Clinical practice guidelines for the care and treatment of breast cancer: 10. The management of chronic pain in patients with breast cancer (2001 update)

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Abstract

Objective: To help health care professionals develop optimal strategies for managing the chronic pain caused by breast cancer.

Outcomes: Pain relief, absence of adverse effects, good quality of life.

Evidence: Systematic review of the literature up to December 2000, with nonsystematic coverage to May 2001.

Recommendations:

- There are many reasons why a patient with breast cancer may experience pain. Identifying the cause and understanding the pathophysiology can lead to more effective management.
- The nature and severity of pain should be carefully evaluated using the history and physical, psychosocial and emotional assessments**.** Adequacy of pain relief should be evaluated regularly.
- The patient's self-report of pain intensity is the primary source of assessment data in all initial and subsequent evaluations.
- The development of a comprehensive, effective pain-management plan includes the education and involvement of the patient and family, together with an interdisciplinary team approach.
- The first objective in the management of pain is to identify the cause and treat it whenever feasible.
- The first priority of treatment is to control pain rapidly and completely, as judged by the patient. The second priority is to prevent recurrence of pain.

- Analgesic medication should be administered on a regular schedule, around the clock, with additional doses for breakthrough pain when necessary.
- When drug therapy is necessary, the World Health Organization's 3-step approach to the use of analgesics is recommended. The severity of the individual's pain will determine at which step the treatment regimen is commenced.
- The oral route should be the first choice for opioid administration. If the oral route fails, transdermal or rectal administration should be considered. When parenteral administration is necessary, the subcutaneous route is the first choice. Intramuscular administration of opioids is not recommended.
- Accurate conversion with careful observation and titration are required when switching from one opioid to another.
- When switching from long-term oral use of morphine or hydromorphone to parenteral use, a ratio of 2:1 should usually be used.
- After initiating opioid therapy or making any change in dose or route of administration, the dosage should be evaluated after approximately 24 hours.
- Tolerance to opioids is not common and must not be confused with addiction. Physical dependence to opioids is common and is not a symptom of addiction.
- Adjuvant analgesics should be administered, when necessary, with an opioid or nonopioid analgesic.
- Nonpharmacological measures such as psychosocial interventions, physical modalities and complementary therapies may offer relief.
- Neuroinvasive procedures can be considered when all other interventions have failed.

Validation: The authors' original text was revised by a writing committee, primary and secondary reviewers, and the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. The final document reflects a consensus of all these contributors. The current update did not undergo an external review. A writing committee updated the original guideline and then submitted it for further review, revision and approval by the steering committee.

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There are many situations in which a patient with breast cancer may experience pain. Pain is common in women in whom metastatic breast cancer develops and is experienced by more than 50% of this group.[1] Women who have been treated for breast cancer and are currently free of disease may also experience pain. Whatever the cause, pain can be successfully managed and reduced to a level acceptable to the patient. These guidelines aim to provide essential information to health care professionals to help patients achieve optimal pain relief with a minimum of side effects.

Method

A systematic review was conducted of the English-language literature retrieved through MEDLINE (published from January 1996 to December 2000) and through CANCERLIT (published from January 1996 to November 2000). The terms used in the overall search strategy were "breast neoplasms," "pain," "pain measurement" and "chronic pain." Additional terms used to supplement the main search were "narcotics," "constipation," "alternative medicine," "therapeutic touch," "massage" and "reiki." References from the Internet, review articles and textbooks were also examined. A nonsystematic literature review was continued to May 2001. The quality of the evidence on which conclusions were based was categorized into 5 levels (see Levels of Evidence).[2] The iterative process used to develop this guideline has been described previously.[3] A writing committee updated the original guideline and then submitted it for further review, revision and approval by the steering committee.

Recommendations (including evidence and rationale)

Cause

- **There are many reasons why a patient with breast cancer may experience pain. Identifying the cause and understanding the pathophysiology can lead to more effective management.**

The focus of this guideline is the management of chronic pain. Unlike acute pain, chronic pain is not self-limiting and often there is no clear pattern of onset and resolution. The distinction must be made between pain caused by direct tumour involvement (including recurrence), pain resulting from cancer treatment (e.g., the severe discomfort and pain that can result from lymphedema, see guideline 11) and pain due to comorbid syndromes such as osteoporosis, osteoarthritis or degenerative disc disease. Some of the causes of pain syndromes associated with breast cancer are listed in Table 1.

Pain from cancer can be further defined on the basis of the anatomic structure involved. *Somatic* pain results from tumour spread into the musculoskeletal system and is usually well localized and constant. *Visceral* pain results when disease spreads into the solid and hollow organs and is often continuous and poorly localized. Both somatic and visceral pains are nocioceptive (pain stimuli are transmitted and interpreted by an intact nervous system). *Neuropathic* pain is the result of damage to the peripheral or central nervous system. It is often described as shooting, stabbing or burning and is considered the most difficult to manage.[4] Cancer patients may have more than one type of pain simultaneously.

There are 3 common pain syndromes that can occur in women with breast cancer that deserve special mention. They are postmastectomy pain syndrome, brachial plexopathy and metastatic bone pain.

Postmastectomy pain syndrome: This is a fairly common sequel of breast surgery. All patients should be warned that it may occur and that, if it does, it does not signify a recurrence of cancer. Between 10% and 30% of patients will suffer from this syndrome and experience persistent pain after axillary dissection, total mastectomy and, to a lesser extent, breast-conserving surgery (BCS).[5–7] Postmastectomy syndrome is usually due to injury to the intercostobrachial nerve (a cutaneous branch of T1–2) in the course of surgery. The characteristic pain syndrome usually develops 30 to 60 days postoperatively. The patient will complain of a burning pain in the chest wall, axilla and arm. Clothing may irritate involved skin, and movement of the arm may exacerbate the pain.[6] This may cause the patient to restrict arm activity, with subsequent development of a frozen shoulder. Intraoperative damage to other peripheral nerves may cause comparable chronic pain syndromes. These nonmalignant causes of pain must be distinguished from similar, tumour-related brachial plexopathy.

Brachial plexopathy: Brachial plexopathy often heralds the recurrence of cancer in the axilla or adjacent tissues. It may rarely result from damage to the brachial plexus at the time of surgery or after radiotherapy. When brachial plexopathy results from metastatic cancer, the most common presenting symptom is pain in the distribution of the lower roots of the brachial plexus. In contrast, radiation-induced plexopathies often present as numbness and weakness in the distribution of nerve fibres emanating from the upper roots of the brachial plexus.[8] A patient with a brachial plexopathy due to cancer will usually complain of neuropathic pain in the shoulder girdle, elbow, medial side of the forearm and the fourth and fifth fingers.[9] In time, the pain is accompanied by evidence of weakness, muscle atrophy and, occasionally, complex regional pain syndrome type 1 (sympathetic reflex dystrophy). Cord compression is of particular risk in patients with tumour-induced brachial plexopathy if the tumour extends into the adjacent epidural space.[10]

Bone pain: The most common cause of cancer-induced pain in patients with breast cancer is the spread of tumour to bone.[1] Metastatic disease to bone should be identified early. Whenever breast cancer patients complain of new, persistent pain, appropriate diagnostic tests should be carried out to exclude the presence of bone metastases. When metastasis to the bone occurs, the most frequently involved parts of the skeleton include the vertebrae, ribs, pelvic bones, femur, humerus and skull. Unbridled metastatic growth in these areas can produce hypercalcemia, debilitating fractures, loss of limb function and neurologic problems, including quadriplegia and paraplegia due to spinal cord compression as the result of epidural invasion. Breast cancer is the most common cause of spinal cord compression in women.

Evaluation

- **The nature and severity of pain should be carefully evaluated using the history and physical, psychosocial and emotional assessments. Adequacy of pain relief should be evaluated regularly.**

The initial evaluation of pain should include a detailed history to elicit the characteristics of the pain, a physical examination emphasizing the neurologic examination and provocative measures to pinpoint the anatomic site of pain, a psychosocial assessment, and appropriate

investigations to confirm the specific cause(s) of the pain.[11–13] The following issues should be addressed in the history:

(a) How many pains do you have?

(b) Where is the pain located? Does it spread*?*

(c) How severe is the pain? (Patients should be asked to rate their pain according to a scale [described below]).

(d) What is the nature of the pain? Is it dull, burning, lancinating, etc.?

(e) When does the pain occur? Is it constant or intermittent? What is its relationship to activities or events?

(f) How does the pain affect activities of daily living?

(g) What factors make the pain better or worse?

(h) What do you believe is causing the pain?

In addition to physical factors, it is important to identify psychosocial and emotional factors that may affect the severity and presence of pain and influence attitudes toward treatment. These include, but are not limited to, depression and anxiety,[14] the significance that the patient and family attribute to the pain, and the patient's culture and religious beliefs. This is the concept of "total pain," and all components must be addressed in order to provide the most effective, comprehensive approach to pain management.[15] It is also important to review past and current pharmacological and nonpharmacological interventions for controlling symptoms and to assess other symptoms, such as nausea and constipation, that can contribute to unrelieved pain.

- **The patient's self-report of pain intensity is the primary source of assessment data in all initial and subsequent evaluations.**

Since clinicians tend to underestimate the severity of pain, the patient's self-report of pain intensity must be the primary source of assessment data in diagnosis and follow-up.[11,16–18] Although subjective, pain can be quantified, and there are a variety of standardized scales available to help patients describe pain severity. Examples of simple, effective tools include visual colour analogue pain scales, 11-point pain scales (0 = no pain and 10 = the worst pain ever experienced) and the Edmonton Symptom Assessment Scale.[11] Standard scales such as these can enhance communication, validate successive interventions, aid in comparing pain from one instance to another and provide more reliable evaluation of relief methods.[18,19]

Management

- **The development of a comprehensive, effective pain-management plan includes the education and involvement of the patient and family, together with an interdisciplinary team approach.**

A patient–family education program is an important component of an effective pain-management plan.[20,21] Considerable learning is required for the patient and family to understand

pain assessment, pharmacological and nonpharmacological interventions and management of drug side effects. A lack of knowledge concerning cancer pain and its control, fear of addiction or side effects, aversion to medication, cognitive dysfunction and other concerns must be addressed because they may affect whether a patient and family is able to adhere to a particular plan.

As in assessment, the pain-management plan must reflect the input and preferences of the patient and family. Attention to their needs, wishes and abilities, particularly with regard to type of medication, mode of delivery and administration schedules, may facilitate adherence and contribute to successful pain management. The skills, knowledge and cooperation of a variety of health care professionals (nurses, physicians, pharmacists, pain specialists and others) help to ensure that the pain-management plan is carried out in a manner most effective for the patient and family.[15]

- **The first objective in the management of pain is to identify the cause and treat it whenever feasible.**

Recurrent disease should be identified or ruled out with physical examination and appropriate diagnostic tests. However, no investigation is 100% sensitive or specific, and therefore pain should be treated with adequate analgesia even before results of investigations are known.

If identified, systemic anticancer therapy, using either hormonal therapy or chemotherapy, can bring about temporary remission in most women with previously untreated metastatic disease. Patients should be warned, however, that tamoxifen can produce a temporary exacerbation of metastatic bone pain (a "flare") and that this does not necessarily reflect progression of disease.[22]

Radiotherapy can be highly effective in the treatment of localized bone metastases and may bring about complete pain relief in over 50% of patients (level III evidence).[23] Prompt referral to a radiotherapy facility is recommended. Since relief from radiotherapy may be delayed by 2 to 4 weeks, adequate pharmacological analgesia is required in the interim.

- **The first priority of treatment is to control pain rapidly and completely, as judged by the patient. The second priority is to prevent recurrence of pain.**

Because chronic pain can cause changes in the processing of the pain message in the central nervous system,[24,25] a patient will not get used to pain. Rather, unrelieved pain may lead to reinforcement, with consequent onset of a more severe pain syndrome that is more difficult to treat. Rapid and complete control through a preventive approach is important.[26,27]

Pharmacological approaches to pain control

- **Analgesic medication should be administered on a regular schedule, around the clock, with additional doses for breakthrough pain when necessary.**

A regular dosage schedule, based on the duration of effect, with additional doses for breakthrough pain as necessary, is more effective than giving analgesics only when pain recurs. This recommendation is based on clinical experience and consensus within the steering committee.

- **When drug therapy is necessary, the World Health Organization's 3-step approach to the use of analgesics is recommended. The severity of the individual's pain will determine at**

which step the treatment regimen is commenced.

Analgesic drugs can be divided into 3 groups: nonopioid, opioid and adjuvant. A simple, effective method of using analgesics that provides adequate pain relief to 90% of cancer patients was developed by a consensus group of experts convened by the World Health Organization (WHO).[13,28,29] It consists of 3 steps; however, the severity of the individual's pain will determine at which step the treatment regimen is commenced. Patients with moderate pain (rating of 5–6 on a 10-point scale) may need to proceed immediately to step 2, while patients with severe pain (rating of 7 or higher) may need to proceed immediately to step 3.[18] For cancer patients whose pain does not respond to the WHO 3-step approach, interventional measures such as nerve blocks, spinal anesthesia, neurolysis, supportive psychotherapy and cognitive-behavioural therapy may be considered.[21,29]

Step 1. Mild to moderate pain can be managed with the use of acetaminophen or an NSAID, or both.

NSAIDs probably act by inhibiting the production of pain-causing substances in the periphery, although they may also have central actions. NSAIDs are particularly helpful in the management of pain caused by bone metastases, because of their ability to block the production of prostaglandins.[30] No single NSAID has been shown to be superior to any of the others for pain relief.[31] For primary management, the safest, least expensive NSAID that the patient will tolerate should be selected. Adverse effects of NSAIDs include impairment of renal function, exacerbation of asthma, congestive heart failure, and gastric and duodenal ulceration and bleeding. It has been recommended that patients over the age of 65 years who require long-term NSAID therapy or those with a history of peptic ulcer disease should receive prophylactic therapy such as misoprostol to reduce the frequency of gastrointestinal complications (level I evidence).[32,33]

Recently, a new class of NSAIDS has become available: selective cyclooxygenase 2 (COX-2) inhibitors. These drugs have been evaluated in patients with osteoarthritis and rheumatoid arthritis.[34,35] For example, in a double-blind, randomized controlled trial reported by Bombardier and associates,[34] 8076 patients who had rheumatoid arthritis were randomly assigned to receive either 50 mg of rofecoxib, a selective COX-2 inhibitor, daily, or 500 mg of naproxen twice daily. The primary end point was confirmed clinical upper gastrointestinal events (gastroduodenal perforation or obstruction, upper gastrointestinal bleeding and symptomatic gastroduodenal ulcers).The median follow-up was 9.0 months. Both medications had similar efficacy against rheumatoid arthritis. The relative risk of confirmed upper gastrointestinal events in the rofecoxib group as compared with those in the naproxen group was 0.5 (95% confidence interval [CI] 0.3 to 0.6; $p < 0.001$). The relative risk of confirmed complications (perforation, obstruction and severe upper gastrointestinal bleeding) was 0.4 (95% CI 0.2 to 0.8; $p = 0.005$) (level I evidence). Although selective COX-2 inhibitors have significantly reduced the risk of gastrointestinal bleeds, the occurrence of renal and central nervous system side effects is just as common as with the nonselective NSAIDS. There are no randomized controlled trials that have compared the analgesic efficacy of COX-2 inhibitors in cancer patients with bone metastases. However, based on the available data, a selective COX-2 inhibitor should be considered if dyspepsia develops.

Acetominophen has an analgesic potency similar to that of NSAIDs but lacks the peripheral anti-inflammatory activity. It is useful for mild pain and is commonly used in combination with oxycodone or codeine (see step 2). Because it does not have the gastrointestinal toxicity associated

with NSAIDs, it is useful in patients who are sensitive to ASA or NSAIDs. With long-term high dosage it can be hepatotoxic and should be used cautiously in patients with metastatic liver disease.

Both acetominophen and NSAIDs display a "ceiling" effect, and when the doses are greater than recommended, the risk of toxicity increases without any increase in analgesia.

Step 2. When pain is not adequately controlled, a weak opioid such as codeine or oxycodone should be added to the NSAID.

Opioids mimic the actions of the natural inhibitory peptides in the central nervous system. and have also been demonstrated to inhibit primary sensory stimulation in the periphery.[36,37] Codeine may be considered the "gold standard" for weak opioids and is most widely used in combination with acetaminophen or ASA. The most effective combination includes at least 60 mg of codeine. It is rarely useful to exceed 120 mg of codeine orally every 4 hours (720 mg/d), and patients requiring more than this for effective pain relief should be switched to a more potent opioid.[15] Oxycodone is considered a weak opioid only when prescribed in combination with acetaminophen or ASA. Patients who take more than 2 tablets of combination products every 4 hours should be moved to a step 3 regimen.

Step 3. When pain is severe *or* unresponsive to step 2 medication, one should switch immediately to potent opioids with or without NSAIDs and adjuvant analgesics.

Initially, the patient should be given short-acting morphine, with conversion to a long-acting preparation when the pain has stabilized. If uncontrollable adverse effects occur with morphine, hydromorphone is a suitable alternative with similar opioid properties. Hydromorphone is 5 times more potent than morphine and has far fewer active metabolites that can cause toxicity.[38] Oxycodone or fentanyl have no active metabolites and are useful alternatives if patients have uncontrollable side effects.

Methadone provides good pain relief but is more difficult to use because of its very variable and long half-life.[39] Methadone should be considered when first-line agents have not been effective or are not tolerated, and only under the supervision of an expert in pain management. A licence to prescribe methadone for pain relief is required. Diamorphine (heroin) has no advantages as an oral agent over morphine. It is a "prodrug" that is rapidly converted to morphine after oral ingestion. Meperidine is not recommended. It cannot be administered subcutaneously, and its long-term use is associated with accumulation of a toxic metabolite, normeperidine, which causes hyperirritability of the central nervous system, myoclonus and seizures.[40] Pentazocine, a mixed agonist–antagonist, can cause psychotomimetic effects and precipitate a withdrawal reaction.[41,42] It should never be used in the management of cancer-related pain.

There is no such thing as a standard dose of an opioid. Oral bioavailability and opioid receptor availability varies from person to person and requires individual titration of the dosage. Inadequate pain relief should be addressed by escalating the opioid dose until adequate analgesia is achieved or intolerable side effects supervene.[38] Usually, immediate-release opioids are not required more often than every 4 hours, and slow-release preparations are generally adequate when given at a minimum frequency of every 12 hours.[43] A once-a-day morphine is available.

Slow-release preparations of morphine, codeine, hydromorphone and oxycodone are available and should be used primarily for patients with readily controlled cancer pain once a stable, effective dose has been reached. Their use may assist in addressing problems of adherence.[18] They should never be used on an as-needed basis for breakthrough pain or for initiation of analgesia.

Opioid Administration

- **The oral route should be the first choice for opioid administration. If the oral route fails, transdermal or rectal administration should be considered. When parenteral administration is necessary, the subcutaneous route is the first choice. Intramuscular administration of opioids is not recommended.**

The bioavailability, relative potency and duration of analgesia of orally and rectally administered morphine are similar,[43] and the recent introduction of long-acting morphine suppositories facilitates the use of this drug.[43,44] Transdermal fentanyl should be considered for patients who cannot take oral medication, for those with a nonfunctioning gastrointestinal tract or for patients who tolerate other opioids poorly.[45–47]

Opioids are generally well tolerated when administered subcutaneously. The use of the subcutaneous route reduces nursing time, can readily be taught to patients and family members and is appropriate for either intermittent injection or continuous infusion. Under ordinary circumstances a subcutaneous site requires changing only every 4 to 7 days.[48] Intravenous administration of opioids does not have any advantage over subcutaneous administration and necessitates frequent, painful intravenous site changes. Intramuscular administration of opioids is painful, inconvenient and not recommended.[49,50]

Some opioid metabolites (e.g., morphine and codeine*)* are active and excreted through the kidneys.[51] Patients who are dehydrated, elderly, diabetic or have reduced renal function are particularly prone to adverse effects of opioids. These problems can usually be avoided by ensuring adequate hydration, reviewing the drug profile and, in some cases, switching to an alternative opioid (e.g., hydromorphone, oxycodone or fentanyl).[52]

Although opioids are metabolized in the liver, in general only patients with severe hepatic disease may require a change in opioid therapy.

- **Accurate conversion with careful observation and titration are required when switching from one opioid to another.**

Patients may vary in their response to different opioids, and partial cross-tolerance may occur. The approximate relative potency of the opioids is shown in Table 2.[53–55] If switching an opioid because of intolerable side effects, the new opioid should be started at 50% of the published equivalent dose. However, if the patient has uncontrolled pain at the time of drug change, an equivalent dose should be given, with early titration to the effective dose.[27]

- **When switching from long-term oral use of morphine or hydromorphone to parenteral use, a ratio of *2*:1 should usually be used.**

The determination of equivalent analgesic doses of oral versus subcutaneous administration

of the same narcotic or of 2 different agents is derived from single-dose studies, which may not be generalizable to long-term use.[55] This recommendation is based on consensus and clinical experience.

- **After initiating opioid therapy or making any change in dose or route of administration, the dosage should be evaluated after approximately 24 hours.**

The plasma elimination half-life of morphine is 2 to 4 hours, and it takes approximately 24 hours before a steady state is reached after initiation of morphine or any change in dose.[43] If a patient requires 3 or more doses for breakthrough pain in 24 hours, the total daily dose of the opioid should be recalculated by adding the total amount of breakthrough medication given to the base 24-hour total. Information recorded by the patient is invaluable when adjusting the medication, and patients should be encouraged to maintain a diary recording dosages of pain medications taken, the level of pain before and 1 hour after each dose, and any adverse effects.

- **Tolerance to opioids is not common and must not be confused with addiction. Physical dependence to opioids is common and is not a symptom of addiction.**

Tolerance: Tolerance is the gradual development of resistance to the effects of a drug such that a higher dose is needed to provide the same effect. There is rapid tolerance to adverse effects of opioids such as respiratory depression, sedation and nausea and a much slower tolerance to constipation. In most patients, analgesic tolerance develops slowly.[56] Fear of this tolerance must not influence the physician to withhold opioids from a patient experiencing pain. Increasing pain usually reflects increasing disease activity rather than analgesic tolerance.

Physical dependence: Physical dependence is caused by the physiologic adaptation of tissues to the effects of a drug, such that withdrawal of the drug or administration of an antagonist leads to a withdrawal syndrome. All patients who take an opioid become physically dependent after several weeks. However, it is relatively easy to stop opioids in a patient who no longer requires them. The initial opioid dose can immediately be reduced by 75%, and the remaining 25% gradually decreased over a period of 10 days to 2 weeks.

Psychological dependence: Addiction in the context of chronic pain treatment with opioids is characterized by a persistent pattern of dysfunctional opioid use that may involve any or all of the following: adverse consequences associated with the use of opioids (e.g., decreasing function despite pain relief), loss of control over the use of opioids (e.g., not following the prescribed dose and obtaining multiple prescriptions) and preoccupation with obtaining opioids despite the presence of adequate analgesia.[57] Only exceedingly rarely does psychological dependence develop in patients who are taking opioids for pain due to cancer. It is estimated that the risk of psychological dependence, or addiction, in a patient with no previous history of substance abuse is in the range of 1000 to 1 or less.[58,59]

Pseudoaddiction: Individuals who have severe, unrelieved pain may become intensely focused on finding relief for their pain, and this behaviour may be perceived as suggestive of addiction. This pseudoaddiction is rapidly eliminated by the administration of adequate analgesia.[60]

Adverse effects of analgesics

Patients' responses to opioids vary.[61] Thus, adverse effects that occur with one drug may not occur with another from the same class.

Constipation: Constipation occurs in 90% of patients receiving opioid therapy.[62–64] Therefore, an order for an opioid should automatically be accompanied by instructions for a prophylactic bowel protocol. Regular laxatives are needed for as long as the opioids are used. There are no large trials comparing one laxative with another, but a stimulant laxative is usually necessary. Because patients frequently require more than one type of laxative,[65] common bowel protocols often combine a detergent laxative (stool softener) and a stimulant laxative to be used in increasing doses until an elimination pattern acceptable to the patient is achieved.[18]

Nausea and vomiting: These side effects occur in approximately one-third of patients when an opioid is first instituted. Normally they are short-lived complications that can be overcome by using antinauseants for a short time. If nausea persists, use regular antiemetics or consider switching opioids. Consider the use of more than one type of antiemetic (motility agent, phenothiazines, steroid) as nausea is often multifactorial.

Sedation: Sedation may occur, particularly in elderly patients. Patients should be cautioned against driving or using complex equipment at times when opioid therapy is being started or adjusted.[66,67] Sedation is often worse in the first 3 to 5 days after switching opioids or adjusting the dosage and may subside thereafter, allowing a return to driving.[68] Methylphenidate counteracts opioid sedation and may be used in patients who have no contraindications to drugs that stimulate the central nervous system.[69]

Confusion: Analgesics may cause confusion, particularly in elderly or debilitated patients. If confusion occurs, assessment of the many possible causes should be carried out. Since there is great individual variation in susceptibility to opioid-induced side effects, an alternative opioid should be tried if no other cause for the confusion is found.[27,70]

Respiratory depression: Clinically significant respiratory depression is rarely a problem in patients with cancer who are taking opioids on a long-term basis. Naloxone, a specific antagonist of opioids, can be used in certain cases. However, injudicious use of naloxone may cause the patient to have an acute withdrawal reaction, with attendant suffering and pain. Thus, naloxone should not be used in patients who are not hypoxic, who have only a moderate degree of respiratory slowing and in whom further opioid-related respiratory depression is not anticipated. If the patient is close to death, respiratory slowing is due to advancing disease, and naloxone should not be used, nor should the opioid be stopped.

Allergic reactions: True allergic reactions to opioids occur in less than 1% of patients. Often, patients believe they are allergic to morphine because of the side effects. Nevertheless, it is reasonable to use an alternative opioid if serious adverse effects do occur after the first dose. If true morphine allergy exists, an alternative opioid from a chemically different family may be used (e.g., methadone, oxycodone or fentanyl). Itching with the use of opioids is not an allergic reaction but rather an opioid-related histamine release. If switching opioids does not resolve the itch, the addition of an antihistamine for a few days will help until resolution of the histamine release after a few days.

Adjuvant analgesics

- **Adjuvant analgesics should be administered, when necessary, with an opioid or nonopioid analgesic.**

Adjuvant analgesics are drugs with other primary indications that have been found useful in the management of pain. Commonly used adjuvant analgesics are outlined below.

Corticosteroids: There is increasing evidence that, in addition to improving appetite and sense of well-being, corticosteroids are capable of relieving metastatic bone, liver and nerve-compression pain.[71,72] Patients suffering from metastatic cord compression have had pain relief from dexamethasone. Oral prednisolone therapy has been reported to have significant analgesic effects in a controlled study involving patients with advanced cancer (level I evidence).[73,74]

Antidepressants: Tricyclic antidepressants are helpful in the management of neuropathic pain,[75] and they most likely act by inhibiting nocioceptive transmission in the dorsal horn of the spinal cord. The most widely reported experience has been with amitriptyline; however, its use in patients with cancer is often difficult because of its anticholinergic side effects such as dry mouth and constipation. The dose required for pain relief is usually less than that required for managing depression, and beneficial effects may be observed earlier, often within 3 to 5 days. Alternative antidepressants with less anticholinergic effects include desipramine and nortriptyline. Paroxetine, a selective serotonin re-uptake inhibitor that is effective in the treatment of pain due to diabetic neuropathy has also been found to be helpful in other types of neuropathic pain (level V evidence).[76]

Anticonvulsants: These agents may be helpful in managing the lancinating component of neuropathic pain, as demonstrated in studies of patients with trigeminal neuralgia.[77] Commonly used drugs include carbamazepine, gabapentin, phenytoin, valproic acid, topiramate and clonazepam. Carbamazepine used to be the drug of first choice, but gabapentin has been found to be effective in relieving neuropathic pain from post-herpetic neuralgia and in improving mood and quality of life (level I evidence).[78] At this time there are no randomized controlled trials comparing gabapentin with other anticonvulsants.

Local anesthetics: Systemically administered local anesthetics such as mexiletine, tocainide or flecainide may be used for the management of refractory neuropathic pain.[79] Care should be exercised in combining mexiletine with tricyclic antidepressants, because some patients may have suffered psychotomimetic adverse effects. The relative role of each class of agent and the incidence of combined toxicity remains to be determined. Topical local anesthetics have been used to control neuropathic pain, particularly if a cutaneous nerve is involved, as in post-herpetic neuralgia.[80]

Substance P inhibitors: Capsaicin, a substance P inhibitor and topical analgesic, has been advocated for reducing cutaneous hyperalgesia and burning neuropathic pain, but its efficacy is still unproven.[81]

Bisphosphonates: The current drugs of first choice for the management of malignant hypercalcemia are the bisphosphonates (e.g., pamidronate). By inhibiting osteoclastic bone resorption, these drugs can also prevent or relieve malignant bone pain and other skeletal complications in some women with bone metastases (level I evidence).[82–90] In a patient with

multiple painful metastatic sites, an infusion of a bisphosphonate should be considered early in the treatment plan. Currently, there is conflicting evidence about whether the use of bisphosphonates in women with early breast cancer reduces the frequency of bone metastases.[89–91] In a randomized controlled trial reported by Hortobagyi and associates,[89] 382 women with metastatic breast cancer to the bone received either intravenous pamidronate therapy or placebo every 3 to 4 weeks. Patients were assessed monthly for 2 years. Significantly fewer women in the pamidronate group than in the control group had increased pain scores (41% v. 55%, $p = 0.015$), had an increase in their analgesic use (26% v. 40%, $p = 0.011$), and required radiation to bone for pain control (28% v. 45%, $p < 0.001$).

Nonpharmacological approaches to pain control

- **Nonpharmacological measures such as psychosocial interventions, physical modalities and complementary therapies may offer relief.**

A combination of pharmacological and nonpharmacological approaches to pain control provides effective pain management.[21,31]

Psychosocial interventions

Cognitive-behavioural therapies include relaxation training, hypnosis, guided imagery, distraction, coping self-statements and problem solving.[21,80,92] Relaxation techniques can be very useful in reducing the distress associated with pain and may incorporate specific breathing patterns, visualization and auditory stimulation such as music or nature sounds. Relaxation with guided imagery through hypnosis was the most effective pain control strategy in a meta-analysis of cognitive-behavioural therapy.[93] In a randomized controlled trial reported by Spiegel and Bloom,[94] interventions involving support group therapy and hypnosis were effective in reducing depression, fatigue and pain (level I evidence).

Physical modalities

These include exercise, immobilization, transcutaneous electrical nerve stimulation (TENS) and the use of superficial heat, cold, massage or vibration.[95] These noninvasive techniques are easily taught, may help patients to relax, relieve muscle spasm or distract patients from their pain. Although the use of superficial heat in its various forms is safe, modalities that involve deep heat, such as diathermy or ultrasonography, may influence tumour growth. Cold therapy reduces inflammation and swelling soon after an injury and can help relieve muscle spasm. Although scientific evidence supporting the role of massage in pain relief is limited, it is commonly useful in relieving muscle spasm and promoting relaxation.[96]

Lymphedema, which can cause extreme discomfort and sometimes pain, may respond to compression therapy (see guideline 11).

When a patient experiences pain on movement, despite overall good pharmacological therapy, specific positioning or immobilization methods may be useful.[65] However, prolonged immobilization, either of the whole body or a limb, should be avoided whenever possible to prevent joint contractures, muscle atrophy, cardiovascular deconditioning and loss of function.

Complementary therapies

Common complementary, alternative or unconventional therapies include mind techniques (meditation, prayer, biofeedback), types of exercise (Qi Gong, Tai Chi, yoga), energy healing modalities (therapeutic touch, reiki, healing touch) and homeopathic or herbal medicines. Acupuncture is a widely accepted complementary treatment for pain, although no randomized controlled trials have been done for chronic pain.[96] Despite the lack of rigorous scientific evidence to support the effectiveness of these strategies for the relief of cancer-induced pain,[96,97] an increasing number of patients are incorporating them into their pain-management plan. Patients are often hesitant to discuss the use of these strategies with their physician, even when they find that a particular complementary therapy is helpful.[98] Open communication and an atmosphere of respect for the patient's preferences will facilitate the patient's adherence to a pain-management plan that considers a variety of therapies in a combination most effective for the individual.[99]

Neurosurgical interventions

- **Neuroinvasive procedures can be considered when all other interventions have failed.**

Patients with refractory pain should be referred to pain specialists. Noninvasive treatment of pain should always precede invasive palliative approaches.[28] Except for spinal cord compression, neurosurgical interventions are rarely required in the management of cancer pain. Peripheral nerve blockade or central nervous system blockade should be considered only when a well-defined pain syndrome has been diagnosed. These strategies include neurolytic sympathetic blockade for brachial plexopathy, intercostal blockade for localized chest pain, and anterolateral cordotomy for unilateral limb pain arising from spinal segments below C3–4. As in other areas of treatment, the success of neurolytic procedures is operator-dependent. Intraspinal or intraventricular infusions of opioids may be indicated in certain patients in whom systemic opioid use is not effective or produces intolerable side effects, and where clinicians have access to skilled and experienced anesthetists.[100]

References

1. Foley KM. Pain syndromes in patients with cancer. In: Bonica JJ, Ventafrida V, Fink BR, Jones LE, Loeser JD, editors. *Advances in pain research and therapy*. Vol. 2. New York: Raven Press; 1979. p. 59-75.

2. Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest* 1989;95(Suppl):2S-4S.

3. Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer. *CMAJ* 1998;158(3 Suppl):S1-83. Available: www.cma.ca/cmaj/vol-158/issue-3/breastcpg

4. Regan JM, Peng P. Neurophysiology of cancer pain. *Cancer Control* 2000;7(2):111-9.

5. Temple WE, Ketcham AS. Preservation of the intercostobrachial nerve during axillary dissection for breast cancer. *Am J Surg* 1985;150:585-8.

6. Wallace MS, Wallace AM, Lee J, Dobke MK. Pain after breast surgery: a survey of 282

women. *Pain* 1996;66:195-205.

7. Carpenter JS, Andrykowski MA, Sloan P, Cunningham L, Cordova MJ, Studts JL, et al. Postmastectomy/postlumpectomy pain in breast cancer survivors. *J Clin Epidemiol* 1998;51(12):1285-92.

8. Kori SH, Foley KM, Posner JP. Brachial plexus lesions in patients with cancer: 100 cases. *Neurology* 1981;31:45-50.

9. Vecht CJ. Arm pain in the patient with breast cancer. *J Pain Symptom Manage* 1990;5:109-17.

10. Hagen N, Stulman J, Krol G, Foley K, Portenoy R. The role of myelography and magnetic resonance imaging in cancer patients with symptomatic and asymptomatic epidural disease. *Neurology* 1989;39(Suppl 1):309.

11. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. *J Palliat Care* 1991;7:6-9.

12. Foley KM. Pain assessment and cancer pain syndromes. In: Doyle D, Hanks GWC, MacDonald N, editors. *Oxford textbook of palliative medicine*. New York: Oxford University Press; 1993. p.148-65.

13. World Health Organization. *Cancer pain relief and palliative care*. Report of a WHO expert committee. Vol 804 of the World Health Organization Technical Report series. Geneva: The Organization; 1990. p. 1-75.

14. Aapro M, Cull A. Depression in breast cancer patients: the need for treatment [review]. *Ann Oncol* 1999;10(6):627-36.

15. Librach SL, Squires BP. 1997 *The Pain manual: principles and issues in cancer pain management.* Pegasus: Montreal.

16. Portenoy RK, Miransky J, Thaler HT, Hornung J, Bianchi C, Cibas-Kong I, et al. Pain in ambulatory patients with lung or colon cancer. Prevalence, characteristics, and effect. *Cancer* 1992;70:1616-24.

17. Von Roenn JH, Cleeland CS, Gonin R, Hatfield AK, Pandya KJ. Physician attitudes and practice in cancer pain management. A survey from the Eastern Cooperative Oncology Group. *Ann Intern Med* 1993;119:121-6.

18. Cleary JF. Cancer pain management. *Cancer Control* 2000;7:120-31.

19. Yadgood MC, Miller PJ, Mathews PA. Relieving the agony of the new pain management standards. *Am J Hospice Palliative Care* 2000;17(5):333-41.

20. Vachon ML, Kristjanson L, Higginson I. Psychosocial issues in palliative care: the patient, the family, and the process and outcome of care. *J Pain Symptom Manage* 1995;10:142-50.

21. Thomas EM, Weiss SM. Nonpharmacological interventions with chronic cancer pain in adults.

Cancer Control 2000;7(2):157-64.

22. Kurman MR. Systemic therapy (chemotherapy) in the palliative treatment of cancer pain. In: Patt RB, editor. *Cancer pain*. Philadelphia: J.B. Lippincott; 1993. p. 251-74.

23. Stam HJ, Goss C, Rosenal L, Ewems S. Cancer pain and distress in patients undergoing radiotherapy. *Pain* 1984;20(Suppl 2):S181.

24. Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. *Pain* 1993;52:259-85.

25. Mao J, Price DD, Mayer DJ. Mechanisms of hyperalgesia and morphine tolerance: a current view of their possible interactions. *Pain* 1995;62:259-74.

26. Hoskins PJ. Radiotherapy in symptom management. In: Doyle D, Hanks GWC, MacDonald N, editors. *Oxford textbook of palliative medicine*. New York: Oxford University Press; 1993. p. 117-29.

27. MacDonald N, Der L, Allan S, Champion P. Opioid hyperexcitability: the application of alternate opioid therapy. *Pain* 1993;53:353-5.

28. Zech DF, Grond S, Lynch J, Hertel D, Lehmann KA. Validation of World Health Organization guidelines for cancer pain relief: a 10-year prospective study. *Pain* 1995;63:65-76.

29. Miguel R. Interventional treatment of cancer pain: The fourth step in the World Health Organization analgesic ladder? *Cancer Control* 2000;7(2):149-56.

30. Rawlins MD. Non-opioid analgesics. In: Doyle D, Hanks GWC, MacDonald N, editors. *Oxford textbook of palliative medicine*. New York: Oxford University Press; 1993. p. 182-7.

31. Jacox A, Carr DB, Payne R, Berde CB, Brietbart W, Cain J, et al. *Management of cancer pain* [clinical practice guideline no 9; AHCPR publication no 94-0592]. Rockville (MD): Agency for Health Care Policy and Research, US Department of Health and Human Services, Public Health Service; March 1994. p. 49.

32. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for monitoring drug therapy in rheumatoid arthritis. *Arthritis Rheum* 1996;39:723-31.

33. Silverstein FE, Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind placebo-controlled trial. *Ann Intern Med* 1995;123:241-9.

34. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;343:1520-8.

35. Fitzgerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001;345:433-42.

36. Stein C, Hassan AH, Lehrberger K, Giefing J, Yassouridis A. Local analgesic effect of endogenous opioid peptides. *Lancet* 1993;342:321-4.

37. Stein C. The control of pain in peripheral tissue by opioids. *N Engl J Med* 1995;332:1685-90.

38. Hanks GWC, Cherny N. Opioid analgesic therapy. In: Doyle D, Hanks GWC, MacDonald N, editors. *Oxford textbook of palliative medicine*. New York: Oxford University Press; 1997. p. 29.

39. De Conno F, Groff L, Brunelli C, Zecca E, Ventafridda V, Ripamonti C. Clinical experience with oral methadone administration in the treatment of pain in 196 cancer patients. *J Clin Oncol* 1996;14(10):2836-42.

40. Kaiko RF, Foley KM, Grabinski PY, Heidrich G, Rogers AG, Inturrise CE, et al. Central nervous system excitatory effects of meperidine in cancer patients. *Ann Neurol* 1983;13:180-5.

41. Hoskin PJ, Hanks GW. Opioid agonist-antagonist drugs in acute and chronic pain states. *Drugs* 1991;41:326-44.

42. Houde RW. Analgesic effectiveness of the narcotic agonist-antagonists. *Br J Clin Pharmacol* 1979;7:297S-308S.

43. Expert Working Group of the European Association for Palliative Care. Morphine in cancer pain: modes of administration [review]. *BMJ* 1996;312:823-6.

44. Bruera E, Fainsinger R, Spachynski K, Babul N, Harsanyi Z, Darke AC. Clinical efficacy and safety of a novel controlled-release morphine suppository and subcutaneous morphine in cancer pain: a randomized evaluation. *J Clin Oncol* 1995;13:1520-27.

45. Ahmedzai S, Allan E, Fallon M, Finlay IG, Hanks GW, Hanna M, et al. Transdermal fentanyl in cancer pain. *J Drug Dev* 1994;6:93-7.

46. Ahmedzai S, Brooks D. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. The TTS-Fentanyl Comparative Trial Group. *J Pain Symptom Manage* 1997;13(5):254-61.

47. Donner B, Zenz M, Strumpf M, Raber M. Long term treatment of cancer pain with transdermal fentanyl. *J Pain Symptom Manage* 1998;15(3):168-75.

48. Bruera E, Macmillan K, Selmser P, MacDonald RN. Decreased local toxicity with subcutaneous diamorphine (heroin): a preliminary report. *Pain* 1990;43:91-4.

49. Storey P, Hill HH, St. Louis RH, Tarver EE. Subcutaneous infusions for control of cancer symptoms. *J Pain Symptom Manage* 1990;5:33-41.

50. McQuay HJ. Opioid clinical pharmacology and routes of administration. *Br Med Bull* 1991;47:703-17.

51. Osborne R, Joel S, Grebenik K, Trew D, Slevin M. The pharmacokinetics of morphine and morphine glucuronides in kidney failure. *Clin Pharmacol Ther* 1993;54:158-67.

52. Bruera E, Franco JJ, Maltoni M, Watanabe S, Suarez-Almazor M. Changing pattern of agitated impaired mental status in patients with advanced cancer: association with cognitive monitoring, hydration and opiate rotation. *J Pain Symptom Manage* 1995;10:287-91.

53. Cherny NI, Portenoy RK. The management of cancer pain [review]. *CA Cancer J Clin* 1994;44:263-303.

54. Max M, Payne R. Principles of analgesic use in the treatment of acute pain and cancer pain. American Pain Society; 1999.

55. Anderson R, Saiers JH, Abram S, Schlicht C. Accuracy in equianalgesic dosing: conversion dilemmas. *J Pain Symptom Manage* 2001;21:397-406.

56. Twycross R. *Pain relief in advanced cancer*. London: Churchill Livingstone; 1994. p. 339.

57. American Society of Addiction Medicine. Public policy statement on definitions related to the use of opioids in pain treatment. Chevy Chase (MD): The Society; 1997.

58. Porter J, Jick H. Addiction rare in patients treated with narcotics [letter]. *N Engl J Med* 1980;302:123.

59. Kanner RM, Foley K. Patterns of narcotic use in a cancer pain clinic. *Ann N Y Acad Sci* 1981;362:161-72.

60. Weissman DE, Haddox JD. Opioid pseudoaddiction: an iatrogenic syndrome. *Pain* 1989;36:363-6.

61. Insel PA. Analgesic-antipyretic and antiinflammatory agents and drugs employed in the treatment of gout. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, editors. *Goodman and Gilman's the pharmacologic basis of therapeutics*. 9th ed. New York: McGraw-Hill; 1996. p. 624.

62. Manara L, Bianchetti A. The central and peripheral influences of opioids on gastrointestinal propulsion. *Annu Rev Pharmacol Toxicol* 1985;25:249-73.

63. Wald A. Constipation in elderly patients. Pathogenesis and management. *Drugs Aging* 1993;3:220-31.

64. Mancini I, Bruera E. Constipation in advanced cancer patients. *Support Care Cancer* 1998;6(4):356-64.

65. Groenwald SL, Frogge MH, Goodman M, Henke Yarbro C, (1997) *Cancer nursing: principles and practice.* Sudbury (MA): Jones & Bartlett; 1997.

66. Hanks GW. Morphine sans morpheus. *Lancet* 1995;346:652-3.

67. Vainio A, Ollila J, Matikainen E, Rosenberg P, Kalso E. Driving ability in cancer patients receiving long-term morphine analgesia. *Lancet* 1995;346:667-70.

68. Bruera E, Macmillan K, Hanson J, MacDonald RN. The cognitive effects of the administration of narcotic analgesics in patients with cancer pain. *Pain* 1989;39:13-6.

69. Bruera E, Watanabe S. Psychostimulants as adjuvant analgesics. *J Pain Symptom Manage* 1994;9:412-5.

70. De Stoutz ND, Bruera E, Suarez-Almazor M. Opioid rotation for toxicity reduction in terminal cancer patients. *J Pain Symptom Manage* 1995;10:378-84.

71. Ettinger AB, Portenoy RK. The use of corticosteroids in the treatment of symptoms associated with cancer. *J Pain Symptom Manage* 1988;3:99-103.

72. Tannock I, Gospodarowicz M, Meakin M, Panzarella T, Stewart L, Rider W. Treatment of metastatic prostate cancer with low dose prednisone: evaluation of pain and quality of life as pragmatic indices of response. *J Clin Oncol* 1989;7:590-7.

73. Posner JB. Back pain and epidural spinal cord compression [review]. *Med Clin North Am* 1987;71:185-205.

74. Bruera E, Roca E, Cedaro L, Carraro S, Chacon R. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. *Cancer Treat Rep* 1985;69:751-4.

75. Watson CP. Antidepressant drugs as adjuvant analgesics. *J Pain Symptom Manage* 1994;9:392-405.

76. Sindrup SH, Gram LF, Brosen K, Eshoj O, Mogensen EF. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. *Pain* 1990;42:135-44.

77. McQuay H, Carroll D, Jadad RJ, Wiffen P, Moore A. Anticonvulsant drugs for management of pain: a systematic review. *BMJ* 1995;311:1047-52.

78. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized trial. *JAMA* 1998;280(21):1837-42.

79. Beckonja MM. Local anaesthetics as adjuvant analgesics. *J Pain Symptom Manage* 1994;9:491-9.

80. Portenoy RK, Foley KM. Management of cancer pain. In: Holland JC, Rowland JH, editors. *Handbook of psychooncology*. New York: Oxford University Press; 1989. p. 369-83.

81. Watson CP. Topical capsaicin as an adjuvant analgesic. *J Pain Symptom Manage* 1994;9:425-33.

82. Conte PF, Latreille J, Mauriac L, Calabresi F, Santos R, Campos D, et al. Delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate: results from a multinational randomized controlled trial. The Aredia Multinational Cooperative Group. *J Clin Oncol* 1996;14:2552-9.

83. Ernst DS, MacDonald RN, Paterson AH, Jensen J, Brasher P, Bruera E. A double-blind, crossover trial of intravenous clodronate in metastatic bone pain. *J Pain Symptom Manage* 1992;7:4-11.

84. Hortobagyi GN, Theriault RL, Porter L, Blayney D, Lipton A, Sinoff C, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. *N Engl J Med* 1996;335:1785-91.

85. Lipton A, Glover D, Harvey H, Grabelsky S, Zelenakas K, Macerata R, et al. Pamidronate in the treatment of bone metastases: results of 2 dose-ranging trials in patients with breast or prostate cancer. *Ann Oncol* 1994;5(Suppl 7):S31-5.

86. Paterson AHG, Powles TJ, Kanis JA, McCloskey E, Hanson J, Ashley S. Double-blind control trial of oral clodronate in patients with bone metastases from breast cancer. *J Clin Oncol* 1993;11:59-65.

87. Theriault R, Lipton A, Leff R, Gluck S, Stewart J, Costello S, et al. Reduction of skeletal related complications in breast cancer patients receiving hormone therapy by monthly pamidronate sodium (Aredia) infusion [abstract]. *Proc Annu Meet Am Soc Clin Oncol* 1996;15:A122.

88. Thiebaud D, Leyvraz S, von Fliedner V, Perey L, Cornu P, Thiebaud S, et al. Treatment of bone metastases from breast cancer and myeloma with pamidronate. *Eur J Cancer* 1991;27:37-41.

89. Hortobagyi GN, Theriault RL, Lipton A, Porter L, Blayney D, Sinoff C, et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. *J Clin Oncol* 1998;16(6):2038-44.

90. Theriault RL, Lipton A, Hortobagyi GN, Leff R, Gluck S, Stewart JF, et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. *J Clin Oncol* 1999;17(3):846-54.

91. Paterson AHG, McCloskey EV, Ashley S, Powles TJ, Kanis JA. Reduction of skeletal morbidity and prevention of bone metastases with oral clodronate in women with recurrent breast cancer in the absence of skeletal metastases [abstract]. *Proc Annu Meet Am Soc Clin Oncol* 1996;15:A104.

92. Breitbart W, Passik SD. Psychological and psychiatric interventions in pain control. In: Doyle D, Hanks GWC, MacDonald N, editors. *Oxford textbook of palliative medicine*. New York: Oxford University Press; 1993. p. 244-56.

93. Devine EC, Westlake SK. The effect of psychoeducational care provided to adults with cancer: meta-analysis of 116 studies. *Oncol Nurs Forum* 1995;22:1369-81.

94. Spiegel D, Bloom JR. Group therapy and hypnosis reduce metastatic breast carcinoma pain. *Psychosom Med* 1983;45:333-9.

95. Thompson JW, Filshie J. Transcutaneous electrical nerve simulation (TENS) and acupuncture. In: Doyle D, Hanks GWC, MacDonald N, editors. *Oxford textbook of palliative medicine*. New York: Oxford University Press; 1993. p. 229-43.

96. Sellick SM, Zaza C. Critical review of 5 non pharmacologic strategies for managing cancer pain. *Cancer Prevent Control* 1998;2(1):7-14.

97. Jacobson JS, Workman SB, Kronenberg F. Research on complementary/alternative medicine for patients with breast cancer: A review of the biomedical literature. *J Clin Oncol* 2000;18(3):668-83.

98. Rhiner M, Dean GE, Ducharme S. Non pharmacologic measures to reduce cancer pain in the home. *Home Health Care Manage Prac* 1996;8(2):41-7.

99. Cassileth BR, Chapman CC. Alternative and complementary cancer therapies. *Cancer* 1996;77:1026-34.

100. Swarm RA, Cousins MJ. Anaesthetic techniques for pain control. In: Doyle D, Hanks GWC, MacDonald N, editors. *Oxford textbook of palliative medicine*. New York: Oxford University Press; 1993. p. 204-21.

Table 1: Common causes of chronic pain in patients with breast cancer

Pain due to direct tumour involvement
Bone metastases
Neural metastases
Brachial plexopathy
Spinal cord compression
Meningeal carcinomatosis
Peripheral neuropathy due to tumour infiltration
Visceral metastases
Pleura
Liver
Bowel
Peritoneum
Pain due to antineoplastic treatment
Procedure-related pain in breast and shoulder
Postmastectomy syndrome
Lymphedema-related discomfort and pain
Postirradiation pain
Peripheral neuropathy
Pain due to drug extravasation
Phlebitis
Mucositis
Chemical cystitis (with cyclophosphamide)
Osteoporosis or avascular necrosis
Pre-existing conditions
Dermatomal herpes zoster

Table 2: Recommended opioid agonist drugs

Drug	Route	Equivalent dose, mg	Duration, h	Comments
Morphine	Subcutaneous Oral	10 20	3–4 3–4	Standard for comparison
Codeine	Oral	200	2–4	Usually combined with a nonopioid
Oxycodone	Oral	15–20	2–4	Used for step 2* with a nonopioid. Used for step 3 as a single agent
Hydromorphone	Subcutaneous Oral	2 6	2–4 2–4	
Diamorphine	Subcutaneous	5	3–4	Reserved for patients with local reaction to other opioids
Fentanyl	Transdermal	Approximately 100 to 200 times the potency of morphine in an acute pain context. Equivalence in chronic pain is not well established. Patches deliver 25, 50, 75 and 100 µg/h. A 25-µg/h patch is roughly equivalent to 45 mg/d of sustained-release morphine[54]		

Slow-release preparations of morphine, codeine, oxycodone and hydromorphone with a duration of action of approximately 12 h are available in Canada.
*World Health Organization's 3-step approach to the use of analgesics.