain: a retrospective data analysis in Germany. *Clin Ther.* **28:** 1144–1154.
125. Sorge, J. & R. Sittl. 2004. Transdermal buprenorphine in the treatment of chronic pain: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther.* **26:** 1808–1820.
126. Christoph, T. 2005. Broad analgesic profile of buprenorphine in rodent models of acute and chronic pain. *Eur. J. Pharmacol.* **507:** 87–98.
127. Likar, R. & R. Sittl. 2005. Transdermal buprenorphine for treating nociceptive and neuropathic pain: four case studies. *Anesth. Analg.* **100:** 781–785.
128. Griessinger, N., R. Sittl & R. Likar. 2005. Transdermal buprenorphine in clinical practice—a post-marketing surveillance study in 13,179 patients. *Curr. Med. Res. Opin.* **21:** 1147–1156.
129. Likar, R., H. Kayser & R. Sittl. 2005. Transdermal buprenorphine for long-term management of chronic cancer and non-cancer pain. Results of an open-label, multicentre, follow up study. Book of Abstracts, International Forum on Pain Medicine. (Sofia).
130. Sittl, R. 2006. Transdermal buprenorphine in cancer pain and palliative care. *Palliat Med.* **20**(Suppl 1): s25–s30.
131. Mystakidou, K. 2003. Long-term management of noncancer pain with transdermal therapeutic system-fentanyl. *J. Pain* **4:** 298–306.
132. Nugent, M. 2001. Long-term observations of patients receiving transdermal fentanyl after a randomized trial. *J. Pain Symptom Manage.* **21:** 385–391.
133. Filitz, J. 2006. Effects of intermittent hemodialysis on buprenorphine and norbuprenorphine plasma concentrations in chronic pain patients treated with transdermal buprenorphine. *Eur. J. Pain.* **10:** 743–748.
134. Summerfield, R.J., M.C. Allen & R.A. Moore. 1985. Buprenorphine in end-stage renal failure. *Anaesthesia* **40**(Letter): 914.
135. Bulka, A. 2002. Reduced tolerance to the antihyperalgesic effect of methadone in comparison to morphine in a rat model of mononeuropathy. *Pain* **95:** 103–109.
136. Bulka, A., Z. Wiesenfeld-Hallin & X.J. Xu. 2002. Differential antinociception by morphine and methadone in two sub-strains of Sprague-Dawley rats and its potentiation by dextromethorphan. *Brain Res.* **942:** 95–100.
137. Davis, M. & D. Walsh. 2001. Methadone for relief of cancer pain: a review of pharmacokinetics, pharmacodynamics, drug interactions and protocols of administration. *Support Care Cancer* **9:** 73–83.
138. Nicholson, A. 2004. Methadone for cancer pain. Cochrane Database of Systematic Reviews, (1): p. Art. No.: CD003971. DOI: 10.1002/14651858. CD003971. pub2.
139. Fainsinger, R., T. Schoeller & E. Bruera. 1993. Methadone in the management of cancer pain: a review. *Pain* **52:** 137–147.
140. Grochow, L. 1989. Does intravenous methadone provide longer lasting analgesia than intravenous morphine? A randomized, double-blind study. *Pain* **38:** 151–157.
141. Ripamonti, C., E. Zecca & E. Bruera. 1997. An update on the clinical use of methadone for cancer pain. *Pain* **70:** 109–115.
142. Bryson, J. 2006. Methadone for treatment of cancer pain. *Curr. Oncol. Rep.* **8:** 282–288.
143. Reddy, S.F., M. Fisch & E. Bruera. 2004. Oral methadone for cancer pain: no indication of Q-T interval prolongation or torsades de pointes. *J. Pain Symptom Manage.* **28:** 301–303.
144. Roden, M. 2004. Drug-induced prolongation of the QT-interval. *N. Engl. J. Med.* **350:** 1015–1022.
145. Kreek, M.J. & C.L. Gutjahr. 1976. Drug interactions with methadone. *Ann. N.Y. Acad. Sci.* **281:** 350–370.
146. Kreek, M.J. & A.J. Schecter. 1980. Methadone use in patients with chronic renal disease. *Drug Alcohol Dep.* **5:** 197–205.
147. Hanks, G.W.C. & N. Cherny. 1998. Opioid analgesic therapy. In *Oxford Text of Palliative Medicine*. H.G. Doyle D & N. MacDonald, Eds.: 331–351. Oxford University Press. Oxford.
148. Twycross, R., A. Wilcock & S. Thorpe. 1998. *Palliative Care Formulary*. Radcliffe Medical Press. Oxford.
149. Sloan, P., N. Slatkin & H. Ahdieh. 2005. Effectiveness and safety of oral extended-release oxymorphone for the treatment of cancer pain: a pilot study. *Support Care Cancer* **13:** 57–65.
150. Adams, M.A. & H. Ahdieh. 2005. Single and multiple dose pharmacokinetic and dose proportionality study of oxymorphone immediate release tablets. *Drugs RD* **6:** 91–99.