Background: Pain, dyspnea, and anorexia are common symptoms experienced by patients with cancer and often are poorly managed.

Methods: The incidence and causes of these symptoms are described, as well as factors that exacerbate or ameliorate their impact.

Results: Pharmacologic management of cancer pain is based on the use of a sequential "ladder" that incorporates nonopioid, opioid, and adjuvant drugs, depending on the severity of the pain. This approach usually is effective. Other symptoms of advanced disease may be more difficult to control.

Conclusions: Adherence to an adequate pain-control strategy will significantly enhance palliation of pain in patients with cancer.

Introduction

The incidence of cancer over the next decade is expected to rise by 50% in Canada and other developed countries, while the cure rate is expected to remain at approximately 50%.[1] One of every three Canadians is expected to develop cancer, and 50% of these are expected to die of it. For those patients whose cancer progresses to the advanced stage, most will develop debilitating symptoms before death, including asthenia, anorexia, pain, nausea, constipation, sedation/confusion, and dyspnea. Following is a discussion on the management of common and distressing symptoms in advanced cancer patients.

Pain and Its Management

Cancer-related pain afflicts approximately nine million people worldwide annually.[2] The incidence of pain at various stages of the disease is 51% and increases to 74% in the advanced and terminal stages.[2] Among advanced cancer patients, pain is moderate to severe in 40% to 50% and very severe or excruciating in 25% to 30%.[3] In rating their pain, the majority of patients (69%) cite that which causes impairment of their ability to function as the worst pain.[4] Most patients with advanced cancer have two or more types and/or etiologies of cancer-related pain.[5]

Pain associated with cancer may be a result of tumor pressure (75% to 80% of patients) or anticancer treatments (15% to 19%), or it may be unrelated to cancer and treatment (3% to 5%).[6] Numerous distinct cancer pain syndromes are described in Table 1.[5,7,8] The International Association for the Study of Pain has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." Pain is always subjective; it is what the patient says hurts.[9] A patient's threshold of pain is an individual concept. It can be raised by adequate sleep, mood improvement, diversion, empathy, and understanding, while fatigue, anxiety, fear, anger, sadness, depression, and isolation can lower the pain threshold. The perception of the intensity of pain relates to the interactions of physical, psychologic, cultural, and spiritual factors rather than to the type or extension of the tissue damage. Thus, successful pain control requires a multidisciplinary approach to treatment that addresses all aspects of care and suffering.

Despite published guidelines for pain management,[10] many cancer patients experience considerable pain, and approximately half of them receive inadequate analgesia.[4,11,12] The most frequent causes of undertreatment of cancer-related pain are (1) a discrepancy between patient and physician in judging the severity of the patient's pain, (2) the reluctance to prescribe opioid analgesics for fear of developing addiction, tolerance, and side effects, (3) the fact that analgesic treatment is not of primary importance in the health care system, (4) the high cost of analgesic medications, which are nonrefundable and not readily available in some countries, and (5) the fact that analgesic treatment often is considered only for advanced and terminal cancer patients.

Pharmacologic Management of Pain

Clinical studies have shown that the following analgesic approach can alleviate pain in over 80% of cases, thus highlighting the importance of opioids as pain-relieving drugs for cancer patients.[13,14] The pharmacologic strategy to the treatment of cancer pain is based on the use of a sequential “ladder” with nonopioid, opioid, or adjuvant drugs.[10] The drugs are administered alone or in combination according to the type and intensity of pain rather than the patient's prognosis. To be effective, a pain-relieving therapy must meet the following criteria:

1. It prevents the onset of pain. For this purpose, drugs are administered “by the clock” rather than “as required,” and the half-life, bioavailability, and duration of action of the different drugs are considered.
The therapy is simple to administer. This requirement ensures that the patient and family can administer the drugs, especially when the patient is cared for at home. The oral route is the preferential route of administration, if it is well tolerated.

The therapy is designed specifically for the individual patient. The dosage, type, and route of administration is adjusted according to each patient's needs.

A recent review expressed concern about the lack of randomized control studies of the World Health Organization analgesic ladder. However, logistic reasons (placebo analgesia) and ethical reasons (the individual analgesics of the system have been proven effective) make these studies unreasonable.

Nonopioid Drugs

Tumor growth produces inflammatory and mechanical effects in adjacent tissue that can trigger the release of prostaglandins (PGs), bradykinin, and serotonin, which in turn can precipitate or exacerbate pain in the surrounding tissues. Nonsteroidal anti-inflammatory drugs (NSAIDs) appear to exert their analgesic, antipyretic, and anti-inflammatory actions by blocking the synthesis of PG.

Aspirin, paracetamol, and the NSAIDs are recommended as the sole treatment of mild pain or combined with opioids for moderate to severe or very severe pain. Paracetamol and some NSAIDS (eg, ketoprofen) induce a central analgesic effect. Compared with aspirin and other NSAIDs, paracetamol does not affect platelet function, which makes it safer for thrombocytopenic patients.

Used as single agents, NSAIDs have a ceiling effect on their analgesic potential; additional increments above the recommended dosage do not provide greater pain relief. However, nonopioid drugs provide additive analgesia when combined with opioids. Toxicity resulting from the prolonged use limits the role of NSAIDs in cancer pain management.

Common side effects occur in the gastrointestinal tract, liver, kidney, skin, and blood dyscrasia. The NSAID-induced reduction in glomerular filtration may result in the accumulation of active opioid metabolites, including morphine 3 and 6 glucuronide. Therefore, patients who are given both NSAIDs and opioids should be carefully observed for the possibility of increased central opioid toxicity.

Opioid Drugs

Opioid analgesics are the mainstay of therapy for chronic pain associated with cancer. Opioids can be divided into four categories based on their ability to bind the receptor sites and their affinity for such sites: pure agonist (morphine, methadone, codeine, oxycodone, hydromorphone, fentanyl, dextropropoxyphene, heroin), partial agonist (buprenorphine, which is characterized by a "ceiling effect"), mixed agonists/antagonist (pentazocine, nalbuphine, butorphanol), and antagonist (naloxone, which does not produce analgesic effects and can block the pharmacologic action of the previous agonists). The mixed agonist/antagonist classification currently is not used or recommended for cancer pain.

Analogic opioids are classified according to their ability to control mild to moderate pain (codeine, tramadol, dextropropoxyphene) and those used for moderate to severe pain (morphine, methadone, oxycodone, buprenorphine, hydromorphone, fentanyl, heroin). The guidelines for opioid use in opioid-naive patients are given in Table 2. Oral morphine is the drug of choice in the management of moderate or severe chronic cancer pain. The administration of short-release tablets allows fast absorption, with plasma peak concentrations appearing after 20 to 90 minutes and effective analgesia lasting approximately four to six hours. Bioavailability varies from 35% to 75%, whereas the plasma half-life variability ranging from one to five hours may require variations of dosage in different patients. Morphine clearance decreases in patients over 50 years of age, which may explain why older patients require relatively lower doses of morphine for the same analgesic results. Using slow-release tablets, morphine administration can be reduced to twice a day. Only 10% of patients find it necessary to receive the drug every eight hours. Every 12-hour administration of slow-release morphine and every four-hour administration of short-release oral morphine provides similar analgesic efficacy and side-effect profiles in the treatment of chronic pain.

Hydromorphone is well absorbed at the gastrointestinal tract level. When administered intramuscularly, 1.3 mg of hydromorphone is equivalent to 10 mg of morphine. Oral hydromorphone reaches its peak effect more rapidly than morphine and has a shorter duration of action. It may be necessary to administer hydromorphone at two- or three-hour intervals. When hydromorphone is administered via injection, most patients require approximately one fifth of the optimal oral dose (1.5 mg intramuscularly = 7.5 mg orally). A controlled study demonstrated a comparable analgesia and side-effect spectrum in patients receiving continuous intravenous hydromorphone when switched to continuous subcutaneous hydromorphone infusions.

Methadone is a synthetic opioid analgesic displaying agonistic activity. It is a basic and lipophilic drug that is subject to considerable tissue distribution. The plasma concentration is sustained during chronic treatment by this peripheral reservoir. Methadone is characterized by a large interindividual variation in pharmacokinetics and by rapid and extensive distribution phases (half-life of two to three hours) followed by a slow elimination phase (beta half-life of 15 to 60 hrs) that may cause accumulation problems if doses are too large or if the dosing intervals are too short over a long period of time. Opinions still differ about the suitable intervals of oral methadone administration. Some authors suggest dosing intervals of six, eight, or 12 hours for analgesia. Sawe et al suggested titrating the analgesic therapy with a loaded dose of the drug that is then reduced during the first week of treatment. In our clinical experience, the administration of oral methadone every eight hours, both in the titration phase and during chronic treatment, is effective with no signs of accumulation or toxicity. Methadone also is efficacious and well tolerated via rectal and intravenous routes, whereas continuous subcutaneous infusion of the drug does not seem to be indicated due to topic adverse skin reactions.

Morphine and methadone demonstrate approximately the same analgesic potency after single-dose administration. Compared with morphine, however, methadone given in a multidose analgesic regimen must be administered at lower doses and with longer dosing intervals to maintain analgesia. In switching from another opioid to methadone, the latter drug often is more potent at steady state than expected, given the data in literature. The policy that a switch from one opioid to another should be accompanied by a reduction of the equianalgesic dose by one third to one half to accommodate incomplete cross-tolerance between drugs should be amended in the case of methadone, in which a reduction of eight to 10 times during titration phase is suggested by clinical experience. Morphine and methadone are being carried out to evaluate the equianalgesia of the two drugs during chronic administration.

Methadone presents some advantages over other strong opioid analgesics: (1) its lower cost (eg, 10 to 20 times cheaper than morphine), (2) the low number of daily administrations relative to opioids with short terminal half-life, (3) its potential to control pain that is unresponsive to morphine or other opioids (methadone shows complete cross-tolerance with other opioid receptor agonist analgesics), and (4) its superiority over other opioids when accumulation of active metabolite causes side effects such as myoclonus, sedation, confusion, nausea, and vomiting. Despite these benefits, we recommend limiting the use of methadone to palliative care and pain therapy specialists because of the large interindividual variation in doses as well as the unpredictable and poorly understood equianalgesic ratios to other opioids.

Fentanyl citrate, a synthetic opioid analgesic that is approximately 75 times more potent than morphine, has high potency, skin compatibility, low molecular weight, and good solubility; thus it is suitable for rate-controlled transdermal delivery. Patches release 25, 50, 75 or 100 µg per hour of fentanyl citrate for 24 to 72 hours.

Pharmacokinetic data suggest that transdermal fentanyl is well absorbed, but there is considerable delay in reaching steady-state plasma levels. Also, a slowly declining plasma concentration occurs after removal of the patch, probably due to a deposition of drug in the epidermal site that causes prolongation of the absorption process.
Although clinical experience in long-term use is limited, it appears to be well tolerated.[36] The first experiences with transdermal fentanyl, however, showed significant side effects such as vomiting, transient somnolence, and respiratory depression after increasing dosage.[37] Transdermal fentanyl treatment should be used in patients who are being treated with morphine, the dose of which is halved during the following 24 hours. Transdermal fentanyl is contraindicated in patients with generalized edema and in the treatment of acute pain and breakthrough pain.

These agonist opioids are accompanied by a linear dose/effect correlation. Each increase of the dose promotes an improvement in pain control for the types of pain that are opioid-responsive. However, accumulation of active (toxic) metabolites of opioids might explain cases of opioid toxicity when high doses are used over long periods of time. Other mechanisms of late toxicity of opioids may be found at the receptor level. Whatever the cause, a change of opioids using equianalgesic doses will improve symptoms of toxicity while maintaining pain control in some patients. Opioid rotation often is necessary to obtain satisfactory long-term pain control in cancer patients.[38]

**Adjuvant Drugs**

Opioid analogues are effective in reducing the pain intensity that most cancer patients experience, but they frequently cause side effects (eg, sedation, nausea, constipation) and may not completely control pain syndromes in some patients. Therefore, adjuvant drugs have emerged to increase the opioid-induced analgesia and to decrease opioid-induced toxicity (Table 3). While many of these drugs may have one or both of these capabilities, few controlled trials of these drugs have been conducted. Some adjuvant drugs are required in most patients who receive analgesia (eg, laxatives and antiemetics), while other drugs such as amphetamine derivatives may be required less often. In addition, some drugs (eg, benzodiazepines and major tranquilizers) are used as adjuvants although they have no demonstrated beneficial effect and can potentiate opioid toxicity. Adjuvant drugs that are used most often are tricyclic antidepressants, corticosteroids, anticonvulsants, local anesthetics, and bisphosphonates.[39]

**Tricyclic Antidepressants**

Tricyclic antidepressants (amitriptyline, imipramine, desipramine) are useful in a variety of neuropathic pain syndromes, especially when pain has a prominent dysesthetic or burning character. Prospective, double-blind, placebo-controlled trials[40,41] found amitriptyline and desipramine to be effective in the management of postherpetic neuralgia. Cross-over, placebo-controlled trials[42] have demonstrated the efficacy of chlorimipramine and nortriptyline in the management of central pain syndromes. Controlled, double-blind studies[42-45] have shown imipramine, clomipramine, desipramine, and fluoxetine to be useful in the management of diabetic neuropathy, while their role in managing malignant neuropathic pain is less clear. In one placebo-controlled study of terminal patients,[46] the administration of imipramine was accompanied by decreased requirements for morphine. A trial of tricyclic antidepressants may be useful in a patient whose pain has responded inadequately to standard pharmacologic management with opioids. The toxic effects of these drugs are mainly autonomic (dry mouth, postural hypotension) and centrally mediated (somnolence, confusion). These drugs may work by stimulating descending inhibitory pathways[47] or by increasing the bioavailability of circulating opioids.[48-50]

**Corticosteroids**

Dexamethasone has been found to be effective in managing spinal cord compression[51,52] and headache due to endocrine hypertension. Uncontrolled studies suggest that the administration of corticosteroids to selected patients with advanced cancer results in decreased pain and improved appetite and activity.[53] Although corticosteroids are used frequently in patients with advanced cancer, their beneficial effects have been reported in few controlled studies.[54-57] The mechanism by which corticosteroids may produce beneficial effects in patients with terminal cancer is unclear but may involve their euphoriant effects or the inhibition of PG metabolism. While reductions in peritumoral edema and inflammation may contribute to relief of pain, the degree to which the beneficial effects of corticosteroids on mood, appetite, and weight contribute to improved subjective pain reports is unclear. Corticosteroid treatment produces limiting side effects, particularly immunosuppression (candidiasis), proximal myopathy, and psychiatric symptoms, in 3% to 50% of cancer patients, with severe symptoms occurring in 5%. The spectrum of disturbances ranges from mild to severe affective disorders (eg, depression, mania), psychotic reactions (eg, steroid psychosis), and global cognitive impairment (delirium).[58]

**Anticonvulsants**

Anticonvulsant drugs such as carbamazepine, phenytoin, valproic acid, and clonazepam have been proposed mainly for the management of the lancinating neuropathic pain similar to pain associated with trigeminal neuralgia.[59,60] However, considerable anecdotal experience has accumulated for the use of these agents for neuropathic cancer pain syndromes, including neural invasion by tumor, radiation fibrosis or surgical scarring, herpes zoster, and deafferentation. Side effects of therapy can be serious, particularly in patients with advanced cancer, and include bone marrow depression, hepatic dysfunction, ataxia, and diplopia. Periodic monitoring of complete blood count and liver function tests are recommended.

**Local Anesthetics**

The efficacy of intravenous administration of local anesthetics to control nonmalignant neuropathic pain has been evaluated in different studies.[61-65] Most protocols use a brief infusion of lidocaine that, when effective, produces short-lived analgesia that typically lasts a few hours. The efficacy of intravenous and subcutaneous administration of lidocaine in cancer patients with neuropathic pain have shown contradictory results.[66-68] The development of sodium channel-blocking agents (oral analogues of the amide local anesthetics) for the treatment of cardiac arrhythmias prompted trials of these drugs in patients with various neuropathic pain syndromes.

Mexiletin was used successfully in the management of painful diabetic neuropathy[69] and painful traumatic mononeuropathy,[70] whereas tocainide was found to be useful in the lancinating pain of trigeminal neuralgia.[71] No controlled trials of mexiletine or tocainide for use in cancer pain have been completed. Mexiletine may worsen pre-existing cardiac arrhythmias and is contraindicated in patients with pre-existing second- or third-degree atrioventricular blockade. Flecaïnine is absorbed well when administered rectally and may have a potential indication in terminal cancer patients when oral drugs cannot be administered.[72]

**Bisphosphonates**

Bisphosphonates (disodium pamidronate) represent a new class of drugs that affect the bone metabolism by inhibiting bone reabsorption by means of osteoclasts.[73] These drugs are used for treatment of metastatic bone disease as well as for analgesic purposes. In a study by Millward et al,[74] no analgesic efficacy or bone repair was observed in breast cancer patients, whereas other studies in patients with multiple myeloma,[75] breast cancer,[76-78] and prostate cancer[76] showed analgesic efficacy and an initial repair of bone lesions to a variable degree. Thurlimann et al[79] showed that the shorter the interval between dose administration, the higher the efficacy of pamidronate. A study by Lipton et al[80] on the efficacy of different dose administration schedules (30 or 60 mg every two weeks; 60 or 90 mg every four weeks) showed that higher doses of pamidronate were related to a better outcome.

**Dyspnea**
Dyspnea is an unpleasant sensation of difficult, labored breathing that occurs in 21% to 70% of patients with advanced cancer before death[80,81] and is found in 60% of patients presenting with non-small cell lung cancer.[82] Dyspnea in cancer patients can derive from one or more causes; those related to the effect of the tumor (eg, primary and/or metastatic tumor, pleural/pericardial effusion, superior vena cava syndrome) and those related to the effect of therapy (eg, postradiation fibrosis, postpneumonectomy). Causes of dyspnea in this population that are not directly related to the tumor or therapy include anemia, cachexia, ascites, metabolic acidosis, and pulmonary embolism. The frequency of dyspnea increases during the last days of life. While it often occurs in patients with primary or metastatic lung cancer, it also occurs in 24% of patients with no evidence of pulmonary or cardiovascular disease.[81] Most patients who develop dyspnea rate it as a significant problem. This symptom is more difficult to control than pain or vomiting[80]

The treatment of dyspnea depends on its cause. Intractable cancers should be treated when possible with systemic or radiation therapy. Chemotherapy in association with corticosteroids is indicated in some patients with carcinomatous lymphangitis. Drainage of pleural fluid can improve dyspnea with longer-term palliation achieved by sclerotherapy.

Patients with lung cancer and other malignancies including head and neck tumors frequently have a history of chronic obstructive pulmonary disease (COPD). These patients may present with episodes of decompensation of their illness requiring bronchodilators, corticosteroids, and antibiotics.

Other conditions associated with dyspnea are anemia, metabolic acidosis, massive ascites, acute exacerbation of chronic asthma, and acute panic attack characterized by hyperventilation. The use of specific therapy can produce rapid relief of dyspnea for these conditions. The main symptomatic therapies of dyspnea are oxygen, drug therapy, and support/counseling.

Patients who are hypoxicemic on room air may benefit from oxygen therapy, possibly by a decrease in the chemoreceptor input to the respiratory center and the brain cortex. Two controlled trials[83,84] randomized patients with cancer to five liters per minute of either oxygen or air. In this population of hypoxicemic patients, oxygen gave a significant symptomatic benefit. Oxygen may be effective in relieving dyspnea at concentrations higher than those required to maintain optimal saturation of hemoglobin. Anecdotal experience in cancer patients and patients with congestive heart failure suggest that oxygen might cause significant symptom relief to patients who are not hypoxicemic. This hypothesis warrants testing in prospective clinical trials.

Most of the controlled clinical trials show that different opioids, at different doses and different routes of administration, also are capable of relieving dyspnea in malignant and nonmalignant chronic conditions.[85-88] Although benzodiazepines are commonly used in the symptomatic treatment of cancer-related dyspnea, a significant difference was not shown in respect to placebo in four of five reported controlled studies. Benzodiazepines are indicated when dyspnea is considered to be a somatic manifestation of a panic disorder or when patients have concomitant severe anxiety.

Both nebulized and orally administered bronchodilators have been found to be useful in the treatment of bronchospasms associated with asthma and COPD.[89] Since many patients with lung cancer present evidence of air flow obstruction, a trial of bronchodilator therapy often is useful.

Aminophylline, theophylline, and caffeine improve diaphragmatic contractility both in normal volunteers and in patients with COPD.[90] Because of the frequent presence of asthenia and generalized muscle weakness with or without cachexia, some cancer patients may benefit from the effect of xanthines on respiratory muscle contractility. This hypothesis should be tested prospectively.

In addition to pharmacologic therapy for the management of dyspnea, several measures can be implemented for the support of both the patient and the family. They can be instructed on the differences between tachypnea and breathlessness, the maneuvers that provoke or worsen dyspnea, the prevention of these events with symptomatic drugs (including opioids 30 to 45 minutes before the dyspnea-causing maneuver), the means to facilitate the mobilization of the patient and/or physiotherapy, and relaxation techniques. Patients and family should be able to contact a nurse or a doctor whenever a critical situation occurs.

**Anorexia and Cachexia Syndrome**

Cancer-induced malnutrition is present in more than two thirds of patients with advanced and terminal disease.[91] The main clinical manifestations of cachexia in patients admitted to a palliative care unit are anorexia and chronic nausea in 85% and 68% of patients, respectively.[92] The numerous causes of malnutrition include decreased food intake, malabsorption, increased consumption, and dysphagia. Anorexia is partially the cause and partially the consequence of the metabolic changes and the malnutrition that occurs in advanced cancer. Frequent causes of chronic nausea in cancer include delayed chemotherapy-induced emesis, radiation therapy, increased intracranial pressure, autonomic failure, and narcotic bowel syndrome. However, cancer cachexia is associated with chronic nausea in many patients even when these factors are absent. In these cases, the most likely cause for chronic nausea is autonomic failure,[93] which is a clinical syndrome including cardiovascular manifestations (postural hypotension, syncope, and fixed heart rate) and gastrointestinal symptoms (nausea, anorexia, constipation, or diarrhea).

Anorexia is found in 90% of advanced cancer patients[92] and is characterized by fatigue, lassitude, and general weakness. The association between anemia and malnutrition has been established in both malignant and nonmalignant populations. Malnutrition causes abnormal muscle function, and some of the mediators of cachexia (eg, cachectin/tumor necrosis factor, interleukin, or interferon) cause significant anemia when administered to animals and humans. In addition, specific substances have been proposed that might cause anemia. However, anemia also has been associated with several psychologic disorders and occurs frequently in patients with no evidence of malnutrition.

Malignant patients have a reduced response to cancer chemotherapy, diminished tolerance to radiation therapy, and shorter overall survival.[94] They also have a higher incidence of infection and other complications after surgical procedures.[92] While the successful treatment of malnutrition implies improved life expectancy and quality of life, randomized, controlled trials have suggested that aggressive nutritional therapy has no impact on tumor response, toxicity, or survival.[95] The potential for increased tumor growth in patients receiving parenteral nutrition remains a theoretical concern.[92]

One approach to malnutrition due to decreased food intake is the use of drugs to stimulate appetite. Corticosteroids may have a significant appetite-stimulating effect that is accompanied by increased oral intake.[56] However, the effect appears to be short in duration and is not accompanied by any significant change in nutritional status. Progestational hormones such as medroxyprogesterone acetate and megestrol acetate[96,97] have significant effects on appetite, food intake, and overall nutritional status, and these drugs can increase food intake and improve nutritional status in patients with a variety of hormone- and nonhormone-responsive cancers. In addition to the effects of these drugs on anorexia, they may minimize chronic nausea.

Metoclopramide is an antidopaminergic drug that is effective with chemotherapy-induced emesis and gastric emptying. On the premise that gastroparesis may be the reason for anorexia and chronic nausea in some patients, a study[98] was conducted on continuous subcutaneous infusion of 60 mg per day of metoclopramide in 19 advanced cancer patients with anorexia or chronic nausea. Most patients showed significant improvement, and after a mean of four days of continuous subcutaneous infusion, treatment in half of the patients could be switched to the oral route without a reduction in caloric intake. The mechanism of metoclopramide in increasing appetite and decreasing nausea in patients with advanced cancer may be the result of its effects on gastric emptying or its central action in inhibiting dopaminergic pathways.
Conclusions

Adherence to the treatment guidelines proposed by the World Health Organization results in effective control of 80% of pain caused by cancer. These guidelines are easily integrated into routine cancer treatment and can be implemented by a physician who is not a specialist in pain therapy. They also are adaptable to the health care systems in other countries. In the advanced or terminal stages of the cancer, this approach should become an integral part of an organized palliative care program. More research is needed to address the following topics:

1. The analgesic efficacy of NSAIDs in treating bone metastases;
2. The equianalgesic dose ratio between morphine and methadone in opioid-naive and tolerant patients;
3. The transdermal route compared with the long-acting oral morphine preparations as well as the continuous subcutaneous infusion of opioids;
4. The efficacy and tolerability of oral and intravenous administration of local anesthetics in the treatment of neuropathic cancer pain; and
5. The efficacy of sodium paminodrate and other bisphosphonates in the prevention of bone lesions and in the delay of their development.

In addition, future research on palliative care should focus on assessing pain and other cancer-related symptoms, as well as managing oral cavity lesions, inoperable bowel obstruction, and neurologic symptoms such as confusion, agitation, and delirium.

References


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