



*Optimal treatment of cancer pain involves assessing its characteristics, considering diverse management strategies, and establishing the most appropriate therapeutic regimen.*

Jacques Carabain. *Queen Street, Auckland, 1889*. Oil on canvas. Courtesy of Auckland Art Gallery Toi o Tamaki. Gift of the P.A. Edmiston Trust, 1986.

# Cancer Pain Management

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**Background:** *Controlling pain in cancer patients is often inadequate. A recent multicenter study of patients with metastatic disease who were experiencing pain reported that 36% still had pain severe enough to compromise their daily function.*

**Methods:** *The author draws on his experiences as well as those of others to review general guidelines and provide specific recommendations for cancer pain management.*

**Results:** *Three components are critical to managing cancer pain: assessing pain, establishing an appropriate therapeutic opioid regimen, and integrating with other therapies. An appropriate therapeutic opioid regimen involves initiating, consolidating and maintaining therapy. Other strategies (eg, advanced pharmacological, adjuvant, interventional, and psychological) can be added to opioid therapy.*

**Conclusions:** *A revision of the Agency for Health Care Policy and Research Cancer Pain Guidelines is currently underway. The management of pain in cancer patients should include more frequent reassessment of both analgesia and side effects to ensure optimal cancer pain relief.*

## Introduction

Pain continues to be a prevalent symptom experienced by cancer patients. Its management is still given too little attention by health professionals. Throughout

the spectrum of health care, including cancer centers, intensive care units, and nursing homes, cancer pain continues to be both prevalent and undertreated.

Pain can be associated with both localized tumors and metastatic cancer. Although Daut and Cleeland<sup>1</sup> reported only 15% of patients with nonmetastatic disease had pain associated with their tumor at the time of diagnosis, pain becomes more pervasive as disease progresses. With the diagnosis of metastatic disease at the University of Wisconsin, the percentage of patients having pain increased to 74%. Direct tumor involvement is the most common cause of pain, present in approximately two thirds of patients with pain from metastatic cancer.<sup>2</sup> Tumor invasion of bone, common in breast and prostate cancer and with multiple myeloma, accounts

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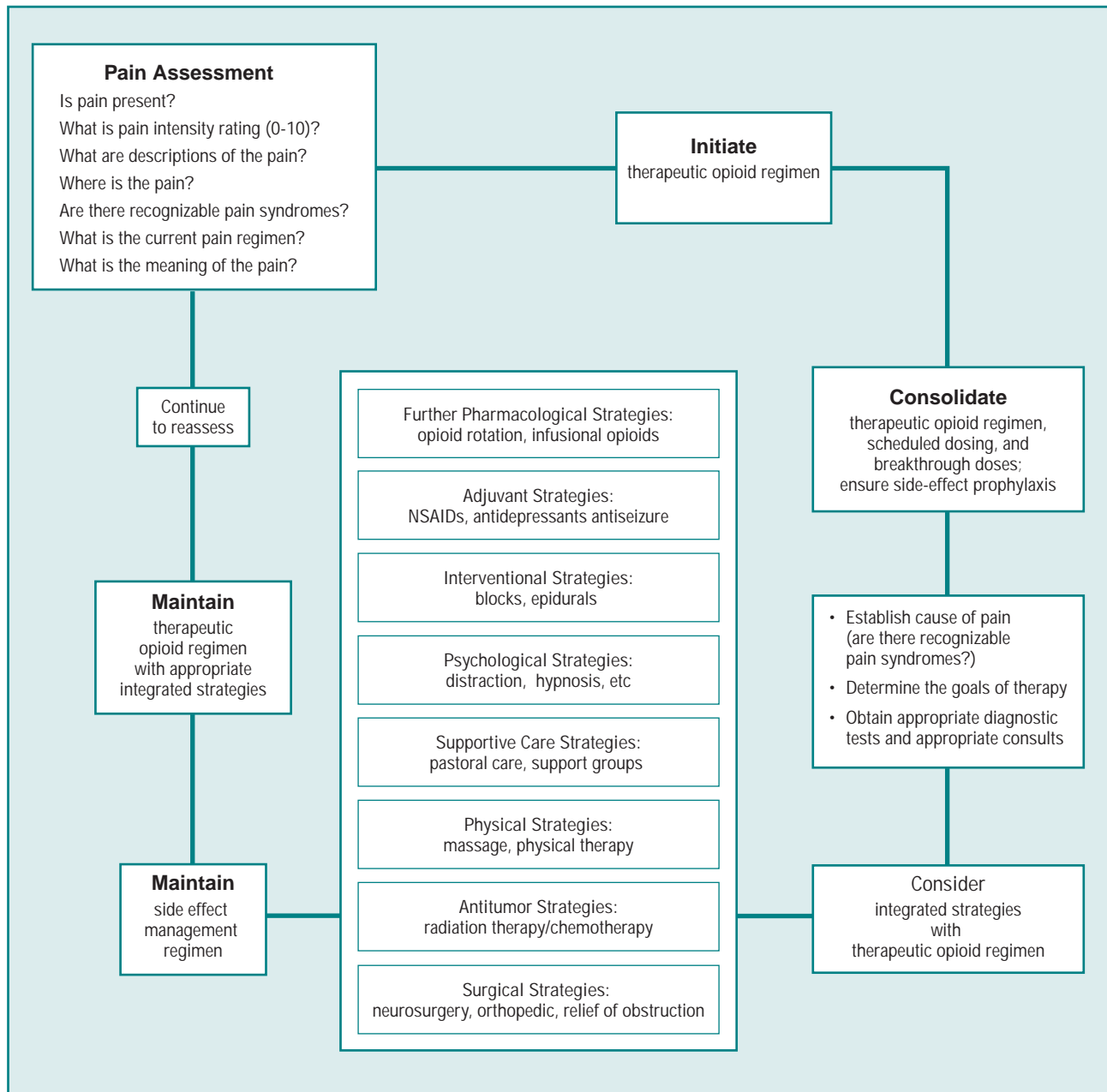
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for pain in approximately 50% of these patients. The remaining 50% experience tumor-related pain that is due to nerve compression or infiltration, or tumor involvement of the gastrointestinal tract or soft tissue.

In a recent multicenter study, 67% of outpatients who had metastatic disease had disease-related pain or were taking analgesia on a daily basis.<sup>3</sup> Thirty-six percent of the patients in this Eastern Cooperative Oncology Group (ECOG) study had pain severe enough to compromise their daily function. Although most cancer-related pain can be adequately controlled with oral analgesics, a minority of cancer patients receives anal-

gesics that are inadequate in type or potency to manage their pain. At least 42% of those with pain did not receive the type of analgesics recommended by standard cancer pain management guidelines. In that study, minority women older than 70 years of age were at greatest risk for inadequate analgesia.

This inadequate pain control has been confirmed through the intensive care units of teaching hospitals, as studied in the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT).<sup>4</sup> Significant pain was reported in 50% of those with colon cancer, non-small cell lung cancer, and



Outline of cancer pain management identifying the three cores: assessment, therapeutic opioid regimen, and integrated strategies. The therapeutic opioid regimen is the core of cancer pain management.

multi-organ system failure associated with cancer, and 9% to 20% of cancer patients reporting pain were dissatisfied with their pain control.

Pain is also undertreated in cancer patients in nursing homes.<sup>5</sup> Of 13,000 cancer patients discharged from hospital to nursing homes, 4,003 reported daily pain. One quarter of these patients were older than age 85, and one half were older than age 75. Of the 4,003 patients with daily pain, 16% received a non-opioid analgesic, 32% received a “weak” opioid, and one quarter received morphine. Only 13% of those patients aged 85 years and older received opioid pain medication. More than a quarter of all the patients (26%) in daily pain did not receive any analgesic agent with older patients at greater risk of receiving no analgesia. Patients who were more likely to be undertreated for pain included those with low cognitive performance, those receiving multiple other medications, and those in a minority ethnic grouping.

Poorly controlled pain may have catastrophic effects on patients and their families. Thus, the proper management of pain needs to be the highest priority for those who care for cancer patients. Three critical components to cancer pain management occur on a cyclical basis (Figure):

- Assessment of pain
- Therapeutic opioid regimen
- Integration with other therapies

## Assessment of Pain

Proper pain management requires the ability to assess the characteristics of pain and its physical basis. The changing expression of cancer pain requires repeated assessment, as new causes for pain can emerge rapidly. The essentials of cancer pain assessment are similar to those taught for disease assessment in the early years of professional education. These principles are used extensively for the diagnosis of ischemic heart disease, appendicitis, or renal colic, to name a few examples. However, health care professionals often do not use these same principles for the assessment of pain in patients with a diagnosis of cancer. Using these principles, a patient can tell us so much about the pain and can provide a guide to the best possible treatment options often without the need to perform invasive tests. Pain assessment needs to occur repeatedly and at regular intervals throughout treatment and especially with any new report of pain.

Patients should be questioned about each component of their pain (Table 1). Data from these individual components may identify pain syndromes. However, in

Table 1. — Elements of Cancer Pain Assessment

Factor	Question
Intensity	How severe is your pain?
Character	How would you describe your pain?
Location	Where is your pain?
Radiation	Does your pain go anywhere else?
Timing	When does your pain occur?
Correlated factors	What makes your pain better or worse?
Implications of pain	How does this pain affect your daily living?
Meaning of the pain	What does the pain mean to you?

seeking such data patterns, clinicians must be careful to ensure that a total assessment is performed, including the pain’s intensity, character, location, and radiation.

**Intensity:** The patient’s communication about pain is aided by using a scale to report pain severity. A simple rating scale ranges from 0 to 10, with 0 being “no pain” and 10 being “pain as bad as you can imagine.” Used properly, pain severity scales can help in titrating analgesics and in monitoring for increases in pain with progressive disease. Daut et al<sup>6</sup> used a numeric rating index (0 to 10) in the Brief Pain Inventory, a tool in which patients rate their pain together with self assessment of pain interference with everyday functions such as activity, mood, and relationships with others. Based on continued work with this tool in cancer patients, Serlin et al<sup>7</sup> have defined three levels of pain. “Pain worst” scores of 0 to 4 are classified as mild pain, which is often well tolerated with minimal impact on a patient’s activities. At “pain worst” scores of 5 to 6 (moderate pain), patients experience some disruption in these daily activities. When the “pain worst” score is 7 or higher, pain is especially disruptive; it becomes the primary focus of attention and prohibits most activity not directly related to pain. Physicians and nurses tend to underestimate pain intensity, especially when it is severe. Patients whose doctors underestimate their pain are at high risk for poor pain management and compromised function.

**Character:** Verbal descriptors of pain used by the patient may help to establish the etiology of pain. Physicians should be aware of the diversity of terms used by patients. For example, a patient may deny having pain, but the “dull ache” in his or her back would rate a 7 on a 0-to-10 pain scale. Other terms used include pressure, tightness, burning, tingling, numbness, and electric shock-like pain. A patient’s description of a shooting pain or an electric shock down the arm would suggest a neuropathic component of the pain. Neuropathic pain is caused by spontaneous activity in nerves damaged by disease or treatment.

**Location:** The distinction between generalized vs localized pain is important in consideration of both diagnoses and treatment options. The distribution of pain over dermatomal patterns is as important in cancer-related pain as in the diagnosis of appendicitis (periumbilical pain) or gall bladder disease (right shoulder tip pain). Knee pain without evidence of joint pathology may in fact be referred pain (not radiating) from the L3 area in the spine or from disease associated with the hip. Localized pain may be best managed with systemic analgesic agents together with a localized therapy, eg, radiotherapy or nerve block. Disseminated pain is usually best managed with analgesic agents, but a particularly painful location in a patient with disseminated pain may need specific treatment, eg, radiotherapy.

**Radiation:** The radiation of pain can be a key factor in the diagnosis of a pain syndrome. For example, the description of pain in the lower back radiating down both legs tells us much about the diagnosis, especially if coupled with the verbal descriptors of a neuropathic component.

**Timing:** Pain that occurs or worsens at specific times of each day may be associated with activity or with the end of an opioid dose. "Breakthrough pain" is the term used to describe a transitory flare of pain in the setting of chronic pain managed by opioids.<sup>8</sup> Such pain is also called "incident pain" when it occurs in association with a specific activity.

**Correlated Factors:** Specifically defining these alleviating and confounding factors can help to establish a diagnosis. For example, coughing that exacerbates low back pain and sends it shooting down the back may indicate spinal cord compression. Straining that makes a headache worse may indicate brain metastases. Emotional disturbances that worsen pain may signify spiritual disturbance. It is important to elicit the medications (not always analgesics) that a patient has been taking for the pain, together with the impact of these medications. This information helps to assess pain severity and, with the use of equianalgesic dose tables, to determine adequate dose of other analgesic agents.

**Implications of the Pain:** Pain may limit the level of a person's activity, a level that already may be dramatically affected by other cancer-related symptoms. Therefore, it is imperative to document the effect of the pain on all patients' lives. When pain is of moderate or greater severity, it can negatively affect quality of life. That impact, including problems with sleep and depression, must be evaluated. Factors such as the number of hours the patient is sleeping compared with the last pain-free interval, difficulties with sleep onset, frequent

interruptions of sleep, and/or early morning awakening may suggest the need for appropriate pharmacological or psychological intervention, which may include the addition of a low-dose antidepressant at bedtime. Equally important is an assessment of how pain interferes with a patient's ability to interact with others. The Brief Pain Inventory, while used initially as a research tool, provides for the assessment of pain interference and has been found to be useful in clinical practice.

**Meaning of the Pain:** An initial minor increase in pain may influence a patient's perceived severity of the pain. Does the pain mean the recurrence of a malignancy that the patient thought had been "cured"? Is the worsening of pain an indication that disease is progressing despite chemotherapy, or is it related to the treatment? Will the pain mean more investigations, many of which are uncomfortable and painful? Considerations such as these may lead to the underreporting of pain or may increase the anxiety associated with pain.

Physical examination should include a full disease assessment as well as a careful examination of the painful areas. This examination should distress the patient as little as possible, but it must be recognized that analgesics may mask some of the signs necessary to arrive at an accurate diagnosis. The treatment of pain should not be postponed for the full diagnosis of a patient's disease. This has now been confirmed in the acute pain setting, where the administration of intravenous opioids to patients with suspected appendicitis has not interfered with the diagnosis of that condition.<sup>9</sup>

## Pain Management

The principles of cancer pain management have been reviewed in a number of forums.<sup>2,10,11</sup> A revision of the Agency for Health Care Policy and Research (AHCPR) Cancer Pain Guidelines<sup>10</sup> is currently underway in the United States through sponsorship by the American Pain Society.

Opioids are increasingly being recognized as the primary treatment for cancer pain management. This is a significant shift from the established view of cancer pain management, the World Health Organization (WHO) analgesic ladder. With this ladder comes the basic tenants of pain control: "by the ladder, by mouth, by the clock, and for the individual." The treatment of cancer pain progresses through the various steps of the ladder until relief from cancer pain is achieved,<sup>11</sup> starting with nonsteroidal anti-inflammatory drugs (NSAIDs) and progressing to weak opioids (eg, codeine) and then to those of greater strength (eg, morphine).

Zech et al<sup>12</sup> reported their experience with the WHO ladder in providing pain relief to 2,266 cancer patients, 74% of whom were on step II or III opioids at the time of admission to their pain service. While useful analgesia was obtained using the ladder (efficacy of pain relief was "good" in 76%), it is difficult to conclude from this study that treatment of all patients should commence at step 1 of the ladder. Twenty-five percent of patients on step 1 analgesics had pain intensity that was rated moderate to severe using a verbal rating scale, which supports concerns that by progressing through each step, many patients were without adequate pain relief for some time. Ventafridda and colleagues<sup>13</sup> also presented their 2-year experience with the WHO ladder with cancer patients. This retrospective study showed that use of the analgesic ladder reduced pain to a third of its initial intensity and was efficacious in 71% of the cases. Over time, however, many patients needed to move up steps of the ladder because their pain medicine regimens were inadequate. Non-opioids were prescribed for an average duration of 19.2 days; treatment was discontinued due to inefficacy in 52% of cases and due to side effects in 42% of cases. Weak opioids were administered on average for 28 days with the shift to strong opioids due to inefficacy in 92% of cases and due to side effects in 8%. Treatment with strong opioids lasted for an average of 46.6 days and was considered the mainstay of cancer pain therapy.

The 1994 AHCPR Cancer Pain Guidelines<sup>10</sup> continued to recommend the use of the WHO ladder for cancer pain management. However, based on the clinical experience at that time, it was recommended patients should be treated according to the severity of their pain. Mild pain (pain score of 1 to 4) should be treated at step 1 with analgesics such as NSAIDs or acetaminophen. For moderate pain (pain score of 5 to 6), weaker opioids were recommended with either codeine or oxycodone usually prescribed as combination formulations. Severe pain (pain score of 7 or higher) should be treated at step 3 with full doses of opioids including morphine, oxycodone, hydromorphone, or fentanyl.

With increased experience with the ladder and with better understanding of opioids, many have suggested the practicality of a two-step ladder, which consists of initial treatment with NSAIDs and acetaminophen and then treatment with opioids. The experiences of Zech et al<sup>12</sup> and Ventafridda et al<sup>13</sup> have been corroborated by others in their clinical practice. To ensure adequate pain control for cancer patients, opioids should be the mainstay of pain management in an oncology setting.

Confusion may exist as to which medications are indeed opioids. Codeine, hydrocodone, oxycodone, tra-

madol, morphine, hydromorphone, oxymorphone, methadone, and fentanyl are all opioids. Some are natural products (eg, morphine), while others (eg, fentanyl) are synthetic derivatives of these compounds. Each has an analgesic effect that has been rated in comparison with morphine as the "gold standard." Some opioids have been formulated primarily as combination products (eg, hydrocodone/acetaminophen, oxycodone/acetaminophen, or codeine/acetaminophen). The total daily dose of these medications that can be given is limited more by the acetaminophen than by the opioids. The dose-limiting side effects of opioids vary greatly among patients and among the different drugs. Compared with other opioids, hydrocodone and codeine cause side effects at lower doses due to the nature of their metabolism. A therapeutic opioid regimen is the mainstay of cancer pain treatment.

## Therapeutic Opioid Regimen

Three steps are recommended in establishing a therapeutic opioid regimen:

- Initiating therapy
- Consolidating therapy
- Maintaining therapy

### *Initiating Therapy*

The initial treatment and titration with opioids in opioid-naïve patients should include immediate-release opioid preparations.<sup>14</sup> The prolonged absorption of a sustained-release product may result in prolonged side effects in a patient who is receiving opioids for the first time. This concern is particularly relevant in the elderly. Once sustained-release products are ingested or absorbed through the skin, little can be done to prevent or reduce further drug effect apart from administering an antagonist. The US Food and Drug Administration defines opioid tolerance as occurring when a patient uses 60 mg or more of morphine per day. However, patients taking less than 60 mg may be opioid-tolerant, and they certainly are not opioid-naïve. The patient who is taking 6 acetaminophen/oxycodone combination tablets daily is not opioid-naïve, and analgesia can be easily changed to and further titrated to a sustained-release product. Six acetaminophen/oxycodone (Percocet) tablets per day are equivalent to 30 mg per day of oral morphine or oral oxycodone. The dose conversion in this patient to 30 mg of sustained release morphine per day is likely to be well tolerated by even elderly patients. The same calculations can be made with all opioids, including codeine and tramadol.

If patients are already taking opioids, longer-acting products can be prescribed with coadministered short-

acting products to enable the patient to titrate to a desired level of analgesia. This level may not always be zero. In many cases, achieving a pain score of 4 or less is an achievable and useful goal. Some patients can be titrated with oral sustained-release oxycodone without the need for short-acting products.<sup>15</sup> This needs to be confirmed in further studies and shown to be safe and efficient outside of the study setting.

Assessment is necessary to determine the nature of pain scores according to the situation. Pain that is rated as severe (7 or higher) and is not responsive to short-acting opioids of increasing strength should be treated as an emergency. An emergent response provides for the rapid delivery of opioids by either the intravenous or subcutaneous route in the inpatient, clinic, or home setting. Transmucosal delivery of opioids also may be beneficial in this setting, although this approach has not been formally tested.

### *Consolidating Therapy*

As pain levels are reduced with the use of either shorter-acting products alone or both shorter- and longer-acting products, analgesic therapies should be consolidated. At the same time, efforts to establish the etiology of the pain should continue. The recognition of specific pain syndromes (eg, herpes zoster, brachial plexopathy) is required.

The therapeutic opioid regimen should be consolidated into longer-acting products administered at regular dosing intervals (1 to 3 times daily for oral products, once every 2 to 3 days for transdermal). Why convert to longer-acting products when these products are often expensive? According to Walsh et al,<sup>16</sup> there was little difference in overall pain control and management of side effects when immediate-release morphine was administered regularly every 4 hours or when sustained-release morphine was administered twice daily. This study was performed in a trial setting with motivated patients who were taking opioids during the night. However, considering that patients may take only one third of the pain medications that are prescribed, dosing with sustained-release products should assist in their compliance.

Shorter-acting opioids should continue to be prescribed on an as-needed basis. A regular review of a patient's use of these shorter-acting medicines allows an assessment of a patient's total analgesic needs. The sum of all opioids used in a 24-hour period can be calculated and converted to longer-acting opioids.

The continued prescription of shorter-acting opioids is also important in the treatment of break-

through pain. Breakthrough pain refers to flares that occur in the background of stable pain, with pain scores rising to the severe level either spontaneously or in association with some activity.<sup>8</sup> Patients may experience peaks of pain that are not controlled with their regular medication. The recommended dose of shorter-acting pain medications is between 10% and 15% of the daily opioid dose. Many are comfortable with this approach when the daily opioid dose ranges between 60 and 180 mg per day. At higher doses, the breakthrough dose may be at the level of 30 to 50 mg of morphine.

Recent experience with oral transmucosal fentanyl citrate (OTFC) shows that the dose of rescue medication needs to be titrated as well.<sup>17</sup> Many patients on higher doses of morphine (>180 mg oral morphine) continue to achieve good breakthrough pain control with 10 to 15 mg of immediate-release morphine. OTFC has been recently shown to be more effective than oral morphine in the treatment of breakthrough pain.<sup>18</sup>

Prophylaxis against and treatment of opioid side effects foster optimal quality of life and continued compliance with prescribed medications. Preventing constipation and nausea is an important prophylactic step that accompanies the prescription of opioids. While not all patients will develop nausea and vomiting, antiemetic agents should be available to them. Preventing constipation, which occurs in almost all patients who use opioids, reduces clinic, emergency room, and inpatient admissions.

### *Maintaining Therapy*

Adjusting dosages by either increasing opioid dose or by decreasing the dosing interval for patients receiving long-acting opioids can be confusing. Assessment of pain, as well as an understanding of the pharmacokinetics of the sustained-release medications, is important. Patients who do not achieve adequate analgesia throughout the dosing interval are more likely to benefit from an increase in dose rather than a decrease in the dosing interval. For patients who achieve excellent analgesia that is not sustained for the full dosing period, a decrease in the dosing interval (eg, from twice daily to 3 times daily) may help to maintain an adequate level of the opioid. The total daily dose of opioids used should continue to be monitored. Most patients can be managed with longer-acting opioids and an average of four breakthrough doses each day.

The long-held concept of "by the clock and for the individual" for pain control still applies. However, the oral route of administration may not always be pre-

Table 2. — Commonly Used Longer-Acting Opioid Preparations

SR morphine	MS Contin Oramorph SR Kadian New formulations under development
SR oxycodone	Oxycontin New formulation under development
Transdermal fentanyl	Duragesic
SR hydromorphone	New formulations under development
SR oxymorphone	New formulation under development
Methadone	Dolophine

ferred, and other routes are available for patients who cannot tolerate oral treatment. One report indicated that 50% of 864 patients who were hospitalized at the time of death could not tolerate oral medications.<sup>12</sup>

Many physicians believe that the sublingual route provides rapid analgesia. However, the sublingual administration of morphine has no pharmacological benefits over oral administration; peak plasma concentrations of morphine occur later and at lower levels with sublingual administration compared with oral administration.<sup>19,20</sup> Also, sublingual tablets have a bitter taste. Rectal administration of opioids is not limited to drugs for which there is a suppository formulation; sustained-release tablets administered rectally may provide effective analgesia.

The transdermal delivery of opioids is currently limited to fentanyl. There is no evidence that morphine is absorbed transdermally. The rate of delivery of fentanyl ( $\mu\text{g/hr}$ ) is dependent on the surface area of the patch. When administered transdermally, the drug accumulates in the subcutaneous fat, which results in sustained plasma concentrations. Current recommendations are that patients should be stabilized on oral opioids prior to starting transdermal fentanyl and that doses should not be changed more often than every 72 hours.<sup>21</sup> Short-acting opioids need to be available to patients for breakthrough pain. Transdermal fentanyl may not be optimal for patients with rapidly escalating pain who are unable to swallow. For these patients, parenteral administration of opioids may be preferable. While applicable to patients at all stages of illness, this is particularly important to patients near the end of life.

Few studies have compared different opioids in a double-blind, randomized, controlled manner. Many of the

comparative studies have been conducted for regulatory reasons to show no difference in the products in terms of side effects or analgesia. Patient preferences recorded in these studies have become strong marketing tools, although patient responses to opioid tolerability can be highly variable.<sup>22</sup>

Table 2 lists the different sustained-release products that are available to treat cancer pain. Oxycodone has an analgesic activity similar to morphine, and it is now available for use either alone or as a sustained-release product. Other sustained-release oxycodone formulations are under development. Hydromorphone and oxymorphone, both currently available in intravenous formulations, are currently under development in sustained-release formulations. Hydromorphone, already available in a short-acting oral formulation, is being developed in both capsule and tablet formulations.<sup>23</sup> Morphine has been developed in a capsule formulation with the sustained-release nature located within each pellet of morphine.<sup>24</sup> This once-daily product can be sprinkled on food as well as delivered through a wider-bore feeding tube. Methadone, another oral opioid more commonly associated with drug withdrawal programs, is an effective and less costly alternative for treating cancer pain. Methadone has a long half-life, and thus dose escalation must be implemented cautiously, especially in the elderly, in order to reduce the occurrence and severity of side effects. Methadone is available in tablet, solution, and parenteral formulations and is less expensive than many other drugs.

The relative analgesic effect for commonly used compounds are shown in Table 3. Equianalgesic conversion charts may provide varying information, and they may be valid for the conversion of Drug A to B but not for the conversion of Drug B to A.

Assessing and managing the symptoms of side effects are ongoing requirements in treating cancer pain. Bowel management should consist of the combination of both stimulants and stool softeners. Patients should be having a bowel movement at least every other day without difficulty. More aggressive cocktails to stimulate bowel function are often used as are suppositories and enemas. The use of bulking agents while

Table 3. — Conversion Ratios of Common Opioids

Opioid	Oral Drug/Morphine Ratio	Simple Conversion
Morphine	1/1	10 mg = 10 mg MS
Oxycodone	0.8 -1.2/1	10 mg = 10mg MS
Hydromorphone	5/1	2 mg = 10 mg MS
Methadone	5 -10/1	1-2 mg = 10 mg MS
Fentanyl	—	17 $\mu\text{g/h}$ = 30 mg/day MS

on opioids may in fact increase the risk of constipation in cancer patients. Many cancer patients may not maintain adequate intake to allow these agents to work, especially as performance status decreases.

Nausea and vomiting can be acute and chronic problems in patients who are taking opioids. The initial ingestion or injection of an opioid may cause temporary nausea. The judicious use of antiemetics may prevent nausea from becoming intractable. Since opioids may delay gastric emptying, gastric motility agents may be very useful. Metoclopramide can minimize opioid-induced nausea and vomiting, and haloperidol is an underused antiemetic agent that also treats agitation. H<sub>2</sub> receptor antagonists do not help opioid-induced nausea and vomiting.

Opioids commonly produce neurological side effects. The initial administration may result in sedation from either the opioid or from pain-free sleep. The patient may sleep regularly over the initial few days of opioid therapy to correct previous sleep deprivation. In a small percentage of patients, fatigue and sedation may continue and be intractable. Sedation may be corrected by using stimulants<sup>25</sup> or by changing to a different opioid.

Confusion is a side effect of opioids. However, when a confused patient on a therapeutic opioid regimen is hospitalized, the opioids are often blamed. The opioid use is then stopped, and the patient experiences significant pain. In the absence of either renal impairment or a recent increase in dose, opioid use is not likely to be the cause of confusion in this clinical setting, although it may be a contributing factor. Near the end of life, the addition of haloperidol to the regimen may correct confusion and delirium without effecting the pain outcome.

## Integrated Strategies

While opioid therapy is the mainstay of cancer pain treatment, other strategies (eg, advanced pharmacological, adjuvant, interventional, psychological, supportive, physical, and anticancer) can be integrated with opioid therapy.

**Advanced Pharmacological Strategies:** The parenteral administration of opioids may be necessary in patients who cannot swallow, who have intractable side effects, or in whom rectal delivery is not desirable. Subcutaneous infusions have been extensively used in Canada<sup>26</sup> and Australia but are not commonly used in the United States, possibly because many patients already have intravenous access. The steady plasma

concentrations of opioids that result from either intravenous or subcutaneous infusions may reduce side effects and thus optimize analgesia.

Another effective pharmacological measure in controlling symptoms is rotating or switching opioids. This has been documented initially by the Edmonton palliative care group.<sup>27</sup> In a retrospective chart review, Bruera and colleagues<sup>26</sup> found that switching opioids improved nausea and pain. The authors suggested that an expanded armamentarium of different opioids was useful in the management of different patients.

**Adjuvant Strategies:** While opioids are the mainstay of cancer pain management, adjunct therapy is recommended by both WHO guidelines and the AHCPR guidelines. Adjuvant medications may result in a decrease in opioid dose with an associated decrease in side effects, although this is the subject of further study. Consideration of the use of adjuvant medications is recommended in all cases and should include the use of NSAIDs together with opioids in the case of bony metastases.

NSAIDs act to block prostaglandin formation that is responsible for bone pain from metastasis. While many prefer to use agents such as ibuprofen and naproxen, aspirin is equally effective in the management of bone pain. Corticosteroids may be also useful in the management of bone pain, but prolonged use causes deleterious side effects. By reducing pressure on the liver capsule, the cause of hepatic pain, corticosteroids are particularly useful in managing painful liver metastases.

Adjuvant therapy is often useful with opioids in the treatment of neuropathic pain. Antidepressants such as amitriptyline and desipramine are useful adjuncts for all cancer pain, but they are particularly important in treating neuropathic or nerve pain. Antiepileptics such as carbamazepine have also been used as second-line treatment for neuropathic pain, but they usually require 3 to 4 weeks to work. Gabapentin is a newer antiepileptic that also has been shown to be useful for neuropathic pain.<sup>28</sup> Randomized, controlled trials of the use of these medications have not been conducted in the cancer pain setting. Lidocaine and other antiarrhythmic agents have also shown response.<sup>29</sup> These therapies are often used as the primary therapy for the treatment of cancer-associated neuropathic pain. Neuropathic pain is not resistant to opioids, but higher doses may be needed,<sup>30</sup> which increases the risk of opioid side effects. The judicious use of the above adjuncts may result in pain control with fewer side effects in some individuals. The author's experience is that many patients, especially the elderly, do not tolerate these medications well and in fact experience increased side effects.

The combination of morphine with dextromethorphan has been proposed to result in increased analgesic effect of morphine; however, studies conducted thus far have not shown a decreased side effect profile. The proposed mechanism for this interaction is an interaction between the mu-opioid and N-methyl D-aspartate receptors. This interaction has been proposed in the analgesic action of methadone, serving as a possible explanation for the activity of methadone in the treatment of neuropathic pain.

**Interventional Strategies:** Only 2% to 5% cancer patients require interventions or the direct delivery of opioids to the central nervous system.<sup>12</sup> Patients with unmanageable side effects may benefit from the epidural or intrathecal administration of opioids. Approximately one tenth of the intravenous dose of an opioid is needed when administered epidurally and one hundredth is needed when administered intrathecally. However, these procedures are expensive, and catheters and pumps are required to deliver the drug. To be cost effective, these devices should be used for longer than 3 months without complications. A randomized study comparing the intraspinal delivery of opioids with standard opioid therapy is currently underway.

Nerve blocks, either with chemicals or neuroablative methods, may be useful in the pain management of some patients. A celiac plexus block can be useful in the treatment of pain associated with pancreatic cancer<sup>31</sup> and may be best performed at the time of laparotomy. Diagnostic blocks with lidocaine are often performed before the instillation of a longer-acting agent. In some cases, chordotomy (ablation of pain pathways in the spinal cord) may be useful for the management of pain. A bilateral chordotomy can be performed but will result in increased incidence of complications, particularly loss of bladder function.<sup>32</sup> As with all procedures, staff must be properly trained and must maintain their proficiency in these procedures in order to minimize potential complications. Improvements in imaging techniques with computed tomography scans have improved the ability to perform many of these procedures.

**Psychological Therapies:** Psychosocial interventions are important in a multimodal approach to pain management. Such interventions are used in conjunction with appropriate analgesics for the management of pain. The success of a psychosocial intervention should not imply that pain was not "real."

Psychosocial intervention may use cognitive or behavioral techniques or both.<sup>33</sup> Focusing on perception and thought, cognitive techniques are designed to

influence how one interprets events and bodily sensations. Providing information to patients about pain and its management and helping them to think differently about pain are both cognitive techniques. Behavioral techniques, by contrast, are directed at helping patients develop skills to cope with pain and to modify their reactions to pain. Included in cognitive-behavioral therapies are relaxation and imagery, distraction and reframing, hypnosis, psychotherapy, and structured support. Educating patients about the ability to control pain effectively and correcting of myths about the use of opioids should be included as part of the treatment plan.

Psychosocial interventions should be introduced early in the course of illness so that patients can learn and practice these strategies while they have sufficient strength and energy. Pain intensity as well as mental clarity may affect a patient's ability to use such techniques. When introduced early, psychosocial interventions are more likely to succeed, which fosters the patient's motivation to continue using them. Patients and their families should be given information that describes strategies commonly used to manage pain and anxiety. They should be encouraged to try several strategies, then select one or more to use regularly when they experience pain.

**Supportive Therapies:** Pastoral and spiritual issues may be confounding factors in cancer pain management and may have a dramatic affect on the pain experience. Spirituality may be defined for clinical purposes as those elements that give meaning to a person's life, whereas religiosity can refer to the organized structures that a person may join to assist in the expression of that spirituality. Having cancer and pain frequently raises issues of spirituality for patients and their families, both of whom may be helped by pastoral counseling. The experience of pain can often lead patients to sense fear and abandonment. They may question both the meaning of the pain and their understanding of hope. Pastoral care members should participate in health care team meetings that discuss the needs and treatment of patients.

Programs of self-help and mutual support of patients with cancer have been available since the 1940s. The experience and empathy of people who have had a similar disease can provide credible support to others with the same disease or problem and can help new patients learn to cope more effectively.<sup>34</sup> Information concerning local support groups should be provided to patients. In addition, the Internet has allowed patients to make contact with many other patients in similar situations, including those with relatively rare diseases.

**Physical Therapies:** Physical therapies<sup>35</sup> involve many techniques including cutaneous stimulation (massage, heat and cold), exercise, immobilization, transcutaneous electrical nerve stimulation (TENS), and acupuncture. These therapies may decrease the need for pain-reducing drugs, but they should not be used as substitutes for medication. Physical modalities should be introduced early to treat generalized weakness and deconditioning as well as aches and pains associated with periods of inactivity and immobility related to cancer diagnosis and therapy. Massage is a comfort measure used to aid relaxation and ease general aches and pains, particularly those associated with periods of treatment-related immobility. Massage may also decrease pain in a specific area by increasing superficial circulation.

**Anticancer Therapies:** Clearly, effective treatment of the underlying cancer is an important component of treating cancer-related pain. This is particularly true for those tumors that are responsive to chemotherapy or radiotherapy. However, clinicians should carefully balance the potential palliative benefit of anticancer therapy with the expected toxicity of the treatment. Patients in whom anticancer therapy is being administered for a palliative intent should have a symptom to be palliated. "Prophylactic" treatment of symptoms may often make further management of a symptom more difficult at a later date. Many of the cancers in which pain is a particular problem, such as pancreatic cancer, rarely respond to chemotherapy agents. More recently, chemotherapy has been shown to improve quality of life in individuals with non-small cell lung cancer, pancreatic cancer, and prostate cancer.<sup>36</sup> It is important in each of these situations to consider the entry criteria of the patients enrolled on study. For instance, the benefit of chemotherapy with non-small lung cancer was found in patients with an ECOG performance status of 0 to 2 (ie, patients with a reasonable level of activity). The studies did not include patients who were inactive for more than 50% of their time.

Bisphosphonates have been shown to be useful in both preventing bony metastases and alleviating the pain of bony metastases. These products are now being incorporated into the practice of oncology for many tumors without definitive evidence of their benefit.

Radiotherapy is a useful tool in the palliation of cancer-associated pain, particularly in the treatment of bone metastases. In the United Kingdom, Canada, and Australia, the common practice is to administer a single fraction of 6 Gy to a painful bone. This provides analgesia equivalent to that obtained by administering 20 Gy over 2 weeks.<sup>37</sup> In some cases, lesions treated

with a single fraction may need to be retreated sooner than those in which multiple fractions were administered. Re-treating with single large fractions can have long-term implications to the vasculature of the irradiated area, but many patients do not live long enough for this to be an issue. It is important to balance the overall prognosis and the quality of life of the patient with the treatment administered. The maximum analgesic effect of radiotherapy may not occur for 2 to 4 weeks from administration of treatment. Adequate pharmacological pain management is required in the interim. With the onset of the antitumor effect of the radiotherapy and with analgesia, dosages of these agents can be slowly decreased. Even in generalized pain, therapy such as hemibody irradiation may provide adequate relief of pain. Radiation may also be delivered attached to compounds with an affinity for bone, thus allowing the radiation to only act at bony metastases.

## Barriers to Cancer Pain Management

Barriers to good cancer pain management may be related to health practitioners, to patients, or to the health care systems (Table 4).

Table 4. — Barriers to Cancer Pain Relief

<p>Problems related to health care professionals:</p> <ul style="list-style-type: none"> <li>Inadequate knowledge of pain management</li> <li>Poor assessment of pain</li> <li>Concern about regulation of controlled substances</li> <li>Fear of patient addiction</li> <li>Concern about side effects of analgesics</li> <li>Concern about patients becoming tolerant to analgesics</li> </ul>
<p>Problems related to patients:</p> <ul style="list-style-type: none"> <li>Reluctance to report pain (concern about distracting physicians from treatment of underlying disease, fear that pain means disease is worse, concern about not being a "good" patient)</li> <li>Reluctance to take pain medications (fear of addiction or of being thought of as an addict, worries about unmanageable side effects, concern about being tolerant to pain medications)</li> </ul>
<p>Problems related to the health care system:</p> <ul style="list-style-type: none"> <li>Low priority given to cancer pain treatment</li> <li>Inadequate reimbursement (appropriate treatment may not be reimbursed or may be too costly)</li> <li>Restrictive regulation of controlled substances</li> <li>Problems of availability or accessibility of treatment</li> </ul>
<p>From <i>Management of Cancer Pain</i>. Rockville, Md: Dept of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research; 1994. DHHS Publication AHCPR 94-0593.</p>

Physicians have acknowledged that they are not properly trained in pain assessment<sup>38</sup> and may not address the issue of pain unless it is raised by the patient. To provide adequate pain control, health professionals need to seek a patient's report of pain as the primary assessment. Many cancer patients fear that reporting pain will distract clinicians from treating their disease and therefore do not report it.<sup>39</sup>

Reimbursement issues are significant in the management of cancer pain. Inclusive pain assessment and management are poorly rewarded as they are time consuming. Cost can be a factor in relation to other issues including the availability of medications. Most cancer patients should be able to have their pain managed as an outpatient. However, many elderly patients in the United States are covered by Medicare, which pays for the cost of inpatient medications but not for the cost of outpatient oral analgesics.

Patient attitudes about pain and its treatment can inhibit adequate pain management. Ward et al<sup>39</sup> assessed concerns about reporting pain and using pain medication in 270 cancer patients. Specific issues included fear of addiction, beliefs that "good" patients do not complain about pain, and concerns about side effects. Some patients felt that doctors were not interested in their pain, over half were concerned about addiction, and most were anxious about constipation as a side effect of cancer pain management. There were more concerns in those with less education, lower incomes, and higher levels of pain and in those who were undermedicated.

Fear of addiction is a special concern for older patients and may also be a concern for their families and health care providers. There is little rational evidence to support the fear of addiction. Confusion in the terminology associated with addiction and physical dependence may contribute to the problem. Physical dependence is a physiological phenomenon characterized by the development of an abstinence syndrome following abrupt discontinuation of therapy, substantial dose reduction, or the administration of an antagonist drug. Physical dependence will develop in patients who use opioids for any length of time in a situation similar to that of any patient who has been prescribed corticosteroids over time. When opioid use is stopped suddenly, the patient experiences physiological withdrawal symptoms that may include fever, tachycardia, and abdominal cramps. The onset of withdrawal symptoms has been used by many, including the authors of the previous versions of the *Diagnostic and Statistical Manual*, to establish the diagnosis of substance dependence. A more appropriate definition of addiction or psychological dependence allows the

diagnosis to be made on the presence of three types of aberrant behavior: (1) a patient's loss of control over drug use, (2) a patient's compulsive use of the drug, and (3) continued use of the drug despite evidence of harm to the patient.<sup>40</sup> Increasing publicity campaigns such as "Say 'no' to drugs" may contribute to the public's misunderstanding of these concerns.

## Conclusions

Pain is a symptom experienced by many cancer patients regardless of disease stage. To ensure proper management of cancer pain, physicians must recognize the components that affect pain relief, including the barriers to treatment of cancer pain and the factors that influence both the pharmacodynamics and the pharmacokinetics of analgesic agents. The management of pain in cancer patients should proceed aggressively with more frequent reassessment of both analgesia and side effects to ensure optimal cancer pain relief.

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