10. The management of chronic pain in patients with breast cancer

The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer

Abstract

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

Outcomes: Pain control, absence of adverse effects.

Evidence: Systematic review of the literature up to Dec. 30, 1996, with nonsystematic coverage to July 1997. Where experimental evidence is lacking, recommendations are based on expert opinion. The evidence was evaluated and graded in "levels" (page S2).

Recommendations:

- The nature and severity of pain should be carefully evaluated using the history and physical examination. Psychosocial and emotional factors must also be identified. Adequacy of pain control should be evaluated regularly.
- The first objective in the management of pain due to cancer 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. The administration of analgesic medication should be based on a regular schedule, around the clock, with additional doses for breakthrough pain when necessary.
- When drug therapy is necessary, the World Health Organization (WHO) 3-step approach to the use of analgesics is recommended.
- 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 intravenous or subcutaneous routes can be used according to circumstances. Intramuscular administration of opioids is not recommended.
- Careful observation and titration are required when switching from 1 opioid to another, particularly when the patient is already receiving a high dosage.
- When converting a patient from long-term oral use of morphine or hydromorphone to parenteral use, a ratio of 3:1 should usually be employed. (This ratio increases to 6:1 for opioid-naive patients.)
- After initiating morphine or making any change of dose or route of administration, the dosage should be evaluated after approximately 24 hours.
- Tolerance to opioids must not be confused with physical dependence or psychological dependence (so-called "addiction").
- Patients should be made aware of possible side effects of medications and should be encouraged to maintain a diary for recording medications taken, dosages and adverse events.
- Adjuvant analgesics should be administered, when necessary, with an opioid or nonopioid analgesic.
- Noninvasive measures such as psychosocial interventions and physical modalities may bring significant relief.
- Neuroinvasive procedures are rarely required and should only be considered when other interventions have failed.

Validation: The guidelines were reviewed and revised by a writing committee, expert primary reviewers, secondary reviewers selected from all regions of Canada and by the Steering Committee. The present guidelines reflect a consensus of all of these contributors. They have been reviewed and endorsed by the Canadian Society of Palliative Care Physicians and the Canadian Association of Radiation Oncologists.

Sponsor: The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer was convened by Health Canada.

Completion date: July 1, 1997
Pain is common in women in whom metastatic breast cancer develops and is experienced by more than 50% of this group. In most cases pain results from tissue injury. However, the extent of tissue injury cannot totally explain certain painful syndromes frequently experienced by patients with cancer, such as headaches and postherpetic pain or the varying degrees of suffering experienced by patients with seemingly similar problems.

Pain is both a somatic and psychic experience, in other words, a physical and affective sensation experienced according to the person’s capacity to control it effectively and understand its cause. Suffering may be much more intense when pain is experienced in association with other troublesome symptoms or feelings such as fatigue, anxiety, insomnia, depression, isolation, fear, anger and uncertainty. All of these will compound suffering and must be addressed as part of a comprehensive approach to pain management.

Irrespective of its cause, pain can usually be managed and reduced to tolerable levels while avoiding the severe side effects of treatment. These guidelines aim to provide essential information to help patients and their physicians achieve optimal pain control with a minimum of side effects.

**Method**

These guidelines are based on published clinical research and, where evidence from this source is lacking, on expert opinion. A systematic review of the English language literature was carried out in 1991 in the course of preparing the *Oxford Textbook of Palliative Medicine*. This database has since been maintained and updated by systematic, regular review of 9 journals (*Pain, Palliative Medicine, the Journal of Palliative Care*, the *Journal of Clinical Oncology, the British Medical Journal*, the *Lancet, the Journal of Pain and Symptom Management, the New England Journal of Medicine and Cancer*) and supplemented by the use of the electronic databases MEDLINE and Current Contents from Jan. 1, 1990, to Dec. 30, 1996. The guidelines of the World Health Organization entitled *Cancer Pain Relief* and the guidelines of the Agency for Health Care Policy and Research of the United States Department of Health and Human Services entitled *Management of Cancer Pain* have also been consulted. Literature review on a nonsystematic basis was continued to July 1997.

The initial draft guidelines were iteratively reviewed and revised with the help of the author, a writing committee consisting of 6 members of The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer, by 3 external primary reviewers with special expertise in pain management and by all members of the Steering Committee. The prefinal draft was then submitted to 15 secondary reviewers consisting of surgical, medical and radiation oncologists, nurses, family physicians and breast cancer survivors from all regions of Canada and, after further revision, received final approval by the Steering Committee. Throughout, all changes were reviewed by the author. The present guidelines reflect a consensus of all of these contributors. Most of the recommendations are based on level III evidence for which the sources are cited. When no such evidence exists, the recommendations are based on level IV and level V evidence (see page S2).

**Recommendations (including evidence and rationale)**

**Etiology of pain associated with breast cancer**

There are many reasons why a patient with breast cancer may experience pain. Once the etiology is identified and the pathophysiology understood, this can lead to more effective management.

Tumours may cause pain, either by stimulating nerve fibres, which respond to mechanical pressure, or through the release of chemical stimuli. A variety of chemicals that sensitize small nonmyelinated nerve endings are generated by the tumour or the host. These include prostaglandins, cytokines, leukotrienes, bradykinin and histamine. Also, important neurotransmitters in the spinal cord include excitatory chemicals (e.g., substance P) and inhibitory peptides (e.g., endorphins, enkephalins and dynorphins).

Opioids mimic the actions of the natural inhibitory peptides in the central nervous system. Recently, opioids have also been demonstrated to inhibit primary sensory stimulation in the periphery. Nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids probably act by inhibiting the production of pain-causing substances in the periphery, although they may also have central actions.

Nociceptive pain (pain stimuli transmitted and interpreted by an intact nervous system) is usually readily managed by opioids and NSAIDs. However, neuropathic pain (resulting from involvement of the sensory nerves) can cause a type of chronic pain that is difficult to control.

Pain resulting from damage to the peripheral nervous system may be accompanied by changes in neurotransmitters and neuronal hyperactivity in the central nervous system. Such pain due to nerve damage may respond in part to opioids, corticosteroids and NSAIDs, but management often requires consideration of alternative therapeutic approaches (see section on adjuvant analgesics).

The distinction must be made between pain caused by the cancer, pain resulting from its treatment (including the severe discomfort and pain that can result from lymphedema) and pain due to comorbid syndromes such as osteoporosis or chronic disc syndrome. Some of the causes of pain syndromes associated with breast cancer are listed in Table 1. Three common syndromes deserve special mention and are discussed below: postmastectomy pain syndrome, brachial plexopathy and metastatic bone pain.

The postmastectomy syndrome 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 persistent pain...
Management of chronic pain

Metastatic disease should be identified early. Whenever breast cancer patients complain of new, persistent pain, particularly in common metastatic sites, appropriate diagnostic tests should be carried out to exclude the presence of bone metastases.

The most common cause of pain due to cancer in patients with breast cancer is the spread of tumour to bone. Pain is generated by the direct stimulation of nerve fibres by the metastatic growth. Metastases also excite a local inflammatory reaction (mediated in part by prostaglandins) and often stimulate osteoclast activity.

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 pressure on the spinal cord as the result of epidural invasion. Pain is almost always the earliest symptom heralding involvement of bone.

The early recognition of metastatic disease will enable the physician to institute antitumour therapy and bisphosphonates, which can limit further complications and, in concert with an analgesic program, maintain a better quality of life.

Evaluation of pain

- The nature and severity of pain should be carefully evaluated using the history and physical examination. Psy-

<table>
<thead>
<tr>
<th>Table 1: Common causes of chronic pain in patients with breast cancer</th>
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<tbody>
<tr>
<td>Pain due to direct tumour involvement</td>
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<tr>
<td>Bone metastases</td>
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<tr>
<td>Neural metastases</td>
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<tr>
<td>Brachial plexopathy</td>
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<tr>
<td>Spinal cord compression</td>
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<tr>
<td>Meningeal carcinomatosis</td>
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<tr>
<td>Peripheral neuropathy due to tumour infiltration</td>
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<tr>
<td>Visceral metastases</td>
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<tr>
<td>Pleura</td>
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<tr>
<td>Liver</td>
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<tr>
<td>Bowel</td>
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<tr>
<td>Peritoneum</td>
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<tr>
<td>Pain due to antineoplastic treatment</td>
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<tr>
<td>Procedure-related pain in breast and shoulder</td>
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<tr>
<td>Postmastectomy syndrome</td>
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<tr>
<td>Lymphedema-related discomfort and pain</td>
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<tr>
<td>Postirradiation pain</td>
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<tr>
<td>Peripheral neuropathy</td>
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<tr>
<td>Pain due to drug extravasation</td>
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<tr>
<td>Phlebitis</td>
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<tr>
<td>Mucositis</td>
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<tr>
<td>Chemical cystitis (with cyclophosphamide)</td>
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<tr>
<td>Osteoporosis or avascular necrosis</td>
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<tr>
<td>Pre-existing conditions</td>
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<tr>
<td>Dermatomal herpes zoster</td>
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</table>

Brachial plexopathy usually precedes 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, commonly in association with lymphedema.

A patient with a brachial plexopathy due to cancer will usually complain of pain in the shoulder, girdle, with radiation to the elbow, the medial side of the forearm and the fourth and fifth fingers. As is characteristic of pain that is due to nerve damage, it is commonly described as burning, often with an aching component; the patient may be particularly bothered by lancinating pain lasting for fractions of a second. Touch sensation may be altered in the area of pain distribution. Also, patchy areas of altered sensation are often noted. In time, the pain is accompanied by evidence of weakness, muscle atrophy and, occasionally, sympathetic reflex dystrophy.

When the pain of brachial plexopathy is due to metastases, the management of this syndrome is primarily through antineoplastic measures; however, therapy appropriate for management of neuropathic pain syndromes must also be used. If the tumour is not controlled it will often extend to the adjacent epidural space. Therefore, cord compression is a particular risk in patients with tumour-induced brachial plexopathy.

When the syndrome is caused by radiation, the same approach should be used as for other nerve damage syndromes.
The first priority of treatment is to control pain rapidly.

Adequacy of pain control should be evaluated regularly.

The initial evaluation of pain should include a detailed history, including assessment of the intensity and type of pain, a physical examination emphasizing the neurologic examination and provocative measures to pinpoint the anatomic site of pain, a psychosocial assessment, and a work-up to determine the specific cause of the pain.

The following issues should be addressed in the history:
- What factors make the pain better or worse?
- What is the nature of the pain? Is it dull, burning, lancinating, etc.?
- Where is the pain located?
- How many pains do you have?
- From its most intense site, where does it spread?
- How severe is the pain?
- When does the pain occur? Is it constant or intermittent? What is its relationship to activities or events?
- Psychosocial and emotional factors that may have an impact on the severity and presence of pain should be identified. These include the effect of activity, the ability to carry out normal functions, interference with sleep and rest, and the significance that the patient or family attributes to the pain. Past and current drugs and nondrug interventions for controlling symptoms should be reviewed since these will influence current decisions.

Although pain is subjective, the dimensions of pain can be quantified. Since clinicians tend to underestimate the severity of pain, it is recommended that patient self-report assessment tools be used routinely in the diagnosis and follow-up of patients with breast cancer who have pain (level IV evidence).

The Edmonton Symptom Assessment Scale provides a simple model of a pain and symptom assessment form for institutional and outpatient use. Regular assessment will reveal changes in the pattern of the pain or the development of new pain. When this occurs the evaluation of the source and type of pain must be repeated and the treatment plan modified appropriately.

Therapeutic principles

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

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). Since relief from radiotherapy may be delayed, prompt referral to a radiotherapy facility is recommended. Systemic anticancer therapy, using either hormonal or chemotherapy, can also bring about temporary remissions in most women with previously untreated metastatic disease. Patients should be warned, however, that tamoxifen can produce a temporary exacerbation of metastatic bone pain and that this does not necessarily reflect progression of disease.

- 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. The administration of analgesic medication should be based on a regular schedule, around the clock, with additional doses for breakthrough pain when necessary.

Rapid and complete control is important because chronic pain can cause changes in the processing of the pain message in the central nervous system. The balance of inhibitory and excitatory neurotransmitters and associated receptors is adversely affected, and previously silent sensory pathways may be recruited. Thus, 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. Therefore, regardless of whether one is employing anticancer therapy or analgesic treatment, a preventive approach is important.

This is best achieved by a regular dosage schedule, with additional doses for breakthrough pain as necessary, rather than by giving analgesics only when pain recurs (level IV evidence).

- When drug therapy is necessary, the World Health Organization (WHO) 3-step approach to the use of analgesics is recommended.

Analgesic drugs can be divided into 3 groups: the nonopioid analgesics, the opioid analgesics and the adjuvant analgesics. A simple, effective method of using analgesics was developed by a consensus group of experts convened by the World Health Organization. Since then it has been field tested and its usefulness demonstrated. It consists of 3 steps, as outlined below.

Step 1. Mild to moderate pain calls for the use of acetaminophen or an NSAID, or both together.

NSAIDs are particularly helpful in the management of pain caused by bone metastases, because of their ability to block the production of prostaglandins. NSAIDs display a “ceiling” effect. Thus, when used in doses that are greater than recommended, the risk of toxicity increases without any increase in analgesia. No single NSAID has been shown to be superior to any of the others for pain relief. 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, and gastric and duodenal ulceration and bleeding. If patients have dyspepsia, an alternative NSAID should be considered. 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 (level IV evidence). The best drug for these situations is probably misoprostol. Level III evidence shows that prophylactic use of antacids or H2-receptor blockers is of limited value in patients receiving long-term treatment with NSAIDs, and level I evidence indicates that, at least in patients with rheumatoid arthritis, misoprostol will effectively reduce the frequency of gastrointestinal complications.
Step 2. When pain is not adequately controlled, an opioid such as codeine or oxycodone should be added to the NSAID.

Codeine is less potent than morphine and oxycodone is slightly more so. Oxycodone is available in Canada as tablets and suppositories and in low-dose combinations with acetaminophen or acetylsalicylic acid. If flexibility in the individual drug dosage is not required, a combination of acetaminophen and oxycodone provides a convenient preparation for patients requiring the step 2 level of pain relief according to the WHO approach.

Step 3. When pain is severe and 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 drug with similar opioid properties. Oxycodone or fentanyl are useful alternatives if patients have uncontrollable side effects while taking other opioids. Methadone is a satisfactory agent but is more difficult to use because of its very variable and long half-life.

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 and drugs of the same class or mixed agonist-antagonist drugs such as pentazocine are not usually recommended. Meperidine 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.

Pentazocine causes psychotomimetic effects in many patients and because it is a mixed agonist-antagonist can precipitate a withdrawal reaction when a patient on long-term opioid therapy is switched from another opioid to pentazocine.

**Opioids**

- The oral route should be the first choice for opioid administration.

All opioids commonly used in Canada are effective by mouth. Some are listed in Table 2. There is no such thing as a standard dose of an opioid. Oral bioavailability 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 that cannot be managed by simple interventions. 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.

Slow-release preparations of morphine, codeine, hydromorphone and oxycodone are available and should be used primarily for patients with readily controlled cancer pain. They should never be used on an “as needed” basis for breakthrough pain (level V evidence).

- If the oral route fails, transdermal or rectal administration should be considered.

The bioavailability, relative potency and duration of analgesic effect of some opioids are listed in Table 2. Slow-release preparations of morphine, codeine, oxycodone and hydromorphone with a duration of action of approximately 12 h are available in Canada.

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**Table 2: Recommended opioid agonist drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Equivalent dose; mg</th>
<th>Duration; h</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Subcutaneous</td>
<td>10</td>
<td>3–4</td>
<td>Standard for comparison</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>30</td>
<td>3–4</td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>Oral</td>
<td>200</td>
<td>2–4</td>
<td>Usually combined with a nonopioid</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Oral</td>
<td>20</td>
<td>2–4</td>
<td>Used for step 2* with a nonopioid. Used for step 3 as a single agent</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Oral</td>
<td>2</td>
<td>2–4</td>
<td></td>
</tr>
<tr>
<td>Diamorphine</td>
<td>Subcutaneous</td>
<td>5</td>
<td>3–4</td>
<td>Reserved for patients with local reaction to other opioids</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Transdermal</td>
<td>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. Morphine subcutaneously every 4 h is approximately equivalent to a 25 to 50 µg/h patch.</td>
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*World Health Organization 3-step approach to the use of analgesics
gesia of orally and rectally administered morphine are similar, and the recent introduction of long-acting morphine suppositories facilitates the use of this drug. Transdermal fentanyl should be considered for patients who cannot take oral medication, for those with a nonfunctioning gastrointestinal tract or for patients who tolerate morphine and drugs in the same class poorly.

- When parenteral administration is necessary, the intravenous or subcutaneous routes can be used according to circumstances. Intramuscular administration of opioids is not recommended.

Morphine may be given intravenously, either in hospital or in the home, as long as an intravenous line is available. However, opioids are generally well tolerated when administered subcutaneously, with the exception of meperidine and methadone, which cause inflammatory reactions in subcutaneous tissue. The use of the subcutaneous route reduces nursing time and, in the home, families and patients can readily be taught to give subcutaneous therapy either by intermittent injection or by continuous infusion through a syringe-driver. Under ordinary circumstances a parenteral site requires changing only every 4 to 7 days. If a subcutaneous reaction is observed with one opioid, an alternative opioid may be used. Diamorphine may cause less subcutaneous irritation and should be considered when other subcutaneous preparations cannot be used due to local toxic reactions.

Intramuscular administration of opioids is painful, inconvenient and difficult to institute in the home setting. The intravenous route can be used when an infusion line is already installed. For a small group of patients, the sustained use of opioid by the epidural route with a local anesthetic may provide optimum analgesia without excess adverse effects.

- Careful observation and titration are required when switching from 1 opioid to another, particularly when the patient is already receiving a high dosage.

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. Usually, it is recommended that a new opioid be started at 50% of the published equivalent dose or at an even lower rate if the patient is already receiving a high opioid dose. However, if the patient has uncontrolled pain at the time of drug change, higher doses may be required.

- When converting a patient from long-term oral use of morphine or hydromorphone to parenteral use, a ratio of 3:1 should usually be employed. (This ratio increases to 6:1 for opioid-naive patients.)

This recommendation is based on experience. However, considerable individual variation can be expected (level IV evidence).

- After initiating morphine or making any change of 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 initiating morphine or making any change of dose.

- Tolerance to opioids must not be confused with physical dependence or psychological dependence (so-called "addiction").

**Tolerance**

This is the gradual development of resistance to the effects of a drug such that a higher dose is needed to provide the same effect. Tolerance to both the beneficial and adverse effects of opioids develops at approximately the same rate (with the exception of the rapid development of tolerance to the nauseating action of opioids and the slow development of tolerance to constipating effects). In most patients, tolerance to orally administered opioids develops slowly. Fear of tolerance must not influence the physician to withhold opioids from a patient experiencing pain. When pain increases it usually reflects increasing disease activity rather than 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 dependent after several weeks. However, it is a relatively easy task 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**

Also called “addiction,” psychological dependence is a behavioural pattern characterized by the craving for a drug and an overwhelming preoccupation with obtaining it. 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 while a patient is taking opioids for medical reasons without previously having taken opioids is in the range of 1000 to 1 or less.

**Pseudoaddiction**

Pseudoaddiction, which refers to the constant demand for more analgesic, may cause behaviour similar to that of addiction in patients who are undertreated for pain. However, it is rapidly eliminated by the administration of adequate analgesia.
Adverse effects of analgesics

- Patients should be made aware of possible side effects of medications and should be encouraged to maintain a diary for recording medications taken, dosages and adverse events.

The patient’s recording of information such as the level of pain before and after medication and the time of onset of pain after the last dose is invaluable when adjusting the medication to the patient’s needs. Also, attention to the following points will help reduce the frequency and severity of unwanted consequences of medication.

Combined therapy

Ordinarily, 2 NSAIDs, or an NSAID and a corticosteroid, should not be used together.50,51

Variable responses

Patients vary in their responses to both NSAIDs and opioids.50 Thus, adverse effects that occur with one drug may not occur when an alternative agent from the same class is used.

Constipation

Constipation almost invariably follows the introduction of opioid therapy, particularly in older patients.52,53 Therefore, unless there is a contraindication, an order for an opioid should automatically be accompanied by an order for a laxative.

Nausea and vomiting

These occur in approximately one-third of patients when an opioid is first instituted. Normally this is a short-lived complication that can be overcome by using antinauseants for a short time.

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 adjusted.54,55 Specifically, sedation is often worse in the first 3 to 5 days after switching opioids or adjusting the dosage and may settle down thereafter, allowing a return to driving.56 Methylphenidate counteracts opioid sedation and may be used in patients who have no contraindications to drugs that stimulate the central nervous system.57

Confusion

Analgesics may cause confusion, particularly in elderly or debilitated patients. If confusion is occurring, 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 it is concluded that opioids are both responsible for the confusion yet necessary for control of pain.58,59

Respiratory depression

Clinically significant respiratory depression is usually not a problem in patients with cancer who are taking opioids on a long-term basis. Naloxone, a specific antagonist of morphine and its sister 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 respiratory depression is not anticipated. If used, it must be titrated, under close supervision, starting with the lowest dose judged to be safe (level V evidence).

Renal function

Some opioid metabolites are active and excreted through the kidneys.59 Therefore, patients who are dehydrated, elderly or have reduced renal function (often compounded by the use of drugs such as angiotensin converting enzyme inhibitors or NSAIDs) are particularly prone to adverse effects while taking opioids.60 These problems can usually be avoided by ensuring adequate hydration, reviewing the drug profile and, in some cases, switching to an alternative opioid.61

Hepatic function

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

Allergic reactions

Allergic reactions to opioids occur in fewer than 1% of patients. Often, patients believe they are allergic to morphine because of nausea at first exposure; however, this is a pharmacologic rather than an allergic reaction. Nevertheless, it is reasonable to use an alternative opioid if serious adverse pharmacologic effects do occur after the first dose. If true morphine allergy exists, an alternative opioid from a chemically different family may be used (methadone, fentanyl).

Adjuvant analgesics

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

Adjuvant analgesics are drugs with primary indications other than for pain that have been found useful in the management of some painful conditions. 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 improving metastatic bone and liver pain and nerve-compression pain.64,65 Patients suffering from metastatic cord compression have been observed to obtain pain relief from dexamethasone, and oral prednisolone has been reported to have significant analgesic effects in a controlled study of patients with advanced cancer (level I evidence).64,65

Antidepressants

Tricyclic antidepressants are helpful in the management of neuropathic pain.66 Aside from their effects on concomitant depression, they most likely act by inhibiting nociceptive 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. On the positive side, 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. Safer alternative antidepressants include desipramine and nortriptyline. Paroxetine, a selective serotonin re-uptake inhibitor that is effective in the treatment of pain due to diabetic neuropathy67 (level III evidence) has also been found to be helpful in other types of neuropathic pain (level V evidence).

Anticonvulsants

These agents are helpful in managing the lancinating component of neuropathic pain, as demonstrated in studies of patients with trigeminal neuralgia.68 However, few studies have examined the use of these agents in treating cancer pain syndromes; almost all clinical studies describe their actions in patients with noncancer neuropathic pain syndrome. Commonly used drugs include carbamazepine, phenytoin, baclofen, valproic acid or clonazepam. Carbamazepine is normally the drug of first choice, but alternative drugs may be used if the initial response is not satisfactory or adverse effects are encountered (level V evidence).

Local anesthetics

Systemically administered local anesthetics such as mexiletin, tocainide or flecainide are normally used for the management of cardiac arrhythmias. However, all may be used for the management of neuropathic pain that is not otherwise responding satisfactorily to treatment.69 Care should be exercised in combining mexiletine with tricyclic antidepressants because some patients have suffered psychotomimetic adverse effects (level V evidence). The relative role of each class of agent and the incidence of combined toxicity remains to be determined.

Substance P inhibitors

Capsaicin, a substance P inhibitor and topical analgesic, has been advocated for reducing cutaneous hyperalgesia and burning neuropathic pain but is still unproven.70

Bone resorption inhibitors

The current drugs of first choice for the management of malignant hypercalcemia are the bisphosphonates (e.g., pamidronate and clodronate). These drugs will prevent or relieve malignant bone pain and other skeletal complications in some women with bone metastases (level I evidence).71-77 Also, evidence from one trial suggests that their use may even reduce the frequency of bone metastases.78 Another adjuvant drug, calcitonin, is sometimes used to relieve the pain of bone metastases.79

Nonpharmacologic approaches

- Noninvasive measures such as psychosocial interventions and physical modalities may bring significant relief.

Psychosocial interventions

All patients need sympathetic support.80 Pain is a sensory experience that is accentuated when patients are anxious or depressed. Thus, in order to help them find mastery over pain, it is important to introduce interventions that may alter consciousness of pain or relieve psychological distress.

Aside from counselling and ensuring that patients are well educated about their problems and have ready access to information and advice, specific psychosocial interventions may be helpful, including the use of cognitive or behavioural techniques.81 There are not yet sufficient data to know which of these techniques is most effective. However, in the randomized controlled trial reported by Spiegel and Bloom,82 interventions involving supportive group treatment and hypnosis were effective in reducing depression, fatigue and pain (level I evidence). Physicians should be aware of the potential benefits and risks of such interventions.

The establishment of a patient-family education program is also important.83 This type of program should concentrate on teaching techniques for patient self-care and clarifying issues that may cause noncompliance in patients, such as popular myths surrounding opioid addiction.

All of these aspects of care, such as patient-family education, the use of nonpharmacologic management techniques and monitoring of drug effects require the participation of an interdisciplinary team. In addition, patients and families should be offered the names of peer support groups for them to contact if they wish.

Physical modalities

These include exercise, immobilization, transcutaneous electrical nerve stimulation, acupuncture and the use of su-
peripheral heat, cold, massage or vibration. These noninvasive techniques (with the exception of acupuncture) are easily taught, may help patients to relax, relieve muscle spasm or distract them from their pain, and provide a means for patient-family participation. Although the use of superficial heat in its various forms is safe, modalities that involve deep heat, such as diathermy or ultrasonography, must be used with caution because of concern that they might influence tumour growth. Cold therapy may reduce inflammation and swelling soon after an injury and may help relieve muscle spasm. Massage can also relieve muscle spasm and aid relaxation.

Lymphedema, which can cause extreme discomfort and sometimes pain, is reported to respond to pneumatic compression, compression garments or massage techniques. However, objective data on the efficacy of these techniques are scarce. In a prospective cohort study of 25 women with affected arms who were followed up for 1 year, the combined use of massage, pneumatic compression bandaging and patient education reduced the volume of the affected arm by 50% or more in 18 women.

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. Maintenance of normal activity in all functional muscle groups will enhance patient mobility and function and prevent joint contracture. Patients will benefit from simple range-of-motion exercises. Also, regular changes of position in nonambulatory patients is important, because this may help to relieve pain and prevent skin complications. When acute pain is present, passive exercises should not be carried out and exercise should be limited to a self-administered range of comfortable motion.

Some patients will use complementary or alternative therapies to manage their pain, which may include meditation, biofeedback, yoga, prayer, visualization, Qi Gong/Tai Chi exercises, therapeutic touch and herbal medicines. Although most of these therapies have not yet stood up to scientific scrutiny, they should be acknowledged by the patient’s physicians. An understanding attitude on the part of physicians toward the use of complementary therapies will likely reduce patients’ frustration with conventional care and will encourage compliance with treatment recommendations.

- Neuroinvasive procedures are rarely required and should only be considered when other interventions have failed.

Neurolytic blockade may be of particular value in certain syndromes. These 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–C4. Intraspinal or intraventricular infusions of opioids may be indicated in certain patients in whom systemic opioid use is not adequate, and where clinicians have access to skilled and experienced anesthetists and neurosurgeons. As in other areas of treatment, the success of neurolytic procedures is operator-dependent. Patients with refractory pain should, whenever possible, be referred to pain specialists.

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References
9. Rothwell NJ, Hopkins SJ. Cytokines and the nervous system II: actions and
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**Suggested reading**

In addition to these guidelines and their accompanying lay versions, many informative and helpful publications are available on the subject of breast cancer. Among these are the following:


*Copies are available from the Canadian Medical Association, 888 855-2555.*
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