Self-Study Module 2:  
Cancer Pain Management
Module 2: Cancer Pain Management

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Abstract

Most patients with cancer experience pain. Adequate assessment by a knowledgeable oncologist, often working closely with an interdisciplinary team, can relieve and control pain effectively. Data suggest that the earlier pain is controlled, the less severe it will become.

Pharmacologic management of nociceptive and neuropathic pain can be conceptualized along the three steps of the World Health Organization (WHO) analgesic ladder. The addition of adjuvant analgesics is often critical to achieving an excellent outcome. Approaches have been developed to switch opioids while maintaining analgesia. Non-pharmacologic approaches may significantly increase the relief achieved.

Adequate pain control is possible in more than 90% of patients if the therapeutic approaches that are within the purview of all physicians are applied systematically. It is important to identify and address patient-related, profession-related, and system-related barriers to good pain control.

Introduction

“Pain is a more terrible lord of mankind than even death itself.” (Ref. 1)

-Albert Schweitzer

Pain is a frequent problem in any oncology practice, whether associated with advanced illness or other acute or chronic conditions. (Ref. 2) (Ref. 3) It is the physical symptom that patients and families fear most. Although oncologists now have effective treatments at their disposal, pain remains poorly assessed and treated. Both the lack of knowledgeable, experienced oncologists and the prevalence of myths about addiction continue to be significant barriers to effective pain management that contribute unnecessarily to the suffering of patients and their families.

Objectives

After studying this module, oncologists and other members of the cancer care team will be able to:

- Compare and contrast nociceptive and neuropathic pain.
- Understand steps of analgesic management.
• Utilize alternative routes of delivery
• Convert between opioids while maintaining analgesia.
• Utilize adjuvant analgesic agents.
• Understand adverse effects of analgesics and their management.
• Understand principle methods of interventional pain management.
• List barriers to pain management.

General Principles

This module focuses on the assessment and management of physical pain. This is not to imply that the other components of suffering (other physical, psychological, social, spiritual, or practical issues) are diminished in importance.

The process of pain management starts with adequate assessment of the pain: its nature; cause; personal context including psychological, social, spiritual, and practical issues; and underlying pathophysiology. Management includes appropriate pharmacologic and non-pharmacologic interventions; education of the patient, family, and all caregivers about the plan; ongoing assessment of treatment outcomes; and regular review of the plan of care.

Enlisting the help of other members of the interdisciplinary team, including nurses, social workers, pharmacists, chaplains, physiotherapists, occupational therapists, child life specialists, etc., is often key to achieving adequate pain management. Flexibility is essential-successful plans are tailored to the individual patient and family. When the plan is not effective at controlling the patient's pain, help should be sought from colleagues with more expertise.

Module 2 - Video 1

Assessment

Pain management requires adequate assessment. Inadequate assessment is the leading reason for poor pain management. Comprehensive Assessment is discussed in EPEC-O Module 1.

The gold standard of assessing pain is to believe the patient. For cognitively intact patients, assess the following pain issues:
• Location and radiation
• Quality, intensity, and duration
• Factors that exacerbate or relieve the pain
• Temporal aspects such as whether the pain is continuous or paroxysmal
• The meaning of the pain to the patient

A careful physical exam coupled with appropriate laboratory and imaging studies can usually identify the relevant pathophysiology underlying the pain. It is important to consider laboratory and imaging tests carefully, selecting those in which the benefits of the study outweigh the burdens it imposes.

Spontaneous pain of short duration could be caused by the paroxysmal firing of a neuroma. Back pain that occurs only with weight bearing could indicate a spinal bony metastasis. Try to determine whether the pain is directly or indirectly related to the cancer, associated with therapeutic intervention(s), or unrelated. These insights may help elucidate the pathophysiology of the pain and may also direct the therapy. (Ref. 4) (Ref. 5)

Quantify pain intensity; ask the patient to rate the pain. This rating can be accomplished using a standard rating system. Verbal ranking on a scale of 0 - 10 is simple and effective. By convention, a rating of 0 is given for no pain; 10 indicates the most severe pain. Visual analog scales are also useful for rating pain. In this system a patient indicates pain with a mark on a 100-mm line delimited by descriptors such as no pain and worst possible pain at either end. Whereas acute pain is accompanied by signs of adrenergic stimulation such as tachycardia and hypertension, chronic pain is not associated with these autonomic responses. Thus, lack of observable vital sign changes does not rule out pain or indicate a patient is malingering.

A careful physical examination combined with the use of select laboratory and imaging studies will usually lead to the identification of the relevant pathophysiology leading to a pain state. The benefits of performing laboratory and imaging studies should outweigh the burdens imposed on the patient.

While this module focuses on physical pain, any particular pain occurs in a whole person. The concept of total pain emphasizes that there may be non-physical causes of pain as well as physical causes. Psychologic (e.g., depression), social (e.g., familial estrangement), and spiritual or existential (e.g., loss of meaning in life) factors can exacerbate pain. (Ref. 6) It is not possible to control pain successfully without also addressing other sources of suffering.
Pathophysiology

Pain is not a homogeneous sensory entity, and several types and subtypes have been described. The neurobiological mechanisms responsible for these different pains provide insight into treatment. (Ref. 7) Pain can be acute or chronic. Acute pain is usually related to an easily identified event or condition, and resolution is anticipated within a period of days or weeks. Chronic pain may or may not be related to an easily identified pathophysiologic phenomenon and may be present for an indeterminate period.

Acute and chronic pain may be conceptualized as either nociceptive or neuropathic in origin. (Ref. 2) A broad description of the predominating pain pathophysiology can usually be inferred through the description, physical findings, and results of laboratory tests and imaging studies. The International Association for the Study of Pain (IASP) has published precise definitions and made them available on their Web site, http://www.iasp-pain.org/defsopen.html.

Nociceptive pain

Nociceptive pain involves direct stimulation of nociceptors that detect mechanical, chemical, and thermal stimuli and mediate nociceptive pain. They transmit this information along normal pathways to be perceived in the brain. Nociceptive pain can be further subdivided into somatic and visceral pain. Somatic pain, mediated by the somatic nervous system, subserves skin, bone, and muscle. Pain localization is precise and is often described as sharp, aching, or throbbing. Visceral pain, mediated by the autonomic nervous system, subserves internal structures such as the gastrointestinal tract. It is typically difficult to localize or describe, and is sometimes characterized as crampy.

Neuropathic pain

Neuropathic pain has been defined as a primary lesion or dysfunction of the nervous system. (Ref. 3) It can be either peripheral or central. The nerves themselves may be damaged by ischemia, compression, infiltration, metabolic injury, or transection. (Ref. 4) For example, postthoracotomy syndrome may be due to the formation of a neuroma caused by aberrant healing after surgical transsection.4 However, neuropathic pain may also involve dysfunction of the nervous system. For example, repetitive nociceptive pain stimuli can create a condition where spinal cord neurons have increased sensitivity in a process called central facilitation. (Ref. 5) Although the nerves themselves are undamaged, an abnormal signaling system has been set up where a given noxious stimulus receives a larger response than normal and non-noxious light touch can stimulate pain pathways. This facilitated sensory state at least partially explains the neuropathic clinical phenomenon of allostynia, where light touch, such as the pressure from a bed sheet, causes pain. The N-methyl-D-aspartate (NMDA) receptor is thought to be involved in setting up this abnormal pathway. (Ref. 5) Thus, there is at least a
subset of neuropathic pain that can develop from repetitive nociceptive pain without structural damage to the nerves themselves. Preliminary evidence suggests that if the initial nociceptive pain impulses are controlled, these neurological changes can be prevented.

Patients tend to describe neuropathic pain with words like burning, tingling, numbness, shooting, stabbing, or electric-like feelings. Although neuropathic pain may respond well to opioids, adjuvant analgesics (tricyclic antidepressants, anticonvulsants, antiarrhythmics, etc.) are often required in combination with opioids to achieve adequate relief.

**Management**

While the diagnosis and treatment of the underlying cause of any pain is an important part of the medical treatment plan, there is no reason to delay the use of analgesics. It is inappropriate to withhold pain management until the investigations and treatment of the underlying disease are complete. Although research is not yet conclusive, unmanaged pain may lead to changes in the nervous system that could reduce its responsiveness to treatment. Equally important, unrelieved pain can have a devastating psychological effect on the patient and family. It is best to combine the use of primary therapies directed against the source of pain (e.g., radiation for a neoplasm) with approaches to manage the pain.

**Placebos**

Some physicians have advocated the use of placebos to see if patients are really in pain. While 30-70% of patients will appear to experience some response, there is no ethical or scientific basis for the use of placebos to assess or treat pain. The Agency for Health Care Policy and Research (AHCPR) (formerly the Agency for Healthcare Policy and Research), American Pain Society (APS), Joint Commission on Accreditation of Healthcare Organizations (JCAHO), and American Nursing Association (ANA) have all issued position statements to this effect.
Adjuvants refers either to medications that are coadministered to manage an adverse effect of an opioid, or to so-called adjuvant analgesics that are added to enhance analgesia.

In 1986, the World Health Organization (WHO) developed a three-step conceptual model to guide the management of cancer pain. (Ref. 8) (Ref. 9) (Ref. 10) It provides a simple, well-tested approach for the rational selection, administration, and titration of myriad analgesics. Today, there is worldwide consensus favoring its use.

Depending on the severity of the pain, start management at the corresponding step. For mild pain (1-3/10 on a numerical analogue scale), start at step 1. For moderate pain (4-6/10), start at step 2. For severe pain (7-10/10), start at step 3. It is not necessary to traverse each step sequentially; a patient with severe pain may need to have step 3 opioids right away.

Effective treatment requires a clear understanding of the pharmacology, potential impact, and adverse effects associated with each of the analgesics prescribed, and how
these may vary from patient to patient. Information about the prescribing of individual analgesics is summarized in Appendix 3 - Common Analgesics Medication Table.

**Step 1 analgesics**

The nonopioid analgesics that characterize step 1 of the WHO ladder all have a ceiling effect to their analgesia (a maximum dose past which no further analgesia can be expected).

**Acetaminophen**

Acetaminophen is an effective step 1 analgesic. It may also be a useful coanalgesic in many situations, including headache. Its site and mechanism of action are not known. It does not have significant anti-inflammatory effects and is presumed to have a central mechanism. Its metabolism in the liver creates a reactive metabolite that can cause liver damage if glutathione stores are depleted. (Ref. 11) Chronic doses >4.0 g/24 h or acute doses >6.0 g/24 h are not recommended for this reason. Hepatic disease or heavy alcohol use increases the risk further.

**Non-steroidal anti-inflammatory drugs**

Non-steroidal anti-inflammatory drugs (NSAIDs, including aspirin) are effective step 1 analgesics. They may also be useful coanalgesics. The doses to achieve analgesia may be lower than the doses to achieve anti-inflammatory effects. They work, at least in part, by inhibiting cyclooxygenase (COX), the enzyme that converts arachidonic acid to inflammatory prostaglandins.

NSAIDs decrease the noxious stimulus normal nociceptors receive. Moreover, there is a group of silent nociceptors that only fire in an inflammatory milieu. (Ref. 12) The same noxious stimulus in the absence of inflammation would fail to cause these silent nociceptors to fire. Finally, cyclooxygenase has also been identified in spinal cord neurons where it appears to play a role in setting up the dysfunctional signaling pattern involved in neuropathic pain. (Ref. 13) These observations help explain why NSAIDs may be so useful in conjunction with opioids for severe pain.

There are several classes of NSAIDs. Some patients respond better to one class of NSAIDs than to another, and serial “n of 1” trials may be needed to find one that is efficacious for a given patient. Extended-release products are likely to enhance compliance and adherence. Intravenous formulations are also available for at least one of the NSAIDs (ketorolac). Details of individual drugs are listed in Appendix 3 - Medication Table.

NSAIDs can have significant adverse effects that include gastropathy, renal insufficiency, and platelet inhibition. (Ref. 14) These side effects may be explained, in part, by the fact that cyclooxygenase exists in two forms—a constitutive form, COX-1, and a form that is inducible under conditions of inflammation, COX-2. There are COX-2-
selective NSAIDs and nonselective NSAIDs that target both forms. Whereas renal insufficiency is a risk of both nonselective and COX-2-selective NSAIDs, the risk of gastropathy and platelet inhibition is significantly decreased with COX-2-selective NSAIDs. (Ref. 15) It is possible to ameliorate the gastropathy associated with nonselective NSAIDs by using cytoprotective agents such as misoprostol, or proton pump inhibitors. (Ref. 15) Recent multicenter trials involving several of the COX-2-selective NSAIDs revealed that patients using COX-2 inhibitors had a significant increase in cardiac events, including cardiac death, nonfatal MI, CHF, and stroke. (Ref. 16) It is not currently known to what extent nonselective NSAIDs have a similar cardiovascular risk profile. (Ref. 17) COX-2-selective NSAIDs are expensive, have not been well studied in the end-of-life population, and may provide less analgesia than nonspecific NSAIDs.

Step 2 and 3 analgesics

Step 2 and 3 analgesics involve opioids that act at opioid receptors. These receptors are found both peripherally and centrally, but the central receptors in the spinal cord and brain are most important for controlling pain. Opioid receptors affect the intracellular levels of potassium and calcium, modifying a nerve's threshold for firing and propensity to release neurotransmitters. Opioids are the first-line therapy for moderate pain in nociceptive, neuropathic, and mixed-pain syndromes. However, for severe neuropathic pain, opioids alone are often insufficient (Ref. 18) and must be combined with adjuvant analgesics, as will be discussed later. In fact, an important clinical clue that there may be a neuropathic component to a pain syndrome is when high-dose opioids are unsuccessful in controlling pain.

The step 2 medications include tramadol and combination formulations of acetaminophen or aspirin with opioids. Tramadol, in addition to having weak activity at opioid receptors, also affects norepinephrine and serotonin levels. (Ref. 19) Although the exact mechanism is unknown, the nonopioid effects of tramadol may mediate its efficacy for neuropathic pain. (Ref. 20) Although tramadol has relatively weak affinities at its sites of action, synergism of its activities may allow for lower doses to be used in comparison with other weak opioids. (Ref. 21) Thus, for moderate pain, tramadol use may result in analgesia with less opioid side effects such as constipation. Commonly available opioids available as combination medications include codeine, oxycodone, and hydrocodone. The opioids combined with acetaminophen or aspirin are limited in dosage due to their nonopioid components. For example, combinations containing acetaminophen 500 mg would be limited to ≤8 tablets per day due to the risk of hepatotoxicity.

The step 3 pure opioids do not share this limitation, and in fact have no theoretical ceiling for efficacy or end-organ toxicity. (Ref. 22) (Ref. 23) They can be titrated to effect limited only by adverse effects. Commonly prescribed agents in this group include morphine, oxycodone, hydromorphone, levorphanol, fentanyl, and methadone.
Opioid pharmacology

Opioids, codeine, hydrocodone, hydromorphone, morphine, oxycodone, etc., all follow first-order kinetics and pharmacologically behave very similarly. They reach peak plasma concentration $C_{\text{max}}$ approximately 60 to 90 minutes after oral (including enteral feeding tube) or rectal administration, 30 minutes after subcutaneous or intramuscular injection, and 6 minutes after intravenous injection. (Ref. 24) (Ref. 25)

The analgesia associated with each opioid has a half-life $t_{1/2}$ that depends both on the rate of liver metabolism and its rate of renal clearance. Except for methadone, which has a half-life that ranges from 15 to 40 hours, codeine, hydrocodone, hydromorphone, morphine, oxycodone, and their metabolites all have effective half-lives of approximately 3 to 4 hours when renal clearance is normal. (Ref. 26) When dosed repeatedly, their plasma concentrations approach a steady state after 4 to 5 half-lives. Thus, steady-state plasma concentrations are usually attained within 1 day.

**Routine oral dosing: immediate-release opioid preparations**

If an immediate-release oral opioid is selected and the pain is continuous or nearly so, give the medication q 4 h. For example, an opioid-naive patient who is in significant pain could be started on morphine 15 mg orally scheduled every 4 hours. Given this dosing, the total 24-hour dose of morphine the patient would receive is 90 mg. The best possible pain control for the dose will be achieved within 1 day (once steady state has
been reached). Provide the patient with access to PRN doses of the same medication that can be used should breakthrough pain occur (rescue dose). This is covered in more detail in the next section.

If pain remains uncontrolled after 24 hours, increase the routine dose by 25-50% for mild to moderate pain, by 50-100% for severe to uncontrolled pain, or by an amount at least equal to the total dose of rescue medication used during the previous 24 hours. Do not wait any longer. Delays only prolong the patient's pain unnecessarily.

If pain is severe and uncontrolled after one or two doses (e.g., crescendo pain), increase the dose more quickly. Observe the patient closely until the pain is better controlled. Guidelines for initial dosing of morphine are given in Appendix 1.

**Routine oral dosing: extended-release and long half-life opioid preparations**

Increasingly, oral extended- or sustained-release formulations of the commonly used opioids are becoming widely available for routine usage. Less frequent dosing with either these preparations or opioids with long half-lives (e.g., methadone, t1/2 \(\approx 12-24\) hours, sometimes longer) is likely to improve patient compliance and adherence.

Extended- or sustained-release opioid tablets are specifically formulated to release medication in a controlled fashion over 8, 12, or 24 hours (depending on the product). They must be ingested whole, not crushed or chewed. Extended-release capsules containing time-release granules can be swallowed whole, or the granules can be mixed with fluid and flushed down a feeding or other tube into the upper GI tract. Best possible pain control for the dose will be achieved within 2 to 4 days (once steady state has been reached). Doses should not be adjusted any more frequently than once every 2 to 4 days. For example, instead of giving 15 mg every 4 hours, the patient would receive 45 mg extended-release morphine q 12 hours.

Extended-release preparations may avoid a potential problem with short-acting opioids called the bolus effect. This phenomenon is related to peak and trough effects of dosing. Peak levels attained after taking an immediate-release preparation may be high enough to induce side effects such as lethargy, but trough levels before the next dose may be insufficient to keep pain under control. Extended-release opioids or continuous infusions of opioids avoid these pitfalls by smoothing out peak and trough extremes.

Methadone has a long and variable half-life. Although the half-life usually approaches 1 day or longer, the effective dosing interval for analgesia is usually as frequent as q 8 h; it is often q 6 h and sometimes even q 4 h. Given the variability of methadone's half-life and the unexpected potency that this medication often demonstrates, it is prudent to increase the maintenance dose only every 4 to 7 days, or less often, if possible. Treat uncontrolled pain with breakthrough doses as needed.
Breakthrough dosing

Transitory flares of pain, called breakthrough pain, can be expected both at rest and during movement. When such pain lasts for longer than a few minutes, extra doses of analgesics (i.e., breakthrough or rescue doses) will likely provide additional relief. To be effective and to minimize the risk of adverse effects, consider an immediate-release preparation of the same opioid that is in use for routine dosing. When methadone or transdermal fentanyl is used, it is best to use an alternative short-acting opioid (e.g., morphine or hydromorphone) as the rescue dose. Oral immediate-acting fentanyl is also available.

For each breakthrough dose, offer 5-15% of the 24-hour dose. As peak analgesic effect correlates with peak plasma concentration (Cmax), a breakthrough dose can be offered once Cmax has been reached. Therefore, morphine, oxycodone, codeine, and hydromorphone can be administered every 1 hour if administered orally, or possibly less frequently for frail patients; every 30 minutes if administered subcutaneously or intramuscularly; and every 10 to 15 minutes if administered intravenously. Longer intervals between breakthrough doses only prolong a patient's pain unnecessarily. For example, for the patient who was receiving 45 mg every 12 hours for a total of 90 mg morphine daily, the breakthrough dose would be 10-15 mg PO q 1 h.

Metabolism and clearance concerns

Opioids are metabolized in the liver and 90-95% excreted by the kidney. Their metabolic pathways do not become saturated. For example, the liver conjugates morphine to an active metabolite, morphine-6-glucuronide, and an inactive metabolite, morphine-3-glucuronide, that must be cleared renally. (Ref. 22) There is evidence that other opioids such as codeine, hydrocodone, hydromorphone, and fentanyl also have active metabolites. (Ref. 23) Only methadone is excreted unchanged.

When dehydration or acute or chronic renal failure impairs renal clearance, the dosing interval for morphine must be increased, or the dosage size decreased, to avoid excessive accumulation of active drug. If urine output is minimal (oliguria) or none (anuria), stop routine dosing and administer morphine only as needed. This is particularly important when patients are dying.

Opioid metabolism is not usually affected by extensive liver metastases. However, if hepatic function becomes severely impaired by hepatitis or there is clinical liver failure, increase the dosing interval or decrease the dose.

Opioids to avoid

Not all analgesics available today are recommended for acute or chronic dosing.

Meperidine is poorly absorbed orally and has a short half-life of approximately 3 hours. Its principal metabolite, normeperidine, has no analgesic properties of its own, has a
longer half-life of about 6 hours, is renally excreted, and produces significant adverse effects when it accumulates, such as tremulousness, dysphoria, myoclonus, and seizures. The routine dosing of meperidine q 3 h for analgesia leads to unavoidable accumulation of normeperidine and exposes the patient to unnecessary risk of adverse effects, particularly if renal clearance is impaired. Consequently, meperidine is not recommended for routine dosing.

Propoxyphene is typically administered at doses that produce relatively little analgesia. Dose escalation could lead to accumulation of a toxic metabolite.

The mixed-opioid agonist-antagonists, such as pentazocine, butorphanol, nalbuphine, and dezocine, should not be used in a patient already taking a pure agonist opioid (codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone). If used together, competition for the opioid receptors may cause a withdrawal reaction. Further, agonist-antagonists are not recommended as routine analgesics, as their dosing is limited by a ceiling effect. The use of pentazocine and butorphanol is associated with a relatively high risk of psychotomimetic adverse effects.

Addiction

The perception that administration of opioid analgesics for pain management causes addiction is a prevalent myth that inhibits adequate pain control. Confusion about the differences between addiction, tolerance, and physical dependence is in part responsible.

Addiction, as the term is now used, is a complex phenomenon. Its hallmark is psychological dependence on drugs and a behavioral syndrome characterized by compulsive and continued drug use, despite harm. Care must be taken to differentiate a true addiction (which is a substance use disorder) from pseudoaddiction (caused by undertreatment of pain), behavioral/family/psychological dysfunction, and drug diversion with criminal intent.

Pharmacologic tolerance is the reduced effectiveness of a given dose of medication over time. Tolerance to analgesia is rarely significant clinically when opioids are used routinely. Doses may remain stable for long periods if the pain stimulus remains unchanged. When increasing doses are required, worsening disease should be suspected rather than pharmacologic tolerance. On the other hand, developing a tolerance to side effects is beneficial and, fortunately, occurs frequently.

Physical dependence is the result of neurophysiologic changes that occur in the presence of exogenous opioids. Similar outcomes occur in the presence of exogenous
hormones and other medications (beta-blockers, alpha-2 agonists, etc.). Abrupt opioid withdrawal may result in an abstinence syndrome characterized by tachycardia, hypertension, diaphoresis, piloerection, nausea and vomiting, diarrhea, body aches, abdominal pain, psychosis, and/or hallucinations.

Physical dependence is not the same as addiction, nor is it evidence of addiction. Even if physical dependence is present, opioids can be discontinued by slowly reducing the dose. If the pain stimulus decreases or disappears, opioid doses usually can be reduced in decrements of 50% or more every 2 to 3 days, and finally stopped. If the dose is lowered too quickly and abstinence symptoms occur, a transient increase in the opioid dose, treatment with clonidine, or a small dose of a benzodiazepine (e.g., lorazepam) may be necessary to settle distressing symptoms.

To manage pain effectively, physicians will need to educate patients, families, and other professionals about the inappropriate fear of addiction. Opioids by themselves do not cause psychological dependence. Addiction is a rare outcome of pain management when there is no history of substance abuse.

Patients with histories of substance abuse can also develop significant pain and deserve compassionate treatment of their pain when it occurs. Most will need to adhere to strict dosing protocols, and a contract between the patient and oncologist may be necessary. Physicians who are unfamiliar with these situations may need the help of specialists in pain management and/or addiction medicine.

**Pain That Is Poorly Responsive to Opioids**

If dose escalation results in adverse effects, there are a few options. More sophisticated adverse effect therapy, such as a psychostimulant, may help attenuate sedation. An alternate route of administration or a different opioid may be effective without causing some of the side effects. An adjuvant analgesic may help reduce the amount of opioid required. Finally, a non-pharmacologic approach should be considered. These possibilities are discussed later in the module.

**Ongoing Assessment**

If pain control is inadequate, the dose of analgesics should be increased until pain relief is achieved or unacceptable adverse effects occur. In contrast with acetaminophen and the NSAIDs, there is no maximum dose of a pure agonist opioid. If adverse effects become intolerable, an alternative analgesic or route of administration may be more effective at controlling the pain without producing the same adverse effects. Some patients will also experience less pain spontaneously or with changes in their underlying
cause. If the pain decreases or disappears, analgesic doses may need to be reduced or discontinued.

If patients have good pain control on stable doses of an opioid, and are not experiencing any adverse effects (especially drowsiness), it is safe for them to drive a car.

**Alternative Routes of Administration**

In general, the **oral** route is the least invasive, most convenient route for administering opioids on a routine basis. However, selected patients may benefit from other routes of administration if oral intake either is not possible (due to vomiting, dysphagia, or esophageal obstruction) or causes uncontrollable adverse effects (nausea, drowsiness, or confusion).

**Enteral** feeding tubes provide alternatives for bypassing gastroesophageal obstructions. They deliver the medications to the stomach or upper intestine, where the medications behave pharmacologically as though they had been ingested orally.

**Transmucosal** (buccal mucosal) administration of more concentrated immediate-release liquid preparations provides a similar alternative, particularly in the patient who is unable to swallow. This route is particularly effective for patients who are dying.

Oral transmucosal fentanyl citrate is a new formulation of fentanyl, in a candy matrix on a stick, that is approved for the treatment of breakthrough pain. To date, experience with the formulation is limited to the United States.

**Rectal** administration of immediate- or extended-release rectal preparations behave pharmacologically like related oral preparations. (Ref. 27) This route may be very effective if oral intake is suddenly not possible, although many patients do not like this route for continuous administration.

**Transdermal** patches present an effective alternative route of administration for patients receiving stable routine opioid dosing. Currently, transdermal patches are only manufactured for fentanyl. Transdermal patches behave quite differently from other extended-release formulations. Steady-state equilibrium is established between the medication in the patch, a subdermal pool that develops, and the patient's circulation. On average, best possible pain control is achieved within 1 dosing interval (i.e., 3 days) with peak effect at about 24 hours. The effect usually lasts for 48 to 72 hours before the patch needs to be changed. Care must be taken to ensure that patches adhere to the patient's skin (avoid hairy areas) and do not lift off with bathing or sweating.

**Parenteral** administration using injection or infusion can be very useful in selected patients. When renal function is normal, provide routine parenteral bolus doses every 3
hours and adjust the dose every 12 to 24 hours once steady state is reached. Doses are effectively the same for subcutaneous, intravenous, or intramuscular administration. If a parenteral route will be used for some time, continuous infusions may produce a more constant plasma level, reduce the risk of adverse effects, be better tolerated by the patient, and require less intervention by professional staff. Patient-controlled analgesia has been shown to be both effective and well tolerated by patients.

While intravenous infusions may be preferable if intravenous access is already established and in use for other medications, all opioids available for parenteral use may be administered subcutaneously without the discomfort associated with searching for an IV site or the risk of serious infection. Either 25- or 27-gauge needles can be used for both bolus dosing and infusions. The needles can be left in place for 7 days or more as long as there is no sign of infection or local irritation. Family members can be taught to change them.

Intramuscular injections are not recommended. Intermittent subcutaneous doses are much less painful and just as effective.

Intraspinal opioids, epidural or intrathecal, may be useful in selected patients who have pain in the lower part of their body, or pain that is poorly responsive to routine systemic opioid therapy. Intraspinal delivery allows much lower doses of opioids to be used and consequently reduces systemic side effects. Opioids such as morphine, hydromorphone, or fentanyl are used. They are typically combined with a local anesthetic and/or an alpha-2-adrenergic agonist. Other invasive chemical and surgical neurolytic procedures are sometimes used in specific pain syndromes. A specialist who is knowledgeable about their specific indications and pharmacology, and who is skilled in their delivery, is usually required to administer them.

Bolus effect

As the total dose of opioid in the bloodstream changes, some patients may experience drowsiness ½ to 1 hour after ingestion of a dose of medication as the plasma level peaks, followed by pain just before the next dose is due as the plasma level falls. This syndrome, known as the bolus effect, can only be resolved by switching to an extended-release formulation (oral, rectal, or transdermal) or a continuous parenteral infusion to reduce the swings in plasma concentration after each dose.

Changing routes of administration of opioids

When changing routes of administration, an equianalgesic table is a useful guide for initial dose selection. Significant first-pass metabolism necessitates larger oral or rectal doses to produce analgesia equivalent to parenteral doses of the same opioid. Equivalent dosing recommendations represent consensus from limited available evidence, so they are guides only, and individual patients may require doses to be adjusted. Tables, such as the one indicated here, are clinically convenient and easy to use. Large between-patient variability makes firm ratios elusive.
### Clinical Guide for Changing Opioid Analgesics

<table>
<thead>
<tr>
<th>ORAL/RECTAL DOSE (MG)</th>
<th>ANALGESIC</th>
<th>PARENTERAL DOSE (MG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 (MG)</td>
<td>Codeine</td>
<td>50</td>
</tr>
<tr>
<td>150 (MG)</td>
<td>Meperidine</td>
<td>50</td>
</tr>
<tr>
<td>150 (MG)</td>
<td>Tramadol</td>
<td>-</td>
</tr>
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<td>15 (MG)</td>
<td>Hydrocodone</td>
<td>-</td>
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<tr>
<td>10 (MG)</td>
<td>Oxycodone</td>
<td>-</td>
</tr>
<tr>
<td>3 (MG)</td>
<td>Hydromorphone</td>
<td>1</td>
</tr>
<tr>
<td>2 (MG)</td>
<td>Levorphanol</td>
<td>1</td>
</tr>
<tr>
<td>- (MG)</td>
<td>Fentanyl</td>
<td>0.05</td>
</tr>
</tbody>
</table>

A clinical guide for changing opioid analgesics such as this one, adapted with permission from Levy, can be used on the horizontal axis to switch routes of administration and on the vertical axis to switch from one opioid to another. (Ref. 28)

### Changing opioids

When converting to or from transdermal fentanyl patches, published data from the manufacturer suggest that a 25-μg patch is equivalent to 45 to 135 mg of oral morphine per 24 hours. However, published clinical experience suggests that most patients will use the lower end of the range of morphine doses (i.e., for most patients, 25 μg is about equivalent to 45 to 60 mg of oral morphine per 24 hours). (Ref. 29) (Ref. 30)
Opioid rotation

For reasons that remain obscure, two or three different opioids may need to be successively tried until a drug that provides good analgesia with minimal adverse effects is found for an individual patient. (Ref. 31)

Opioid cross-tolerance

While pharmacologic tolerance may develop to the opioid in use, tolerance may not be as marked relative to other opioids. (Ref. 32) Incomplete cross-tolerance is likely due to subtle differences in the molecular structure of each opioid and the way each interacts with the patient’s opioid receptors. Consequently, when switching opioids, there may be differences between published equianalgesic doses of different opioids and the effective ratio for a given patient. Start with 50-75% of the published equianalgesic dose of the new opioid to compensate for incomplete cross-tolerance and individual variation, particularly if the patient has controlled pain. If the patient has moderate to severe pain, do not reduce the dose as much. If the patient has had adverse effects, reduce the dose more.

An important exception is methadone, which appears to have higher than expected potency during chronic dosing compared with published equianalgesic doses for acute dosing. (Ref. 33) (Ref. 34) (Ref. 35) Because methadone has both opioid and NMDA receptor antagonistic effects, the apparent equianalgesic ratio changes based on dose.
### Methadone Conversion Ratios

<table>
<thead>
<tr>
<th>Daily morphine-equivalent dose (mg/24 hr PO)</th>
<th>Morphine PO</th>
<th>Methadone PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td></td>
<td>3 : 1</td>
</tr>
<tr>
<td>101 – 300</td>
<td></td>
<td>5 : 1</td>
</tr>
<tr>
<td>301 – 600</td>
<td></td>
<td>10 : 1</td>
</tr>
<tr>
<td>601 – 800</td>
<td></td>
<td>12 : 1</td>
</tr>
<tr>
<td>801 – 1,000</td>
<td></td>
<td>15 : 1</td>
</tr>
<tr>
<td>&gt;1,001</td>
<td></td>
<td>20 : 1</td>
</tr>
</tbody>
</table>

#### Methadone SC Dosing

Convert from daily morphine-equivalent dose PO/24 hr to methadone PO dose/24 hr using the Methadone PO Dosing Table above. Then divide by 3 to convert to Methadone SC Dose/24 hr.

### Adjuvant Analgesics

Adjuvant analgesics (or coanalgesics) are medications that, when added to primary analgesics, further improve pain control. They may themselves also be primary analgesics (e.g., tricyclic antidepressant medications for postherpetic neuralgia). They can be added into the pain management plan at any step in the WHO ladder.

The classes of medication used to treat neuropathic pain include anticonvulsants, antidepressants, NMDA-receptor antagonists, local anesthetics, and alpha-2-adrenergic agonists. There is no clear consensus on what adjuvant category to utilize first, but...
many clinicians choose to initially prescribe an anticonvulsant or antidepressant medication.

**Anticonvulsants**

The molecular mechanism by which **anticonvulsants** produce analgesia is not clear, but presumably is related to their effects on neuronal discharge. Gabapentin has emerged as the most common initial therapy. Studies have shown it to be efficacious in the control of postherpetic neuralgia and diabetic neuropathic pain. (Ref. 36) (Ref. 37) Levels need not be followed and it has a relatively safe side effect profile. The most troublesome side effect is lethargy. (Ref. 36) This symptom can usually be controlled by “starting low and going slow” in titration. Doses as low as 300 mg per day may be effective, but 900 mg per day is the typically effective dose. If necessary, doses can be gradually increased to a level of 3,600 mg/day limited by efficacy or side effects. Clonazepam is also effective, with a relatively good side effect profile. (Ref. 38) Other anticonvulsants such as carbamazepine and valproic acid are effective but require monitoring of levels and monitoring for signs of organ toxicity. (Ref. 39) Newer anticonvulsants such as lamotrigine also seem to be effective in early clinical studies. (Ref. 40) If one anticonvulsant is not effective, it is rational to try another one.

**Antidepressants**

The tricyclic antidepressants are the best-studied antidepressant class that shows efficacy in neuropathic pain, and the pain effect has been separated from the antidepressive effect. (Ref. 41) Doses effective for neuropathic pain are usually lower than doses needed for depression. Amitriptyline has been most extensively studied. It blocks reuptake of serotonin and norepinephrine and appears to also block the NMDA receptor. (Ref. 42) Amitriptyline is the most anticholinergic of the tricyclics. This fact can be used to advantage if patients have trouble sleeping at night. Often, however, the anticholinergic effects of dry mouth, sedation, constipation, and urinary retention are obstacles to use. Desipramine and nortriptyline have also been demonstrated to be effective for neuropathic pain and have much less anticholinergic activity. (Ref. 43) All of these agents are usually started at 10 mg orally at bedtime and titrated up to about 100 mg per day limited by effect or side effect. It typically takes 1-2 weeks to titrate up to an effective dose to determine if the therapy is working. Newer atypical antidepressants (such as venlafaxine) show some evidence of efficacy but have not been well studied. (Ref. 44) Studies have shown selective serotonin reuptake inhibitors (SSRIs) to be much less effective. (Ref. 41)

**NMDA-receptor antagonists**

The N-methyl-D-aspartate (NMDA) receptor may be involved in the spinal neural circuitry that leads to a neuropathic pain state that is resistant to high-dose opioids. Clinically available NMDA-receptor antagonists include dextromethorphan, ketamine, and methadone. Clinical studies with dextromethorphan and ketamine have shown some mild pain effects, but have been significantly limited by dose-related side effects.
Methadone, however, is inexpensive and well tolerated. It exists as a racemic mix of levo and dextro isomers. The levo form binds at opioid receptors, while both forms can block the NMDA receptor. As previously discussed, the equianalgesic dose of methadone varies dependent upon how much oral morphine equivalent a patient takes. It is hypothesized that by being both an opioid receptor agonist and an NMDA-receptor antagonist, methadone is much more potent than expected. Thus, methadone can be an extremely effective second-line opioid for neuropathic pain. (Ref. 33) (Ref. 34) (Ref. 35)

**Local anesthetics**

Local anesthetics that are nonselective inhibitors of sodium channels have also been utilized to treat neuropathic pain. Parenteral lidocaine has been studied and in general has been found to have efficacy in diabetic neuropathy, trigeminal neuralgia, and other neuropathic pain syndromes. (Ref. 46) Typically effective serum levels range from 2-5 mg/liter. However, there is little data in the end-of-life population. Oral anesthetics/antiarrhythmics such as mexiletine have also been used with success in neuropathic pain. (Ref. 46) Monitoring for cardiac toxicity is necessary. Topical lidocaine patches have been approved for use in postherpetic neuralgia. (Ref. 47) Research has identified many subtypes of sodium channels, and in the future it may be possible to block a specific subset involved in mediating pain transmission.

**Alpha-2-adrenergic agonists**

Alpha-2-adrenergic agonists such as clonidine can also be effective adjuvant analgesics for both nociceptive and neuropathic pain. (Ref. 48) They act at the level of the spinal cord in two ways. First, they act in a mechanistically similar way to the opioids. They act on the same neurons in the cord and lead to the same intracellular events but act through a different receptor. (Ref. 49) Thus, it is likely that they can enhance the nociceptive effects of opioids. Second, researchers believe alpha-2-adrenergic agonists also decrease sympathetic outflow that is involved with neuropathic pain. (Ref. 50) Clonidine can be given systemically or delivered intraspinally. Systemic delivery may be limited by the side effects of lethargy, dry mouth, and hypotension.

**Corticosteroids**

Corticosteroids are potent anti-inflammatory agents that are useful in treating both nociceptive and neuropathic pain. Reducing inflammation and peritumor edema can be important in relieving pressure on a nerve or the spinal cord, decreasing intracranial pressure from a brain tumor, or decreasing obstruction of a hollow viscus. At the end-of-life, dexamethasone is considered the corticosteroid of choice because of its minimal mineralocorticoid effects and thus its decreased tendency to cause salt and fluid retention. (Ref. 51) (Ref. 52) Corticosteroids may also enhance pain control through the creation of a sense of euphoria. Most of the complications of steroid use are long-term sequela and are not a concern at the end-of-life. However, steroid psychosis is occasionally a problem that may require either cessation of the drug or treatment with
neuroleptics. (Ref. 53) Dexamethasone has a long half-life and need only be dosed once a day. Typical doses range from 4 mg per day up to 100 mg intravenous bolus used for spinal cord compression. (Ref. 54)

Bone Pain

**Bone pain** is a frequently occurring problem that may be both constant at rest and much worse with movement. It is frequently the result of mechanical changes due to metastases, or compression or pathologic fracture, etc. Prostaglandins produced by concurrent inflammation and/or metastases may increase bone pain severity. Cord compression should always be considered when there is significant back pain in the patient with metastatic cancer.

Bone pain is associated with inflammation. NSAIDs and/or corticosteroids are important components of the treatment of this pain syndrome. However, the treatment of choice for an isolated bone lesion is radiation therapy. At the end-of-life, when duration of effect is less important than efficacy and convenience, it can be delivered in a single fraction and promote improved pain within 1-2 weeks. When bony lesions are more diffuse or when they recur in a previously irradiated field, the bisphosphonates can play an important role. Osteoclasts are activated in bony metastasis. Bisphosphonates, like pamidronate, inhibit osteoclast activity, thus stabilizing bone, and through an unknown mechanism can also relieve bone pain. It is effective for both lytic and sclerotic bone lesions. (Ref. 55) Typical dosing of pamidronate is 90 mg intravenously over 2 hours every month.

Radiopharmaceuticals such as strontium-89 are also available to treat diffuse lesions. They are typically more effective for sclerotic lesions but have also been shown to be effective in lytic lesions. (Ref. 56)

Pain from Bowel Obstruction

Mechanical bowel obstruction, due to internal blockage from constipation or external compression by tumor or scars, can lead to significant abdominal pain as the bowel wall is stretched or inflamed. The pain is frequently described as constant, sharp, and cramping. It may be associated with considerable bloating, distention, gas, or even nausea/vomiting. Relief of constipation (see EPEC™-O Module 3f: Symptoms - Constipation) or surgical removal or bypass of external blockages may be definitive; in some patients, the obstruction will be irreversible.

Most patients will find the abdominal pain associated with bowel obstruction distressing. While some people will find opioids sufficient to manage this pain, many will need adjuvant medications to effectively relieve their discomfort. Corticosteroids or NSAIDs
may be helpful. Anticholinergic medications (e.g., scopolamine) or octreotide will reduce
the volume of fluid entering the intestine, thus relieving the bowel wall stretch and the
pain. Early consultation with a pain management expert can reduce patient distress
even when awaiting definitive intervention.

**Topical Analgesia**

Even simple procedures such as venipuncture may be painful. Topical anesthetic
creams should always be considered. If trained, patients can always apply these
analgesics in advance of office visits.

Open wounds may also be a source of considerable pain, particularly during dressing
changes or debridement. If incident pain is significant, consider topical analgesics such
as 10% lidocaine endotracheal spray or nitrous oxide puffers.

**Adverse Effects**

Opioids have many possible adverse effects; some are common, and some are not.
(Ref. 57) (Ref. 58) (Ref. 59) If unmanaged, they may be a reason for nonadherence.
(Ref. 60) Addiction (psychological dependence), tolerance, and physical dependence
are not considered among the adverse effects. The ethical considerations of “double
effect” and unintended consequences of opioids and other medications are discussed in
EPEC™-O Module 3: Symptoms.

**Opioid allergy**

Many people believe that opioid-induced nausea/vomiting, constipation, drowsiness, or
even confusion is an allergic reaction. However, these are not allergic reactions; they
are adverse effects. While one or more may present on initial dosing, adverse effects
can be easily managed and patients generally develop pharmacologic tolerance to all
but constipation within a relatively brief period.

Anaphylactic or true allergic reactions to opioids are rare. Urticaria and bronchospasm
could be direct opioid effects or signs of allergy. Sudden onset of breathlessness or
other signs of anaphylaxis should be taken very seriously and the offending opioid
replaced with another from a different class.
Urticaria, pruritus

In some patients, opioids produce urticaria or pruritus. These effects are the result of mast cell destabilization by the opioid and subsequent histamine release. Usually the rash and pruritus can be managed by routine administration of long-acting, nonsedating antihistamines while opioid dosing continues (e.g., fexofenadine, 60 mg PO bid; diphenhydramine, loratadine, or doxepin, 10-30 mg PO nightly).

Constipation

Constipation secondary to opioid administration is almost universal. It is primarily the result of opioid effects on the central nervous system, spinal cord, and myenteric plexus of gut that, in turn, reduce gut motor activity and increase stool transit time. The colon has more time to desiccate its contents, leaving large, hard stools that are difficult to pass. Other factors, such as dehydration, poor food intake, other medications, etc., may make the problem worse.

Tolerance to constipation may develop very slowly, if at all. (Ref. 34) (Ref. 35) It requires anticipatory and ongoing management. Dietary interventions alone (e.g., increased fluid and fiber) are often insufficient. Bulk-forming agents (e.g., psyllium) require substantial fluid intake and are not recommended for those with advanced disease and poor mobility.

To counteract the slowing effect of opioids, start by prescribing a routine stimulant laxative (e.g., senna, bisacodyl, glycerine, casanthranol, etc.) and escalate the dose to effect. While stool softeners (e.g., docusate sodium) are not usually effective by themselves, combination stimulant/softeners (e.g., senna + docusate sodium or calcium) can be useful. Prokinetic agents (e.g., metoclopramide, cisapride, etc.) may also significantly counteract the opioid effect. If constipation persists, some patients will benefit from the addition of an osmotic agent, such as milk of magnesia, lactulose, or sorbitol, to increase the stool's moisture content. If the constipation proves to be refractory to basic therapy, interventions that are more aggressive may be necessary (see EPEC™-O Module 3: Symptoms).

Nausea/vomiting

Many patients starting opioids experience nausea with or without vomiting. It is easily anticipated and treated with antiemetics and usually disappears as tolerance develops within a few days. Young women seem to be most at risk. Opioid-induced nausea may be related to stimulation of the chemoreceptor trigger zone or vestibular apparatus, and to delayed gastric emptying. Nausea typically responds well to antiemetics that target: the chemoreceptor trigger zone, such as antidopaminergic agents; the vestibular apparatus, such as antihistamines; and gastric motility.
Dopamine-blocking agents (e.g., prochlorperazine, 10 mg before opioid and q 6 h; haloperidol, 1 mg before opioid and q 6 h; metoclopramide, 10 mg before opioid and q 6 h) are most often effective. In refractory cases, a more aggressive approach or use of an alternative opioid may become necessary (see EPEC™-O Module 3: Symptoms).

**Sedation**

Patients sometimes complain of feeling sedated or mentally clouded immediately after beginning an opioid analgesic. Care must be taken to distinguish true sedation (inability to fully wake up) from exhaustion due to previous sleep deprivation with the unrelieved pain (sleeps a lot, but is able to wake fully between sleeps). Opioid-induced sedation usually disappears over a few days as tolerance develops. Most patients also catch up on their lost sleep over a week or two.

For patients with very advanced disease, mental clouding and excessive somnolence are often issues, particularly when patients have multiple concomitant medical conditions, medications, and declining function, even in the absence of opioid analgesics. Pain may, in fact, be the primary stimulant keeping them alert. Once pain is managed, the patient's natural level of sedation may become apparent.

If sedation occurs, encourage patients and families to clearly articulate their goals (see EPEC™-O Module 9: Negotiating Goals of Care) and develop a pain management plan that balances alertness and pain control to suit the individual. Some patients may prefer to be sleepy and comfortable rather than alert and in pain.

If undesired sedation persists, a different opioid or an alternate route of administration may provide relief. The use of a psychostimulant (e.g., methylphenidate, 5 mg q am and q noon and titrate) can also be considered, particularly if the opioid is providing effective analgesia. (Ref. 33)

**Delirium**

The onset of confusion, bad dreams, hallucinations, restlessness, agitation, myoclonic jerks, a significantly depressed level of consciousness, or seizures suggests delirium due to opioid excess. If opioid dosing guidelines are followed closely, delirium rarely occurs in patients who have normal renal clearance. However, one or more of these adverse effects may present gradually (e.g., in the patient who is not passing much urine and is accumulating opioid due to decreased intake or dehydration) or rapidly (e.g., in the patient who is developing sepsis) (see EPEC™-O Module 3: Symptoms)

**Respiratory depression**

Many physicians have an exaggerated view of the risk of respiratory depression when using opioids to relieve pain. (Ref. 33) The inappropriate application of animal and human models from acute pain research is in part responsible for this fear.
Pain is a potent stimulus to breathe, and pharmacologic tolerance to respiratory depression develops quickly. Opioid effects on a patient in pain are quite different from those experienced by a patient who is not in pain and receives similar doses. As doses of the opioid given to the patient in pain are appropriately titrated upward, respiratory depression does not occur suddenly in the absence of other signs of overdose. The development of somnolence as a symptom always precedes the onset of respiratory depression. Adequate ongoing assessment and appropriate titration of opioids based on pharmacologic principles will prevent accidental overdosing of the patient in pain. Patient-controlled analgesia with an appropriate dosing interval (10-15 minutes if IV, 30 minutes if SC) can be used safely, because the patient who takes too many extra doses of opioid will fall asleep and stop pushing the button before respiratory depression occurs.

If delirium due to opioid excess does occur, but respirations are not compromised (i.e., remain >6/min), the routine opioids may be stopped temporarily while the patient receives appropriate interventions for possible dehydration or sepsis, until the adverse effects abate.

If respirations are compromised (i.e., drop to <6/min), administration of a dilute solution of naloxone may be necessary to reverse respiratory depression. Dilute 0.4 mg of naloxone in 10 ml of sterile water. Administer 0.1 to 0.2 mg IV q 1 to 2 minutes until the patient is alert. Since the effective plasma half-life is short (10 to 15 minutes) due to naloxone's high affinity for lipids, monitor the patient closely every few minutes for recurrent drowsiness. If drowsiness recurs, repeat the above dosing schedule as required until the patient is no longer compromised.

Interventional Pain Management for Refractory Pain

About 14% of cancer pain patients suffer severe unrelieved pain even when treated with opioids, adjuvant drugs, and other accepted therapies. (Ref. 60) In addition, at times drugs relieve pain but have side effects severe enough to preclude continued use at effective levels. (Ref. 61) Interventional pain management can help this subgroup of patients through the use of intraspinal therapy, splanchnic nerve blocks, or local nerve blocks. (Ref. 62) Interventional pain management works quickly if it is going to work; unlike chemotherapy, the patient will either say, “I wish I had done that months ago!” or note no difference.

Prognosis

Pain is associated with a poor prognosis, but it is not clear if pain itself or the disease causing the pain is the root issue. Pain itself dampens immune system function, as do therapeutic doses of morphine. (Ref. 63) (Ref. 64) (Ref. 65) In patients with pain due to pancreatic cancer, relief of pain by an alcohol celiac plexus block vs. placebo saline block at the time of pancreaticoduodenectomy was associated with a markedly
improved median survival of greater than 6 months. (Ref. 66) Relief of pain and drug side effects was associated with a near doubling of median survival in patients with refractory pain. (Ref. 62)

Intraspinal therapy

The two most common ways of giving intraspinal therapy are by epidural or intrathecal treatment. (Ref. 67) (Ref. 68) (Ref. 69) (Ref. 70) (Ref. 71) (Ref. 72) The reduced systemic exposure to opioids can help relieve refractory side effects of opioids such as constipation, nausea, and sedation. Epidural catheters are commonly used to produce mostly a local effect on the nerves in the area where the catheter instills drugs for relatively short periods of time (days to weeks). Intrathecal catheters instill drugs directly into the spinal canal and can be used to give both local and systemic pain relief for periods of months to years.

Epidural therapy provides pain relief in the small number of patients for whom it is appropriate. (Ref. 73) (Ref. 74) However, complications such as dislodged or broken catheters, pain on injection, bruising, bleeding, and infection occur in half of these patients.

Intrathecal therapy provides pain relief by instilling small doses of morphine or other drugs directly into the cerebrospinal fluid. (Ref. 75) An implanted pump is used for long-term administration. Prior to implantation of a pump, all patients receive a screening trial of intraspinal morphine to determine response. About 95% of patients who have a trial have successful treatment of pain and can go on to an implanted system. The implanted system consists of a small battery-powered pump that is implanted in the abdomen and connected to a small catheter tunneled to the site of spinal entry, usually the L1-L2 interspace. Patients with implanted pumps may continue to use systemic medications to manage breakthrough pain.

There are two types of pumps: a programmable pump that allows the rate of infusion to be changed just like changing the rate on a pacemaker, and a nonprogrammable pump that requires changing the concentration of the infusate.

Relative contraindications to intraspinal therapy include active infection, coagulopathy or heparin therapy, or spinal cord obstruction that would prevent diffusion of the drugs. Patients with a short time to live are best served by catheters connected to external reusable pumps; those with 3 or more months to live are candidates for implantable pumps.

Celiac plexus block

Celiac plexus block (CPB) is used to treat the severe, boring, progressive pain of upper abdominal cancers (most commonly pancreas, stomach, liver, gallbladder, and colon) that fails to respond to conventional treatment. A review reported a satisfactory response in 87% of pancreas cancer patients, with the expected relief of pain and also
relief of anorexia and constipation. (Ref. 76) About 10-20% of patients have complete resolution of their pain, and for many patients the pain relief lasts until death. (Ref. 77) (Ref. 78)

The celiac plexus partly innervates all of the abdominal structures, including the diaphragm, stomach, adrenal glands, liver, spleen, intestines, and even gonads. CPB is the injection of a local anesthetic into the celiac plexus in front of the L1 vertebra, which if successful, can be followed by injection of a neurolytic substance such as alcohol or phenol. CPB can be done percutaneously with CAT or fluoroscopic guidance, or intraoperatively. Serious complications are rare in experienced hands. (Ref. 79) (Ref. 80) More common and predictable complications include hypotension and postural hypotension, which require careful postop observation, and transient postblock diarrhea (due to sympathetic block) which remits in several days.

CPB should be considered early in the course of the disease-not done as a last-ditch effort when the patient is close to death. Data showing a high success rate with CPB, a low complication rate, the ability to relieve upper abdominal pain without need for high-dose opioids, and improvement in overall survival support this claim.

Other nerve stimulations or ablations

Invasive techniques should be considered if their purpose is to provide better function. Some procedures have been shown to be useful in highly selected patients and include stimulation of the spinal cord, cortical brain, or brain stem, and temporary nerve blocks followed by radiofrequency or cryosurgical ablation. Although large-scale randomized clinical trials have not been conducted, there is substantial evidence that these techniques are effective. Lack of clinical trials is a consequence of several factors. Refractory pain (or perhaps the recognition of refractory pain) occurs relatively infrequently. A scarcity of professional expertise and insufficient opportunity for appropriate consultation exist. In all cases, there is an opportunity to test the procedure first to see if it proves to be effective. If so, a more permanent procedure is indicated. (Ref. 81) (Ref. 82) (Ref. 83)

Non-pharmacologic Pain Management Techniques

While pharmacologic approaches may be the mainstay of pain management, physicians should consider all available therapies as they develop an individual's plan of care. Many patients have realized significant relief through neurostimulatory techniques, including TENS (transcutaneous electrical nerve stimulation) and acupuncture; physical therapy, including therapeutic exercises, heat, and cold; psychological approaches including cognitive therapies (relaxation, imagery, hypnosis), biofeedback, behavior therapy, and psychotherapy; art or music therapy; massage, and body work; etc. Members of the interdisciplinary team who may be more familiar with non-
pharmacologic interventions can frequently help the physician identify and refer patients appropriately.

**Barriers**

Today, pain management remains inadequate in spite of the fact that the information discussed in this module has been available for more than 20 years. While this inadequacy may reflect insufficient knowledge, it also reflects barriers to pain relief that are pervasive and (in some cases) institutional. To effectively relieve patients' pain, we need to overcome real or perceived barriers, which include: beliefs by physicians and other professionals that pain management is not important; poor assessment techniques; inadequate dissemination of available knowledge; unfounded fear of addiction, tolerance, and adverse effects; and inappropriate regulatory oversight. To be effective, individual care plans must encourage patients to report their pain freely and take into account each patient's willingness to take medication, or not. In addition to adequate knowledge, health care systems and institutions may need to change in order to facilitate the implementation of appropriate pain relief.

**Summary**

Pain management is key to achieving the goal of relief of suffering. Although pain control alone is not sufficient to relieve suffering, there can be little progress in the other spheres of experience if pain is uncontrolled. If we simply apply the knowledge we have, we will adequately relieve pain in the majority of patients. Careful assessment and appropriate use of opioids as outlined in the WHO three-step ladder approach will go a long way toward improving the quality of patients' lives.

**Key Take-Home Points**

**Assessment**

1. Characterize the nature of the pain (nociceptive, neuropathic, psychological/social/spiritual). Try to establish the cause of the pain. Understand the personal context in which the pain is experienced.

**Management**

2. There is no reason to delay the use of analgesics while diagnosing and treating the underlying cause of the pain.
3. There is no ethical or scientific basis for the use of placebos to assess or treat pain.

WHO analgesic ladder

4. The WHO three-step model can be used to guide analgesic choice relative to the severity of the patient's pain.

5. The nonopioid analgesics that characterize step 1 of the WHO ladder (acetaminophen, NSAIDs) all have a ceiling effect to their analgesia. Start with moderate to maximal doses to achieve optimal efficacy quickly.

6. The step 1 analgesics have the greatest risk of severe adverse effects. Anticipate and monitor for them carefully.

7. Step 2 and 3 opioid analgesics (e.g., codeine, hydrocodone, hydromorphone, morphine, oxycodone) follow first-order kinetics. They reach their peak effect and plasma concentration (Cmax) approximately 60 to 90 minutes after oral or rectal administration, 30 minutes after subcutaneous or intramuscular injection, and 6 minutes after intravenous injection.

Opioid dosing

8. In general, the oral route is the least invasive, most convenient route for administering opioids on a routine basis.

9. If the pain is continuous, or nearly so, start with an appropriate dose of an immediate-release opioid routinely q 4 h around the clock.

10. If pain remains uncontrolled after 24 hours, increase the routine dose by an amount at least equal to the total dose of rescue medication used during the previous 24 hours, or by 25-50% for mild to moderate pain, and 50-100% for severe to uncontrolled pain.

11. Once the continuous pain is controlled, switch to an extended-release preparation to simplify routine dosing and increase the chance of patient adherence.

Breakthrough pain

12. Transitory flares of pain, called breakthrough pain, can be expected both at rest and during movement.

13. For each breakthrough dose, offer 5-15% of the total 24-hour dose of opioid at a frequency equal to Cmax for the chosen route of administration.

PO/PR ≈ q 1 h PRN
SC/IM ≈ q 30 min
IV ≈ q 10-15 min
Clearance concerns

14. As some morphine metabolites remain active until they are excreted in the urine, adjust routine dosing for decreased renal clearance when oliguria or anuria is present (e.g., dehydration, renal failure, dying patient).

Opioids to avoid

15. Meperidine is not recommended for routine dosing because of the high risks of adverse effects from accumulation of the metabolite normeperidine.

16. Propoxyphene is typically administered at doses that produce relatively little analgesia and is not recommended as a routine analgesic.

17. The mixed-opioid agonist-antagonists, such as pentazocine, butorphanol, nalbuphine, and dezocine, should not be used in the patient already taking a pure agonist opioid as there is a high risk they will precipitate withdrawal.

Addiction, tolerance, physical dependence

18. The perception that the administration of opioids and analgesics for pain management causes addiction is a prevalent myth that inhibits adequate pain control.

19. Addiction is a complex phenomenon. The hallmark of addiction is psychological dependence on drugs, a behavioral syndrome characterized by compulsive drug use and continued use despite harm. It is important to recognize the difference between true addiction and pseudoaddiction (caused by undertreatment of pain), behavioral/family/psychological dysfunction, and drug diversion with criminal intent.

20. Pharmacologic tolerance is defined as the reduced effectiveness of a given dose of medication over time. The occurrence of pharmacologic tolerance is of little concern in the clinical setting. When increasing doses of analgesics are required, worsening disease rather than pharmacologic tolerance should be suspected.

21. Physical dependence is the result of neurophysiologic changes that occur in the presence of exogenous opioids. Withholding opioids after physical dependence develops results in transient withdrawal symptoms. Physical dependence is not the same as addiction.

Alternate routes and changing opioids

22. All opioids available for parenteral use may be administered subcutaneously without the discomfort associated with searching for an IV site, the risk of serious infection, or the discomfort of intramuscular (IM) injection.

23. Intramuscular injections are not recommended.

24. When changing routes of administration or switching between opioids an equianalgesic table is a useful guide for initial dose selection.
25. Incomplete cross-tolerance is likely caused by subtle differences in the molecular structure of each opioid and the way each interacts with the patient's opioid receptors. Consequently, when switching opioids, there may be differences between published equianalgesic doses of different opioids and the effective ratio for a given patient. Start with 50-75% of the published equianalgesic dose of the new opioid if pain is otherwise well controlled.

**Neuropathic pain**

26. Opioids may contribute significantly to the management of neuropathic pain.

27. For burning, tingling pain with or without numbness, tricyclic antidepressants or gabapentin are the most widely used adjuvant medications.

28. Desipramine has minimal anticholinergic adverse effects and is the tricyclic antidepressant of choice, particularly in elderly and frail patients. Start with 10 to 25 mg orally at bedtime and escalate every 4 to 7 days. This may be effective in only a few days.

29. For episodic shooting, stabbing, electrical pain, the anticonvulsants gabapentin, carbamazepine, and valproic acid are the most widely used adjuvant medications. Start with low doses and escalate after a steady-state equilibrium has been reached (varies by medication).

**Bone pain**

30. Opioids remain the mainstay of bone pain management. NSAIDs and steroids may be effective adjuvants.

**Steroids**

31. Corticosteroids are frequently helpful and commonly used in advanced illness. Dexamethasone, with its long half-life (>36 hours) and minimal mineralocorticoid effect, is the adjuvant steroid of choice. It can be administered once a day.

**Adverse effects of opioids**

32. Addiction (psychological dependence), tolerance, and physical dependence are not considered adverse effects of opioid analgesics.

33. Concerns about the Principle of Double Effect in the use of opioids are overrated. The term is frequently misused. If opioid dosing guidelines are followed, the risk of a secondary, potentially severe unintended consequence is minimal. Severe and predictable adverse effects such as death are almost unknown when accepted principles of use are followed.

34. Many people believe that opioid-induced nausea/vomiting, constipation, drowsiness, and even confusion are allergic reactions. They are in fact adverse effects, not allergic reactions.
35. Urticaria and pruritus are usually the result of mast cell destabilization by opioids that lead to histamine release. This can be managed by the routine administration of long-acting, non-sedating antihistamines or mast cell stabilizers.

36. Adverse effects of opioids can be managed. Patients generally develop pharmacologic tolerance to all but constipation within a relatively brief period.

37. Constipation secondary to opioid administration is almost universal. When starting opioid therapy, prevent it by prescribing a routine stimulant laxative and escalate the dose to effect.

38. Many patients starting opioids (up to 30%) experience nausea with or without vomiting. Tolerance develops. Treat with antiemetics or change to a different opioid.

39. Opioid-induced sedation usually disappears over a few days as tolerance develops. For patients with far-advanced disease near the end-of-life, pain may in fact be the primary stimulant keeping them alert. Once pain is managed, the patient's natural level of sedation may become apparent. Encourage patients and families to clearly articulate their goals and priorities in order to develop a pain management plan that balances alertness and pain control.

40. The onset of confusion, bad dreams, hallucinations, restlessness, agitation, myoclonic jerks, a significantly depressed level of consciousness, or seizures suggests delirium caused by opioid excess.

41. Physicians often have an inordinate fear of respiratory depression caused by opioids. Pain is a potent stimulus to breathing. Opioids may induce respiratory depression in the patient who is opioid naive, but pharmacologic tolerance to respiratory depression develops quickly. The symptom of somnolence always precedes the development of respiratory depression.

**Non-pharmacologic approaches**

42. Non-pharmacologic approaches to pain management may have a significant adjunct effect on pain management.

**Barriers**

43. There are many unnecessary and remediable barriers to pain management.

**Pearls**

1. Believe the patient.
2. Be the physician you would want to have if you were in pain.
3. Dehydration may present as confusion caused by opioid accumulation.
4. Opioids used for pain management do not cause the psychological dependence involved in addiction.
5. Doxepin is a potent H1 histamine antagonist.
6. Teach the patient and family about potential adverse effects. Unexpected adverse effects may cause the patient to refuse any further opioid therapy.

7. Constipation is easier to prevent than treat.

8. Psychostimulants may be useful adjuncts to counteract sedation.

9. Sepsis may present as delirium caused by opioid excess.

10. Make a partnership with your patient and the family caregiver; draw them into the interdisciplinary team and foster their active participation in the care plan.

11. Additional information may be found in the Health Professional Resources and Patient Resources sections of this module.

**Pitfalls**

1. Using extended-release preparations for initial dose titration.

2. Mixing opioids; this is rarely indicated.

3. Using detergent stool softeners alone (e.g., docusate) at conventional doses, which does not counteract the constipating effect of opioids.

4. Failing to distinguish sleepiness caused by exhaustion once pain is relieved from sedation caused by overmedication.

5. Mismanaging terminal delirium with opioids, which may make it worse.

6. Unfounded fear of respiratory depression and lack of skill with opioid dosing, leading to significant unnecessary pain, loss of function, and suffering.

**Problem Solving**

The following cases illustrate common issues in cancer pain management. Answers can be found at the end of the Appendix 1.

**Case 1**

Mrs. D. is a 45-year-old attorney who has breast cancer metastatic to bone. She is comfortable on a continuous infusion of morphine at 6 mg/h SC. Your goal is to change to oral medications before discharging her home. What should your prescription be?

**Case 2**

Mr. T. is a 73-year-old man with lung cancer, a malignant pleural effusion, and chronic chest pain. He has undergone therapeutic thoracentesis and pleurodesis. He is currently receiving meperidine, 75 mg IM q 6 h, for pain. You want to change to oral
morphine. Without adjusting for cross-tolerance, what dose and schedule would you choose?

**Case 3**

Ms. M. is a 41-year-old teacher who has ovarian cancer with ascites and has been taking 2 tablets of acetaminophen/hydrocodone (500 mg/5 mg) every 4 hours and 1 tablet of acetaminophen/oxycodone (325 mg/5 mg) every 6 hours for pain relief. Morphine makes her nauseated. You are concerned about acetaminophen toxicity and want to change to an alternative oral approach. Without adjusting for partial cross-tolerance, what dose of hydromorphone would you choose?

**Case 4**

Mrs. A. is hospitalized and receiving adequate pain control with meperidine, 120 mg intramuscularly every 3 hours. She is now able to take nutrition and medications by mouth. Correcting 25% for incomplete cross-tolerance, what dose and schedule of oral hydromorphone would you prescribe to provide her with an approximately equal amount of analgesia?

1. 2 mg PO q 4 h
2. 4 mg PO q 4 h
3. 8 mg PO q 4 h
4. 12 mg PO q 4 h

**Case 5**

Mr. B. has been taking 3 capsules containing oxycodone (5 mg per capsule) and acetaminophen every 3 hours at home for relief of bone pain from metastatic lung cancer. He is now admitted to the hospital with a chemotherapy-induced aplasia. You do not want him taking an antipyretic (acetaminophen). Without correcting for partial cross-tolerance, how much oral morphine elixir would you prescribe to provide analgesia similar to that which he received from the oxycodone?

1. 5 mg PO q 4 h
2. 10 mg PO q 4 h
3. 20 mg PO q 4 h
4. 30 mg PO q 4 h

**Case 6**

John is a 40-year-old accountant with AIDS (acquired immunodeficiency syndrome). His most recent T4 count is 34. He has noted a burning pain in his hands and feet for the
past 2 years. It initially appeared after he began zalcitabine (ddC) in addition to zidovudine (AZT) and resolved when the ddC was discontinued. However, during the past 6 months the pain has returned. It is severe, keeps him awake at night, and is associated with numbness of his feet. He has trouble buttoning his shirt. How would you manage John's pain?

**Case 7**

Sarah is a 73-year-old attorney who has breast cancer with metastases to bone. She was treated with three cycles of AC (adriamycin, cyclophosphamide) without response. Pain persists, even after 2 months of tamoxifen. How would you manage Sarah's pain?

**Case 8**

David is a 67-year-old farmer with colon cancer metastatic to liver. He has complained of increasing right upper quadrant pain. Examination reveals a tender liver, but no shifting dullness to percussion of his abdomen. How would you manage David's pain?

**Case 9**

George is a 37-year-old otherwise healthy engineer with hepatoma who has excruciating hip and back pain due to bone metastases, treated with radiation. He was barely able to walk due to excruciating pain despite sustained-release oxycodone 80 mg every 8 hours, gabapentin 800 mg every 8 hours, and acetaminophen/oxycodone for breakthrough pain. He rated his pain as 10/10 at rest and 12/10 with motion, and had dose-limiting fatigue, drowsiness, dulled thinking, and constipation despite appropriate remedies of methylphenidate, opioid rotation, treatment of constipation, etc. How would you manage his pain?
Appendix 1

Morphine: Initial dosing for constant pain

A. For a patient with significant previous opioid exposure, calculate the starting dose for an immediate-release opioid using the equianalgesic table (to begin the new opioid you will cut back on this dose as appropriate) and dose q 4 h; or

B. For a patient who is relatively opioid naive and in significant pain, start dosing with 10 to 30 mg of immediate-release oral morphine liquid concentrate or tablet q 4 h; or

C. For a patient with stable pain that is not severe, start extended-release oral morphine at a dose of 15 or 30 mg twice daily or 30 to 60 mg once daily (depending on formulation).

Then, prescribe a breakthrough or rescue dose that is 5-15% of the total dose in use every 24 hours and offer it q 1 h PO PRN. Ask the patient and family to record in a diary all medication taken.

To convert to an extended-release preparation, calculate the total morphine dose required to achieve comfort during a 24-hour period. Either divide by 2 to get the q 12 h dose of extended-release morphine to prescribe routinely, or give the total dose once daily (depending on the product).

Always prescribe a breakthrough dose of immediate-release morphine using liquid concentrate or tablet. Offer 5-15% of the 24-hour dose q 1 h PO PRN.

Monitor closely and titrate as needed.

Morphine: Increasing the dose

1. If a patient requires more than 2 to 4 breakthrough doses in a 24-hour period on a routine basis, consider increasing the dose of the extended-release preparation.

2. Determine the total amount of morphine used (routine + breakthrough) and administer the total in divided doses q 12 h or q 24 h (depending on the product).

3. Recalculate the breakthrough dose so that it is always 5-15% of the total daily dose and offer it q 1 h PO.

In the patient with cancer, the most common reason for an increased dose is worsened pathology, not pharmacologic tolerance.

Answers to problems

For all of these cases, remember non-pharmacologic approaches as a possibility and remember to consider possible barriers to good use of pain interventions.
**Case 1**

Mrs. D. is a 45-year-old attorney who has breast cancer metastatic to bone. She is comfortable on a continuous infusion of morphine at 6 mg/h SC. Your goal is to change to oral medications before discharging her home. What should your prescription be?

**Answer**

1. Figure out total daily dose of IV morphine
   \[6 \text{ mg/h} \times 24 \text{ hours} = 144 \text{ mg/d IV morphine}\]

2. Set up a ratio using values from the table
   \[
   \frac{144 \text{ mg/d IV morphine}}{1 \text{ mg IV morphine}} = \frac{X \text{ mg/d oral morphine}}{3 \text{ mg oral morphine}}
   \]

3. Solve for X
   \[X = \frac{442 \text{ mg/d oral morphine}}{2}\]

4. Divide by 2 for bid formulation of extended-release morphine, or divide by 6 for immediate-release morphine administered every 4 hours.
   **Sig:** 200 mg extended-release morphine PO bid, or 70 mg immediate-release morphine PO q 4 h RTC

5. Also prescribe a breakthrough dose of 5% to 15% of total daily dose
   **Sig:** 20-60 mg immediate-release morphine PO q 1 h PRN

6. Do not forget a stimulant laxative

**Case 2**

Mr. T. is a 73-year-old man with lung cancer, a malignant pleural effusion, and chronic chest pain. He has undergone therapeutic thoracentesis and pleurodesis. He is currently receiving meperidine, 75 mg IM q 6 h, for pain. You want to change to oral morphine. Without adjusting for cross-tolerance, what dose and schedule would you choose?

**Answer**

1. Figure out total daily dose
   \[4 \times 75 \text{ mg IM meperidine} = 300 \text{ mg/d IM meperidine}\]

2. Set up ratio from the table
   \[
   \frac{300 \text{ mg/d IM meperidine}}{50 \text{ mg IM meperidine}} = \frac{X \text{ mg/d PO morphine}}{15 \text{ mg PO morphine}}
   \]
3. Solve for X
   \( X = 90 \text{ mg/d PO morphine} \)

4. Decide on schedule and formulation
   \textbf{Sig: sustained-release morphine, 45 mg PO bid}
   Also prescribe a breakthrough dose of 5\% to 15\% of total daily dose
   \textbf{Sig: 5-15 mg PO immediate-release morphine q 1 h PRN}

5. Remember the stimulant laxative!

\textbf{Case 3}

Ms. M. is a 41-year-old teacher who has ovarian cancer with ascites and has been taking 2 tablets of acetaminophen/hydrocodone (500 mg/5 mg) every 4 hours and 1 tablet of acetaminophen/oxycodone (325 mg/5 mg) every 6 hours for pain relief. Morphine makes her nauseated. You are concerned about acetaminophen toxicity and want to change to an alternative oral approach. Without adjusting for partial cross-tolerance, what dose of hydromorphone would you choose?

\textbf{Answer}

1. Figure out total daily dose of each opioid
   \begin{align*}
   &2 \text{ tablets} \times 5 \text{ mg hydrocodone/tablet} \times 6 = 60 \text{ mg/d hydrocodone} \\
   &1 \text{ tablet} \times 5 \text{ mg oxycodone/tablet} \times 4 = 20 \text{ mg/d oxycodone}
   \end{align*}

2. Set up ratios from the table
   \[
   \begin{array}{c c c}
   \text{60 mg/d oral} & \text{15 mg oral} \\
   \text{hydrocodone} & \text{hydrocodone} \\
   \hline
   X \text{ mg/d oral} & 4 \text{ mg oral} \\
   \text{hydromorphone} & \text{hydromorphone}
   \end{array}
   \]
   \[
   \begin{array}{c c c}
   \text{20 mg/d oral} & \text{10 mg oral} \\
   \text{oxycodone} & \text{oxycodone} \\
   \hline
   X \text{ mg/d oral} & 4 \text{ mg oral} \\
   \text{hydromorphone} & \text{hydromorphone}
   \end{array}
   \]

3. Solve for X in each case
   \begin{align*}
   &X = 16 \text{ mg/d PO hydromorphone} \\
   &X = 8 \text{ mg/d oral hydromorphone}
   \end{align*}

4. Add them together for a total of 24 mg/d oral hydromorphone

5. Decide on schedule
   \textbf{Sig: Hydromorphone, 4 mg PO q 4 h RTC}
6. Don't forget the breakthrough dose  
   **Sig:** Hydromorphone, 1-2 mg PO q 1 h PRN  

7. Do not forget a stimulant laxative!  

**Case 4**  
Mrs. A. is hospitalized and receiving adequate pain control with meperidine, 120 mg intramuscularly every 3 hours. She is now able to take nutrition and medications by mouth. Correcting 25% for incomplete cross-tolerance, what dose and schedule of oral hydromorphone would you prescribe to provide her with an approximately equal amount of analgesia?  

**Answer**  
1. 8 mg PO q 4 h  

**Calculating the answer**  
1. Figure out total daily dose of each opioid  
   \[120 \text{ mg} \times 8 = 960 \text{ mg/d IM meperidine}\]  
2. Set up ratios from the table  
   \[
   \begin{align*}
   960 \text{ mg/d IM meperidine} &= 50 \text{ mg IM meperidine} \\
   X \text{ mg/d oral hydromorphone} &= 3 \text{ mg oral hydromorphone}
   \end{align*}
   \]  
3. Solve for X  
   \[X = 57.6 \text{ mg/d PO hydromorphone}\]  
4. Decide on schedule (divide by 6 for q 4h dosing)  
   \[10 \text{ mg PO q 4 h}\]  
5. Adjust 25% for incomplete cross-tolerance  
   **Sig:** Hydromorphone, 8 mg PO q 4 h  

**Case 5**  
Mr. B. has been taking 3 capsules containing oxycodone (5 mg per capsule) and acetaminophen every 3 hours at home for relief of bone pain from metastatic lung cancer. He is now admitted to the hospital with a chemotherapy-induced aplasia. You do not want him taking an antipyretic (acetaminophen). Without correcting for partial cross-tolerance, how much oral morphine elixir would you prescribe to provide analgesia similar to that which he received from the oxycodone?
Answer

1. 30 mg PO q 4 h

Calculating the answer

1. Figure out total daily dose of each opioid
   3 tablets x 5 mg oxycodone/tablet x 8 = 120 mg/d oxycodone

2. Set up ratios from the table

   \[
   \frac{120 \text{ mg/d oral oxycodone}}{10 \text{ mg oral oxycodone}} = \frac{X \text{ mg/d oral morphine}}{15 \text{ mg oral morphine}}
   \]

3. Solve for X
   \[X = 180 \text{ mg/d oral morphine}\]

4. Decide on schedule
   Sig: Morphine, 30 mg PO q 4 h RTC

Case 6

John is a 40-year-old accountant with AIDS (acquired immunodeficiency syndrome). His most recent T4 count is 34. He has noted a burning pain in his hands and feet for the past 2 years. It initially appeared after he began zalcitabine (ddC) in addition to zidovudine (AZT) and resolved when the ddC was discontinued. However, over the past 6 months the pain has returned. It is severe, keeps him awake at night, and is associated with numbness of his feet. He has trouble buttoning his shirt. How would you manage John's pain?

Answer

Consider opioids, tricyclic antidepressants, gabapentin, and other adjuvants for neuropathic pain.

Case 7

Sarah is a 73-year-old attorney who has breast cancer with metastases to bone. She was treated with three cycles of AC (adriamycin, cyclophosphamide) without response. Pain persists, even after 2 months of tamoxifen. How would you manage Sarah's pain?
Answer

Consider NSAIDs, steroids, and bisphosphonates as well as radiation.

Case 8

David is a 67-year-old farmer with colon cancer metastatic to liver. He has complained of increasing right upper quadrant pain. Examination reveals a tender liver, but no shifting dullness to percussion of his abdomen. How would you manage David's pain?

Answer

Consider opioid analgesics and steroids to decrease capsular stretch.

Case 9

George is a 37-year-old otherwise healthy engineer with hepatoma who has excruciating hip and back pain due to bone metastases, treated with radiation. He was barely able to walk due to excruciating pain despite sustained-release oxycodone 80 mg every 8 hours, gabapentin 800 mg every 8 hours, and acetaminophen/oxycodone for breakthrough pain. He rated his pain as 10/10 at rest and 12/10 with motion, and had dose-limiting fatigue, drowsiness, dulled thinking, and constipation despite appropriate remedies of methylphenidate, opioid rotation, treatment of constipation, etc. How would you manage his pain?

Answer

Admit for a trial of epidural morphine. A catheter was placed at the L1-L2 interspace. Morphine 0.6 mg/hour was started. The dose of oxycodone was reduced by 50% to 40 mg every 8 hours, and Percocet was available for breakthrough pain. Within 2 hours of epidural placement, his pain VAS score was reduced from 10/10 at rest to 2/10, but movement increased the pain to 6/10. Morphine was increased to 1.0 mg/hour, which reduced the pain to 1/10. Bupivacaine at 0.1% concentration, 5 ml/hour, was added. With the combination, his pain score was reduced to 0-2/10 and he was able to bear weight on the right leg for the first time in months. He had no sensory or motor changes with either drug, and felt much less sedated. An implanted pump was placed to maintain the therapy. Oxycodone and gabapentin were tapered, then discontinued.
Appendix 2: Common Analgesics Medication Table

### Common Analgesics

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name(s)</th>
<th>Dosage Forms/ Time C&lt;sub&gt;max&lt;/sub&gt;</th>
<th>Elimination t&lt;sub&gt;1/2&lt;/sub&gt;</th>
<th>Route of Elimination</th>
<th>Adult Doses</th>
<th>Pediatric Doses</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acetaminophen</strong>&lt;br&gt;(paracetamol)</td>
<td>Various; Tylenol&lt;sup&gt;®&lt;/sup&gt; Plain and Extra Strength are examples</td>
<td>tabs: 325, 500 mg elixir: 80 mg/0.8 ml, 160 mg/5 ml supp: 120, 325, 650 mg, 81 mg chew</td>
<td>PO: 1-2 hr PR: 107-288 minutes</td>
<td>2-4 hr in normal individuals</td>
<td>Liver metabolism: 25% on first pass through the liver Renal excretion: 1%-4% unchanged</td>
<td>325-650 mg PO PR q 4 h routinely or PRN</td>
<td>650 mg PO PR q 4 h (4 g/24h )</td>
</tr>
<tr>
<td><strong>NSAIDs and ASA</strong>&lt;br&gt;(salicylic acid derivative)</td>
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<tr>
<td><strong>Acetylsalicylic acid (ASA)</strong>&lt;br&gt;(salicylic acid derivative)</td>
<td>Various; Aspirin&lt;sup&gt;®&lt;/sup&gt; is an example</td>
<td>caplets, tabs: 325, 500, 975 mg children's tab: 80 mg EC tabs: 81, 325, 500 mg elixir: 80 mg/5ml supp: 300, 600 mg</td>
<td>PO: buffered tablet: 20 minutes PO: effervescent solution: 15 minutes</td>
<td>4.7-9 hr (average 6 hr) Half-life is dose related</td>
<td>Liver metabolism Renal excretion: 5.6%-35.6%</td>
<td>325-650 mg PO, PR q 4 h routinely or PRN</td>
<td>650 mg PO PR q 4 h (5 g/24h )</td>
</tr>
<tr>
<td><strong>Celecoxib</strong>&lt;br&gt;(COX-2 selective)</td>
<td>Celebrex&lt;sup&gt;®&lt;/sup&gt;</td>
<td>cap:100, 200, 400 mg</td>
<td>PO: = 3 hr</td>
<td>11 hr</td>
<td>Liver metabolism: extensive Renal excretion: 27% Less than 3% of dose eliminated as unchanged drug Feces: 57%</td>
<td>100-200 mg PO bid</td>
<td>200 mg PO bid</td>
</tr>
<tr>
<td><strong>Choline magnesium trisalicylate</strong>&lt;br&gt;(salicylic acid derivative)</td>
<td>Trilisate&lt;sup&gt;®&lt;/sup&gt;</td>
<td>tab: 500, 750, 1000 mg salicylate elixir: 500 mg/5 ml</td>
<td>PO: tab: 1.5-2 hr Elixir: 3.5 hr</td>
<td>2-12 hr Dose-dependent; higher doses produce longer half-life</td>
<td>Hydrolysis in GI-salicylates Liver metabolism Renal excretion: 5.6%-35.6%</td>
<td>1-1.5 g PO q 12 h or 0.5-1.0 g PO q 8 h</td>
<td>1.5 g PO q 8 h (4.5 g/24h )</td>
</tr>
<tr>
<td>Generic Name</td>
<td>Trade Name(s)</td>
<td>Dosage Forms/ Time C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Elimination t&lt;sub&gt;1/2&lt;/sub&gt;</td>
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<tr>
<td>Diclofenac (acetic acid derivative)</td>
<td>Various; Cataflam®, Voltaren® are examples</td>
<td>IR tabs: 50 mg ER tabs: 25, 50, 75, 100 mg (with 200 mcg misoprostol: Arthrotec® 50, 75 mg)</td>
<td>IR: (diclofenac potassium): 1 hr (range 0.33-2 hr) ER: (diclofenac sodium): 2 hr (range 1-4 hr) PR: 30 minutes</td>
<td>2 hr</td>
<td>Liver metabolism: extensive first pass Renal excretion: 65% Bile: 35%</td>
<td>IR: 50-75 mg PO PR q 6-8 h or ER 75-100 mg PO q 8-12 h</td>
<td>50 mg IR PO q 6 h or 75 mg ER PO q 8 h (225 mg/24h )</td>
</tr>
<tr>
<td>Diflunisal (salicylic acid derivative)</td>
<td>Various; Dolobid® is an example</td>
<td>tabs: 500 mg</td>
<td>PO: 2-3 hr</td>
<td>8-12 hr Half-life dependent on dose</td>
<td>Liver metabolism: extensive Renal excretion: 80%-90% Feces: less than 5%</td>
<td>250-500 mg PO q 8-12 h</td>
<td>500 mg PO q 8 h (1.5 g/24h )</td>
</tr>
<tr>
<td>Etodolac (acetic acid derivative)</td>
<td>Various; Lodine® is an example</td>
<td>IR tabs: 200, 300, 400, 500 mg ER tabs: 400, 500, 600 mg</td>
<td>PO IR: 1-2 hr PO ER: 3-12 hr</td>
<td>6-7 hr</td>
<td>Liver metabolism: extensive Renal excretion: 72% Feces: 16%</td>
<td>200-500 mg PO q 6-12 h</td>
<td>400 mg PO q 8 h ER: 1,200 mg daily</td>
</tr>
<tr>
<td>Flurbiprofen (propionic acid derivative)</td>
<td>Various; Ansaid® is an example</td>
<td>tabs: 50, 100 mg</td>
<td>PO: 1.5-2 hr</td>
<td>5.7 hr</td>
<td>Liver metabolism: extensive Renal excretion: 95%</td>
<td>50-100 mg PO q 12 h</td>
<td>200-300 mg/24h</td>
</tr>
<tr>
<td>Ibuprofen (propionic acid derivative)</td>
<td>Various; Motrin® is an example</td>
<td>tabs: 200, 400, 600, 800 mg elixir: 40 mg/1 ml, 100 mg/5 ml</td>
<td>PO: 1.4-1.9 hr</td>
<td>1.8-2 hr</td>
<td>Liver metabolism: extensive Renal excretion: Major route</td>
<td>200-800 mg PO q 6-8 h</td>
<td>800 mg PO q 6 h (3.2 g/24h )</td>
</tr>
<tr>
<td>Indomethacin (indole)</td>
<td>Various; Indocin® is an example</td>
<td>IR tabs: 25, 50 mg ER tabs: 75 mg supp: 25 mg/5 ml</td>
<td>PO: 2 hr</td>
<td>4.5 hr</td>
<td>Liver metabolism: extensive Renal excretion: 60% = 26% eliminated as unchanged drug Feces: 33%</td>
<td>25-75 mg PO q 8-12 h or 75 mg ER PO q 12-24 h</td>
<td>50 mg PO q 6 h (200 mg/24h )</td>
</tr>
<tr>
<td>Ketoprofen (propionic acid derivative)</td>
<td>Various; Orudis® is an example</td>
<td>cap: 12.5, 50, 75 mg ER tabs: 100, 200 mg</td>
<td>PO IR: 1.2-2 hr PO ER: 6.8-9.2 hr</td>
<td>2-4 hr ER is 5.4 +/- 2.2 hr</td>
<td>Liver metabolism Renal excretion: 80%; Bile: up to 40%</td>
<td>150-200 mg PO/24h IR: q 6-8 h ER: q 12-24 h</td>
<td>75 mg PO q 6 h (300 mg/24h )</td>
</tr>
<tr>
<td>Generic Name</td>
<td>Trade Name(s)</td>
<td>Dosage Forms/ Time $C_{\text{max}}$</td>
<td>Elimination $t_{1/2}$</td>
<td>Route of Elimination</td>
<td>Adult Doses</td>
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<tr>
<td>Ketorolac (acetic acid derivative)</td>
<td>Various; Toradol® is an example</td>
<td>tab: 10 mg inj: 15, 30 mg/ml</td>
<td>PO: 44 minutes IM: 30-45 minutes IV: 1-3 minutes</td>
<td>PO: 44 minutes IM: 30-45 minutes IV: 1-3 minutes</td>
<td>5.6 hr</td>
<td>Liver metabolism Renal excretion: 92% excreted in the urine; 60.6% as unchanged drug Feces: 5.9%–6.3%</td>
<td>10 mg PO qid or 60 mg IM, IV loading dose, then 10-30 mg IM, IV q 6 h 40 mg PO/24h or 120 mg IM, IV /24h</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>Various; Relafen® is an example</td>
<td>tab: 500, 750 mg</td>
<td>PO: 3-6 hr Nabumetone (prodrug): unknown Active metabolite (6-methoxy-2-naphthylacetic acid): 24 hr</td>
<td>PO: 3-6 hr Nabumetone (prodrug): unknown Active metabolite (6-methoxy-2-naphthylacetic acid): 24 hr</td>
<td>12-15 hr</td>
<td>Liver metabolism: extensive Renal excretion: 80% Feces: 10%</td>
<td>1-2 g PO q 12-24 h 1 g PO q 12 h (2 g/24h )</td>
</tr>
<tr>
<td>Naproxen (propionic acid derivative)</td>
<td>Various; Naprosyn® is an example</td>
<td>IR tabs: 220, 275, 250, 375, 500, 550 mg ER tab: 375, 500 mg</td>
<td>PO IR: naproxen: 2-4 hr, naproxen sodium: 1-2 hr PO ER: 3 hr Topical, gel: 24 hr</td>
<td>PO IR: naproxen: 2-4 hr, naproxen sodium: 1-2 hr PO ER: 3 hr Topical, gel: 24 hr</td>
<td>12-15 hr</td>
<td>Liver metabolism: extensive Renal excretion: 95%</td>
<td>250-500 mg PO q 8-12 h 500 mg PO q 8 h (1.5 g/24h )</td>
</tr>
<tr>
<td>Piroxicam (oxicam)</td>
<td>Various; Feldene® is an example</td>
<td>caps: 10, 20 mg</td>
<td>PO: 3-5 hr 50 hr; range:30-86 hr</td>
<td>PO: 3-5 hr 50 hr; range:30-86 hr</td>
<td>50 hr; range:30-86 hr</td>
<td>Liver metabolism: extensive Renal excretion: moderate; 5%-10% of dose eliminated as unchanged drug Feces: small</td>
<td>10-20 mg PO q 12-24 h 20 mg PO q 12 h (40 mg/24h )</td>
</tr>
<tr>
<td>Salsalate (salicylic acid derivative)</td>
<td>Various; Disalcid® is an example</td>
<td>tabs: 500, 750 mg</td>
<td>PO: 1.4 hr</td>
<td>PO: 1.4 hr</td>
<td>1 hr</td>
<td>Liver metabolism: &lt;1% appears as unchanged salsalate; remainder excreted as salicylic acid or metabolites of salicylic acid.</td>
<td>1,000-1,500 mg PO bid 3,000 mg/day</td>
</tr>
<tr>
<td>Generic Name</td>
<td>Trade Name(s)</td>
<td>Dosage Forms/ Time C\textsubscript{max}</td>
<td>Elimination t\textsubscript{1/2}</td>
<td>Route of Elimination</td>
<td>Adult Doses</td>
<td>Pediatric Doses</td>
<td>Adverse Effects</td>
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<tr>
<td>Sulindac (indole)</td>
<td>Various; Clinoril\textsuperscript{®} is an example</td>
<td>tabs: 150, 200 mg</td>
<td>PO: 1 hr</td>
<td>Sulindac: 7.8 hr</td>
<td>Liver metabolism: extensive Sulindac has no pharmacologic activity and must be metabolized by the pharmacologically active metabolite</td>
<td>150 mg PO q 12 h</td>
<td>150 mg PO q 12 h (400 mg/24 h)</td>
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<td>Opioids</td>
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<tr>
<td>Codeine (alone) (methylmorphine, naturally occurring opioid metabolized into morphine)</td>
<td>Various</td>
<td>IR tabs: 15, 30, 60 mg elixir: 15 mg/5 ml inj: 15, 30 mg/ml</td>
<td>PO: 1-2 hr IM: 30 minutes PR: 30 minutes</td>
<td>2.5-3.5 hr</td>
<td>Liver metabolism: 24-89% metabolized to morphine Renal excretion: 90% (3-16% as unchanged drug) Feces: about 5%</td>
<td>15-60 mg PO, SC, IM q 4 h routinely or q 1 h PRN</td>
<td>600 mg/24h</td>
</tr>
<tr>
<td>Codeine + acetaminophen combinations</td>
<td>Various; Tylenol # 3, #4\textsuperscript{®} are examples</td>
<td>tabs: 30, 60 mg codeine + 325 mg acetaminophen (may include caffeine, butalbital) Codeine: PO: 1-2 hr Codeine PR: 30 min APAP: PO: 1-2 hr APAP: PR: 107-288 min</td>
<td>Acetaminophen: 4 hr Codeine: 2.5-3.5 hr</td>
<td>1-2 tabs PO q 4 h routinely or PRN</td>
<td>limited to 12 tabs/24h by acetaminophen</td>
<td></td>
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<tr>
<td>Fentanyl</td>
<td>Various; Duragesic\textsuperscript{®}, Actiq\textsuperscript{®}, Sublimaze\textsuperscript{®} are examples</td>
<td>patch: 25, 50, 75, 100 mcg/hr lozenge: 200, 400, 600, 800, 1200, 1600 mcg inj: 50 mcg/ml</td>
<td>Epidural: 30 minutes Transmucosal: 20-40 minutes Transdermal patch: 24-72 hr</td>
<td>4 hr Transdermal patch: 17 hr</td>
<td>Liver metabolism: to inactive metabolites Renal excretion: 75% (metabolites); 10% (unchanged drug) Feces: 9%</td>
<td>patch: 25–40 mcg/h q 7 h lozenge: 200 μg q 1 h titrate PRN</td>
<td>limited only by need and adverse effects</td>
</tr>
<tr>
<td>Hydrocodone + acetaminophen</td>
<td>Various; Vicodin\textsuperscript{®}, Lortab\textsuperscript{®}, Norco\textsuperscript{®} are examples</td>
<td>tabs: 5/500, 5/325, 7.5/325, 7.5/500, 7.5/750, 10/325, 10/500, 10/660 elixir: 7.5/500 in 15 ml</td>
<td>PO: 1.3 hr for hydrocodone</td>
<td>Hydrocodone: 3.8-4.5 hr Acetaminophen: see above</td>
<td>Liver metabolism: Acetaminophen: see above Hydrocodone: extensive active metabolites Renal excretion: 26%</td>
<td>1-2 tabs PO q 4-6 h routinely or PRN</td>
<td>limited to 4 g acetaminophen in 24 h</td>
</tr>
<tr>
<td>Generic Name</td>
<td>Trade Name(s)</td>
<td>Dosage Forms/ Time C&lt;sub&gt;max&lt;/sub&gt;</td>
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<tr>
<td>Hydrocodone + ibuprofen</td>
<td>Vicoprofen®</td>
<td>tab: 7.5/200 tab up to 2 hr (both components)</td>
<td>PO: within 2 hr</td>
<td>Hydrocodone 3.8-4.5 hr Ibuprofen 1.8-2 hr</td>
<td>Liver metabolism: see above Renal excretion: see above</td>
<td>1-2 tabs PO q 4-6 h routinely or PRN</td>
<td>Limited to 2,400 mg ibuprofen in 24 h</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Various, Dilaudid®, Palladone® are examples</td>
<td>IR tabs: 2, 4, 8 mg ER capsules: 12, 16, 24, 32 mg Elixir: 1 mg/ml inj: 1, 2, 4, 10 mg/ml powder: 250 mg/vial supp: 3 mg</td>
<td>PO IR: 48-60 minutes PO ER: 12-16.5 hr Epidural: 8 minutes</td>
<td>IR: = 3-4 hr</td>
<td>Liver metabolism: extensive Renal excretion: As hydromorphone 1.3%-13.2% Conjugates: 22%-51%</td>
<td>1–2 mg: PO q 4 h routinely or q 1 h PRN, SC, IM q 3 h routinely or q 30 min PRN, SC, IV q 1 h via infusion + breakthrough q 30 min PRN</td>
<td>limited only by need and adverse effects</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>Levo-Dromoran®</td>
<td>tab: 2 mg</td>
<td>PO: 1 hr</td>
<td>11 hr; With chronic PO dosing, half-life can be as long as 30 hr</td>
<td>Liver metabolism: extensive Renal excretion: extensive as conjugate</td>
<td>2–8 mg PO q 6-8 h</td>
<td>limited only by need and adverse effects</td>
</tr>
<tr>
<td>Meperidine (pethidine)</td>
<td>Various; Demerol® is an example</td>
<td>tabs: 50, 100 mg inj: 50, 75, 100 mg/ml syrup: 10mg/1ml, 25 mg/1ml, 50 mg/5 ml</td>
<td>PO: = 1 hr</td>
<td>Meperidine 3.2-3.7 hr Active metabolite: 24-48 hr</td>
<td>Liver metabolism: 50% first pass through liver Renal excretion: 0.5%-5.2% (average 2.2%) unchanged Active metabolite, normeperidine, excreted 0.6%-21% (average 6.2%) unchanged in the urine</td>
<td>50-150 mg PO IM, SC, IV q 4 h PRN NOT RECOMMENDED FOR CHRONIC DOSING as active metabolite, normeperidine, may produce adverse effects</td>
<td>150 mg q 3-4 h, 900-1,200 mg/24h</td>
</tr>
<tr>
<td>Methadone</td>
<td>Various; Dolophine® is an example</td>
<td>tab: 5, 10, 40 mg elixir: 1, 2, 10 mg/ml</td>
<td>PO: 2-4 hr</td>
<td>Methadone: 23 hr Metabolite: 39.8-48 hr After a single PO dose, half-life is biphasic with initial phase range of 12-24 hr and secondary phase of up to 55 hr</td>
<td>Liver metabolism: 4 times greater after PO administration than after IM administration</td>
<td>5 mg PO q 8 h Titrate dose q 3-5 days due to delayed clearance</td>
<td>limited only by need and adverse effects</td>
</tr>
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<tr>
<td>Morphine, IR</td>
<td>Various</td>
<td>IR tabs: 10, 15, 30 mg&lt;br&gt;elixir: 1, 2, 20 mg/ml&lt;br&gt;sups: 5, 10, 20, 30 mg&lt;br&gt;inj: 1, 2, 8, 10, 15, 25, 50 mg/ml</td>
<td>Buccal: 5 hr (range 1.5-12 hr)&lt;br&gt;Colostomy, suppository: 0.5-1 hr&lt;br&gt;Epidural/Intrathecal: 5-10 minutes&lt;br&gt;IV/IM: 10-60 minutes&lt;br&gt;Inhalation (nebulized): 10-45 minutes&lt;br&gt;PO IR: 1 hr&lt;br&gt;PO ER: 8.4 hr&lt;br&gt;PO ER: capsules (Avinza): 30 minutes&lt;br&gt;PR: using PO ER: 5.4-6.7 hr&lt;br&gt;PR: supp IR: 0.75-1 hr&lt;br&gt;SC: 30 minutes</td>
<td>4 hr</td>
<td>Liver metabolism: ≈ 90% of given dose is conjugated-morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G-active)&lt;br&gt;Renal excretion: 90% (metabolites and free drug) within 24 hr&lt;br&gt;Pharmacokinetics of morphine are altered in renal failure; clearance is decreased; M3G and M6G accumulate several fold with associated risk of toxicity&lt;br&gt;Feces: 7-10%</td>
<td>1-8 mg: PO PR q 4 h&lt;br&gt;Routinely or q 1 h PRN&lt;br&gt;SC, IM q 3h routinely or q 30 min PRN, or&lt;br&gt;SC, IV q 1 h via infusion + breakthrough q 30 min PRN</td>
<td>limited only by need and adverse effects</td>
</tr>
<tr>
<td>Morphine, ER</td>
<td>capsule: Kadian\®&lt;br&gt;tabs: Ora-Morph-ER\®, MS-Contin\®, Avinza\®&lt;br&gt;Kadian\® capsules: 20, 50, 100 mg (q 12-24 h)&lt;br&gt;MS-Contin\® tabs: 15, 30, 60, 100, 200 mg (q 8-12 h)&lt;br&gt;Ora-Morph-ER\® tabs: 15, 30, 60, 100 mg (q 8-12 h)&lt;br&gt;(Kadian\® capsules may be opened and pellets mixed with fluids or soft food)</td>
<td>Kadian\® capsules: 20, 50, 100 mg (q 12-24 h)&lt;br&gt;MS-Contin\® tabs: 15, 30, 60, 100, 200 mg (q 8-12 h)&lt;br&gt;Ora-Morph-ER\® tabs: 15, 30, 60, 100 mg (q 8-12 h)&lt;br&gt;(Kadian\® capsules may be opened and pellets mixed with fluids or soft food)</td>
<td>PO IR: 1.6 hr&lt;br&gt;PO ER: 2.1-3.2 hr&lt;br&gt;PO IR: 4 hr&lt;br&gt;PO ER: 4.5-8 hr</td>
<td>Liver metabolism: extensive&lt;br&gt;Renal excretion: extensive, with approximately 20% unchanged</td>
<td>5–10 mg IR PO PR q 4 h routinely, or q 1 h PRN or&lt;br&gt;10–14 mg ER PO q 12 h</td>
<td>limited only by need and adverse effects</td>
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<tr>
<td>Oxycodone (alone)</td>
<td>IR: various&lt;br&gt;ER: OxyContin\®&lt;br&gt;IR tabs: 5, 10, 15, 30 mg&lt;br&gt;ER tabs: 10, 20, 40, 80 mg&lt;br&gt;elixir: 1, 20 mg/ml</td>
<td>IR tabs: 5, 10, 15, 30 mg&lt;br&gt;ER tabs: 10, 20, 40, 80 mg&lt;br&gt;elixir: 1, 20 mg/ml</td>
<td>PO IR: 1.6 hr&lt;br&gt;PO ER: 2.1-3.2 hr&lt;br&gt;PO IR: 4 hr&lt;br&gt;PO ER: 4.5-8 hr</td>
<td>Liver metabolism: extensive&lt;br&gt;Renal excretion: extensive, with approximately 20% unchanged</td>
<td>5–10 mg IR PO PR q 4 h routinely, or q 1 h PRN or&lt;br&gt;10–14 mg ER PO q 12 h</td>
<td>limited only by need and adverse effects</td>
<td></td>
</tr>
<tr>
<td>Oxycodone + Acetaminophen combinations</td>
<td>Various; Percocet\® is an example</td>
<td>5 mg oxycodone + 325 mg acetaminophen 5/500, 7.5/325, 7.5/500, 10/325, 10/650 (may include caffeine)</td>
<td>4 hr for oxycodone 2-4 hr for acetaminophen</td>
<td>1-2 tabs PO q 4 h&lt;br&gt;limited to 12 tabs/24h by acetaminophen</td>
<td>limited only by need and adverse effects</td>
<td>limited only by need and adverse effects</td>
<td></td>
</tr>
<tr>
<td>Generic Name</td>
<td>Trade Name(s)</td>
<td>Dosage Forms/ Time C&lt;sub&gt;max&lt;/sub&gt;</td>
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<tr>
<td>Oxycodone + Aspirin combinations</td>
<td>Various; Percodan&lt;sup&gt;®&lt;/sup&gt; is an example</td>
<td>5 mg oxycodone + 325 mg ASA (may include caffeine)</td>
<td>See above</td>
<td>Oxycodone: 4 hr ASA: 4.7-9</td>
<td>Renal excretion: approximately 20% unchanged See above</td>
<td>1-2 tabs PO q 4 h routinely or PRN</td>
<td>limited to 12 tabs/24h by ASA</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Ultram&lt;sup&gt;®&lt;/sup&gt;</td>
<td>tab: 50 mg</td>
<td>PO: 2 hr</td>
<td>Tramadol: 6.3 hr Metabolite: 7.4 hr</td>
<td>Liver metabolism: extensive Renal excretion: 30% excreted in urine as unchanged drug, 60% of dose excreted as metabolites</td>
<td>1-2 tabs PO q 6 h</td>
<td>2 tabs PO q 6 h</td>
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</tbody>
</table>

Extracted and updated from:


# Appendix 3: Pain Medication Table

## Pain Medication Table

<table>
<thead>
<tr>
<th>Pain (analgesics)</th>
<th>Generic Name</th>
<th>Trade Name(s)</th>
<th>Dosage Forms/Time C&lt;sub&gt;max&lt;/sub&gt;</th>
<th>Elimination t&lt;sub&gt;1/2&lt;/sub&gt;</th>
<th>Route of Elimination</th>
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<th>Adverse Effects</th>
<th>Common Interactions</th>
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<tbody>
<tr>
<td>Capsaicin</td>
<td>Various; Zostrix&lt;sup&gt;®&lt;/sup&gt; is an example: cream: 0.025, 0.075%</td>
<td>Initial response: topical: 14-28 days</td>
<td>NA</td>
<td>NA</td>
<td>apply lightly to affected areas at least 3-4 times/24h (wash hands immediately) (optimal response within 14-28 days of continued application)</td>
<td>2 y or older: same as adults</td>
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<td></td>
<td>transient burning on application avoid contact with eyes do not apply to wounds or damaged skin do not bandage</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Various; Tegretol&lt;sup&gt;®&lt;/sup&gt; is an example: tab: 100, 200 mg ER: 100, 200, 400 mg suspension: 100 mg/5mL</td>
<td>PO IR: 4-5 hr PO chew tablets: 6 hr PO ER: 3-12 hr PO suspension: 1.5 hr</td>
<td></td>
<td>12-17 hr</td>
<td>Liver metabolism: 98% Renal excretion: 72% seizures: 100 mg PO bid-400 mg PO tid hiccups: 100-200 mg PO bid-lid (start low; increase q 3-4 days, monitor blood levels)</td>
<td>initial dose 10 mg/kg/24h + bid-tid increase dose if necessary, up to 30 mg/kg/24h</td>
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<td></td>
<td>aplastic anemia cardiovascular effects ataxia blurred vision confusion drowsiness vertigo headache hepatic effects nausea/vomiting hypersensitivity</td>
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</table>
| Flecainide   | Tambocor ®  | PO: 1.5-6 hr PO cap: 1-8 hr     | 7-22 hr                     | Liver metabolism: extensive | start with 50 mg PO q 12 h; increase 50 mg q 12 h every 4 or more days; max 300 mg/24h (adjust for hepatic or renal impairment) | ☺ | • may cause ventricular or other arrhythmias  
• CHF  
• dizziness  
• visual disturbances (blurred vision, diplopia, photophobia)  
• headache  
• nausea  
• dyspnea | • other antiarrhythmics  
• cimetidine  
• digoxin  
• propranolol  
• phenytoin  
• phenobarbital  
• rifampin  
• carbamazepine |
| Gabapentin   | Neurontin®  | PO: 1.5-4 hr                     | 5-7 hr                       | Not metabolized Renal excretion: 76%-81% unchanged in the urine Feces: 10%-23% | 100-300 mg PO tid and titrate (3,600 mg/24h has been reported) | ☺ | • somnolence  
• dizziness  
• fatigue | • alter for renal function  
• cimetidine  
• PO contraceptives  
• antacids |
## Pain (analgesics)

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<tr>
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<tbody>
<tr>
<td><strong>Lidocaine</strong>&lt;br&gt; Anesthetic: relieves pain due to mucositis, oro–pharyngeal, perianal, and skin lesions/ulcers; endotracheal spray can be used during painful dressing changes</td>
<td>Various; Xylocaine&lt;sup&gt;®&lt;/sup&gt; is an example: topical liquid: 4% viscous: 2% oral &amp; endotracheal spray: 10% jelly: 2% ointment: 5% Inj: 5, 10, 20 mg/ ml IV infusion: 8mg/ml in D5W</td>
<td>IM: 30 min-2 hr Initial response: topical (2% jelly): 3-5 min</td>
<td>1.5-2 hr Metabolites: 1-6 hr</td>
<td>Liver metabolism: 90% Renal excretion: =90%</td>
<td>viscous: 15 ml PO q 3h PRN, gargle, spit, or swallow (mix 50/50 with antacid to make more palatable) liquid/spray: apply to affected areas PRN jelly: apply to urethra before catheterization Max 200 mg/24h</td>
<td>5-15 ml swish and spit q 4 h PRN max 3mg/kg/24h</td>
<td>• no fluids or food within 60 min of PO: ingestion (interferes with second stage of swallowing) • systemic administration may cause CNS excitation or depression, ventricular or other arrhythmias • hypersensitivity</td>
<td>• bupivacaine • phenytoin • other antiarrhythmics, amiodarone • ß-blockers • cimetidine • MAOIs • phenytoin • TMP-SMX</td>
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</tbody>
</table>

<p>| <strong>Lidocaine + Prilocaine</strong>&lt;br&gt; Anesthetic combination to relieve pain associated with local procedures | EMLA&lt;sup&gt;®&lt;/sup&gt;: cream: 25 mg lidocaine and 25 mg prilocaine/g patch: 1 g cream | topical, cream: 2-4 hr topical periodontal gel: 30 minutes | lidocaine 1-2 hr prilocaine 10-150 min | Liver metabolism: lidocaine (extensive), prilocaine (extent unknown) Renal excretion: lidocaine 90% | apply patch, or a thick layer of cream; cover with an occlusive dressing for at least 1 h prior to a painful procedure (may remain up to 5 hr) | apply as for adults (not recommended for infants &lt;6 months, or children 6-12 months receiving Rx for methemoglobin) | • mild local reactions (i.e., edema, itching, transient paleness, erythema, initial burning) | • none significant |</p>
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<tbody>
<tr>
<td>Mexiletine</td>
<td>Mexitil&lt;sup&gt;®&lt;/sup&gt;: caps: 150, 200 mg</td>
<td>PO: 1-4 hr IM: 15 min-2 hr</td>
<td>6-17 hr</td>
<td>Liver metabolism: extensive Renal excretion: ≈8%-15%</td>
<td>start with 100 mg PO q 8 h; increase 100 mg q 8 h every 3 or more days max 1,200 mg/24h (adjust for hepatic impairment)</td>
<td></td>
<td></td>
<td>• may cause ventricular or other arrhythmias • upper GI distress • lightheadedness • tremor</td>
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<td>Generic Name</td>
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<td>Dosage Forms/ Time C&lt;sub&gt;max&lt;/sub&gt;</td>
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<td>Adult Doses</td>
<td>Pediatric Doses</td>
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<td>Valproic acid Antiepileptic for neuropathic pain</td>
<td>Depakene&lt;sup&gt;®&lt;/sup&gt;, Depakote&lt;sup&gt;®&lt;/sup&gt;: capsules: 250 mg</td>
<td>PO: valproic acid capsules Depakene&lt;sup&gt;®&lt;/sup&gt;: 1-4 hr PO: divaprox tablet: 4-8 hr PO: divaprox sprinkle capsule: 3.3-4.8 hr PO: divaprox sodium extended-release tablet: 4-17 hr PO: sodium valproate solution: 1.2 hr Intravenous, Depacon&lt;sup&gt;®&lt;/sup&gt;: at the end of 1 hr infusion PR: diluted Valproic acid syrup: 3.1 hr</td>
<td>6-17 hr</td>
<td>Liver metabolism: extensive Renal excretion: 70%-80% Bile: 7% Lung: 2-18%</td>
<td>seizures: start at 15 mg/kg/24h, increase wkly by 5-10 mg/kg/24h up to max 60 mg/kg/24h (above 250 mg, divide into 3 doses/24h) hiccups, neuropathic pain: 250 mg PO bid-qid</td>
<td>same as adult dosing</td>
<td>• ataxia, tremor, sedation • inhibition of platelet aggregation • nausea/vomiting • thrombocytopenia • hypersensitivity</td>
<td>• alcohol • antacids • ASA • barbiturates • clonazepam • phenytoin</td>
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References

Module 2: Cancer Pain Management


In this study, 50% of 988 terminally ill patients reported having pain. Of those patients experiencing moderate or severe pain, 29% wanted more therapy, 61% wanted therapy to remain the same, while 9% wanted less therapy or to stop their pain treatment altogether. Of these, 34% feared addiction, 31% were averse to physical side effects (e.g., constipation), 33% were averse to mental side effects (e.g., confusion) and 30% were averse to additional pills or injections. Although the majority of patients had cancer, there was no association between disease and level of pain. The authors conclude that the majority of patients experiencing pain are willing to tolerate their pain; they trade off experiencing pain for other benefits. The experience of pain is constant across diseases.


This article describes a systematic assessment of prevalence and characteristics of symptoms in 243 patients at Memorial Sloan-Kettering. Mean age was 55.5 (range 23-86); 123 were inpatients; 40-80% experienced lack of energy, pain, drowsiness, dry mouth, insomnia, or symptoms of psychological distress. The mean number of symptoms per patient was 11.5 ± 6.0; inpatients had more symptoms than outpatients (13.5 vs 9.7); and those with Karnofsky performance score <80 had more symptoms than those with a higher score (14.8 vs 9.2).

The fact that injury to nervous tissues gives rise to clinical pain syndromes is discussed.


Pain is normally secondary to activation of unencapsulated nerve endings that fire in response to stimuli that threaten or actually produce tissue damage.

Saunders, C. Care of patients suffering from terminal illness at St. Joseph's Hospice. Nurs Mirror. February 14;1964:7-10.


The article provides a review of recent pathophysiological data with the goal of illustrating present and future pharmacologic strategies to prevent and manage pain.


This brief outline is intended to make the principles of pain control readily available to all clinicians who care for terminally ill patients. It applies to patients with nonmalignant disease as well as to those with advanced cancer.

An expert working group of the European Association for Palliative Care has revised and updated its guidelines on the use of morphine and the alternative strong opioid analgesics that have been introduced in many parts of the world in recent years. The strength of the evidence on which each recommendation is based is indicated.


Recent studies have demonstrated that many toxic drug reactions result from a common initiating event: the metabolic activation of chemically stable drugs to potent alkylating, arylating, or acylating agents in the body. This review focuses on toxic drug reactions caused by metabolic activation presenting as cell necrosis, neoplasia, and drug allergy.


Fine sensory nerve fibers have been detected that are not excited by physiologic stimuli, even at potentially tissue-damaging intensities. Under inflammatory conditions some silent afferents are sensitized to physiologic stimuli. The activation of silent afferents may lead to sensitization of nociceptive dorsal horn neurons.


Repetitive C afferent input evokes a facilitated state of processing that results in increased receptive fields and exaggerated responses to afferent input ("wind-up"). These phenomena underlie the behavioral phenomena of secondary hyperalgesia. The initiation of this facilitated component is not well blocked by even higher concentrations of volatile anesthetics, but can be prevented by pretreatment with agents known to block afferent input (local anesthetics) or C-fiber transmitter release (opiates) or to act at one of several links to block a complex spinal cascade involving the N-methyl-D-aspartate receptor, nitric oxide synthase, and cyclooxygenase.

Meta-analysis has demonstrated that NSAIDs are associated with serious upper gastrointestinal disorders, with a relative risk of 2.7 in patients receiving NSAIDs compared with subjects not receiving NSAIDs. An increase in the dose and duration of NSAIDs and age >60 are associated with an increase in the risk of upper gastrointestinal toxicity. Case-control studies have demonstrated an association between some NSAIDs and neutropenia, with a relative risk of between 3 and 9. NSAIDs have also been linked with hypersensitivity reactions, although the incidence of such reactions is very low. There are inconsistent data on the potential associations between NSAIDs and renal disease, and there are no epidemiological studies linking NSAIDs with acute liver disease.


Gastrointestinal side effects of NSAIDs range from dyspepsia and gastroduodenal ulcers to serious, potentially fatal GI complications including bleeding and perforation. Risk assessment and cotherapy with acid suppressors (H2-receptor antagonists and proton pump inhibitors) or prostaglandin replacement (misoprostol) and H pylori eradication are beneficial. Cyclooxygenase-1 (COX-1) is a key enzyme in gastroprotective mucosal defenses, and the best way to prevent GI toxicity is to avoid drugs that inhibit COX-1. Clinical studies of the COX-2-selective inhibitors rofecoxib and celecoxib have demonstrated efficacy equivalent to nonselective NSAIDs with lower rates of GI side effects (for example, incidence of endoscopic ulcers equivalent to placebo).


The primary adjuvant analgesics are anticonvulsant and antidepressant medications, but a wide variety of other drugs are also used. To optimize analgesic therapy in patients with neuropathic pain, both opioid and adjuvant analgesics must be used effectively.


The antinociceptive activity of tramadol in the mouse tail-flick test was completely antagonized by naloxone, suggesting an opioid mechanism of action. In contrast to the mouse tail-flick test and unlike morphine or codeine, tramadol-induced antinociception in the mouse abdominal constriction, mouse hot-plate (48 degrees or 55 degrees C) or rat hot-plate tests was only partially antagonized by naloxone, implicating a nonopioid component. Tramadol inhibited the uptake of norepinephrine (Ki = 0.79 microM) and serotonin (0.99 microM). These results suggest that tramadol-induced antinociception is mediated by opioid (mu) and nonopioid (inhibition of monoamine uptake) mechanisms.


This multicenter, outpatient, randomized, double-blind, placebo-controlled, parallel-group study enrolled a total of 131 patients with painful diabetic neuropathy and treated them with tramadol (n=65) or placebo (n=66). Tramadol, at an average dosage of 210 mg/day, was significantly (p<0.001) more effective than placebo for treating the pain of diabetic neuropathy.

In patients with moderate to severe postoperative pain, intravenous or intramuscular tramadol has generally proved to be of equivalent potency to pethidine (meperidine) and one-fifth as potent as nalbuphine. Intravenous tramadol 50 to 150 mg was equivalent in analgesic efficacy to morphine 5 to 15 mg in patients with moderate pain following surgery. Orally administered tramadol was found to be an effective analgesic in step 2 of the World Health Organization’s analgesic ladder. Dizziness, nausea, sedation, dry mouth, and sweating were the principal adverse effects. Respiratory depression was observed in only a few patients after tramadol infusion.


Renal impairment has a serious impact on the clearance of most opioids used in the clinical setting. Biochemical and clinical monitoring will prevent complications.


A systematic review of 69 studies with information on 2,146 subjects (454 patients and 1,692 healthy volunteers) found minimal difference between single and multiple doses, suggesting no accumulation of morphine. For controlled-release formulations, little difference was observed between brands except for once-daily formulations where the Tmax for fed subjects was considerably longer than for those who fasted.


Six healthy volunteers each received 5 mg morphine sulphate by i.v., s.c.b., and short s.c.i. over 4 h, on three separate occasions, in random order, each separated by at least 1 week. Bioequivalence was demonstrated.

The biologic disposition of methadone during acute and chronic administration was studied in 12 human volunteers. The acute primary half-life (t1/2) of 14.3 hr in combination with the acute secondary t1/2 of 54.8 hr were longer than the single exponential chronic t1/2 of 22.2 hr determined in the same subjects.


Steady-state pharmacokinetics of morphine were investigated in six patients. There were no significant differences in the mean steady-state concentrations of morphine, M3G, and M6G between the oral and rectal administrations (p>0.05).


Thirty percent of patients with cancer have pain at the time of diagnosis, and 65 to 85% have pain with advanced disease. Cancer pain can be effectively treated in 85 to 95% of patients with an integrated program of systemic, pharmacologic, and anticancer therapy.


Twelve volunteers were given intravenous fentanyl citrate or oral transmucosal fentanyl 15 micrograms/kg or oral fentanyl solution to swallow. Peak absorption rate and systemic bioavailability were greater and occurred much sooner after OTF than after oral solution administration.

A substantial minority of patients treated with oral morphine (10% to 30%) do not have a successful outcome because of: 1) excessive adverse effects, 2) inadequate analgesia, or 3) a combination of both excessive adverse effects along with inadequate analgesia. This study presents evidence-based recommendations for clinical practice formulated by an Expert Working Group of the European Association of Palliative Care (EAPC) Research Network.


One explanation for incomplete cross-tolerance at the mu opioid receptor could be the presence of multiple receptor subtypes; at least seven different splice variants have been isolated.


Methadone, a synthetic opioid, has unique pharmacodynamics and pharmacokinetics, which contribute to its ability to relieve pain that is unresponsive to other potent opiates. Several guidelines of administration have been established.


Methadone has a number of unique characteristics, including excellent oral and rectal absorption, no known active metabolites, high potency, low cost, and longer administration intervals, as well as an incomplete cross-tolerance with respect to other mu-opioid receptor agonist drugs. Its use is limited by the remarkably long and unpredictable half-life, large inter-individual variations in pharmacokinetics, potential for delayed toxicity, and above all by the limited knowledge of correct administration intervals and the equianalgesic ratio with other opioids when administered chronically.

This case report describes a decrease of the morphine equivalent daily dose (MEDD) from 1,050 to 36 after rotation to methadone.


The article describes an 8-week trial of gabapentin (titrated from 900 to 3,600 mg/d or maximum tolerated dosage) or placebo. By intent-to-treat analysis, gabapentin-treated patients' mean daily pain score at the study endpoint (baseline, 6.4; endpoint, 3.9; n=82) was significantly lower (P<.001) compared with the placebo-treated patients' endpoint score (baseline, 6.5; endpoint, 5.1; n=80).


In this study, 121 consecutive patients with neuropathic pain due to cancer, partially controlled with systemic opioids, were treated with gabapentin titrated from 600 mg/d to 1,800 mg/d in addition to stable opioid dose. Analysis of covariance (ANCOVA) on the intent-to-treat population showed a significant difference of average pain intensity between gabapentin (pain score, 4.6) and placebo group (pain score, 5.4; P = .0250).


Clonazepam seems to be effective in treating idiopathic trigeminal neuralgia. Electrophysiological investigations support the idea that this neuralgia is due to a loss of central inhibition. During the first 1-2 weeks of treatment marked drowsiness is observed in the majority of cases. In one case, presence of a synergism between Clonazepam and L-dopa+ inhibitor was also observed.

The article describes a systematic review of 20 randomized controlled trials of anticonvulsants for acute, chronic, or cancer pain. For treating trigeminal neuralgia, carbamazepine had a combined number needed to treat of 2.6 for effectiveness, 3.4 for adverse effects, and 24 for severe effects (withdrawal from study). For treating diabetic neuropathy, anticonvulsants had a combined number needed to treat of 2.5 for effectiveness, 3.1 for adverse effects, and 20 for severe effects. For migraine prophylaxis, anticonvulsants had a combined number needed to treat of 1.6 for effectiveness, 2.4 for adverse effects, and 39 for severe effects.


In this study, 59 patients received either lamotrigine (titrated from 25 to 400 mg/day) or placebo over a 6-week period. Daily numerical pain score in the lamotrigine-treated group was reduced from 6.4 +/- 0.1 to 4.2 +/- 0.1 and in the control group from 6.5 +/- 0.1 to 5.3 +/- 0.1 (p<0.001 for lamotrigine doses of 200, 300, and 400 mg).


Two randomized, double-blind, crossover studies were done in patients with painful diabetic neuropathy, comparing amitriptyline with the relatively selective blocker of norepinephrine reuptake, desipramine, in 38 patients, and comparing the selective blocker of serotonin reuptake, fluoxetine, with placebo in 46 patients. Desipramine relieves pain with efficacy similar to that of amitriptyline. Fluoxetine, which blocks serotonin uptake, is no more effective than placebo.

Eisenach JC, Gebhart GF. Intrathecal amitriptyline acts as an N-methyl-D-aspartate receptor antagonist in the presence of inflammatory hyperalgesia in rats. Anesthesiology. 1995;83:1046-1054. PMID: 7486155.

Amitriptyline reverses hyperalgesia in rats by a mechanism unrelated to monoamine reuptake inhibition, and likely due to NMDA receptor antagonism.

The article describes a randomized, double-blind, crossover trial in 33 patients. Pain relief occurred without an antidepressant effect, and although there were fewer side effects with nortriptyline, amitriptyline and nortriptyline have a similar analgesic action for most individuals.


The article describes a randomized, double-blind, crossover comparison of venlafaxine and inactive placebo in 13 patients. The average daily pain intensity as reported in the diary (primary outcome) was not significantly reduced by venlafaxine compared with placebo. However, the average pain relief (diary) and the maximum pain intensity (retrospective assessment by the computer program) were significantly lower with venlafaxine compared with placebo.


Two randomized, double-blind, crossover trials comparing 6 weeks of oral dextromethorphan to placebo were conducted. Mean doses were 381 mg/day in diabetics and 439 mg/day in postherpetic neuralgia patients. In diabetic neuropathy, dextromethorphan decreased pain by a mean of 24% (95% CI: 6% to 42%, p=0.01), relative to placebo. In postherpetic neuralgia, dextromethorphan did not reduce pain.


The authors describe a prospective study of nine subjects with chronic neuropathic pain of peripheral origin treated with intravenous lidocaine, 2 mg/kg and 5 mg/kg, over 45 min during separate sessions in random order under double-blind conditions. Subsequent response to oral mexiletine was significantly correlated with the average response to the two IVL.

Thirty-five subjects with established postherpetic neuralgia affecting the torso or extremities completed a four-session, random order, double-blind, vehicle-controlled study of the analgesic effects of topically applied 5% lidocaine in the form of a nonwoven polyethylene adhesive patch. All subjects had allodynia on examination. Up to 3 patches, covering a maximum of 420 cm2, were applied to cover the area of greatest pain as fully as possible. Lidocaine-containing patches significantly reduced pain intensity at all time points from 30 min to 12 h compared to no-treatment and vehicle-only treatment.


Clonidine (range, 100-900 micrograms in 100-microgram increments) was injected in nine patients and produced analgesia, as measured by change in verbal pain scores, lasting more than 6 h. Clonidine also decreased blood pressure, although this effect was well tolerated and no patient met criteria for receiving iv ephedrine (greater than 30% decrease in mean arterial pressure not responsive to 500 ml iv crystalloid infusion). Clonidine decreased heart rate 10-30% and produced transient sedation.

North RA, Williams JT, Surprenant A, Christie MJ. Mu and delta receptors belong to a family of receptors that are coupled to potassium channels. Proc Natl Acad Sci USA. 1987;84(15):5487-5491. PMID: 2440052;full text.

The article describes a randomized, double-blind, crossover trial in 33 patients. Pain relief occurred without an antidepressant effect, and although there were fewer side effects with nortriptyline, amitryptiline and nortriptyline have a similar analgesic action for most individuals.


Lumbar intrathecal injection of alpha-2, but not alpha-1 or an opiate agonist, resulted in a dose-dependent reversal of the allodynia in rats. The failure of morphine to exert an antiallodynic action reflects the facts that: 1) opiates act presynaptically on small primary afferents and the allodynia is mediated by large afferent input; and 2) opiates, unlike alpha-2 agonists, do not have an effect on autonomic outflow.
The enhanced anti-inflammatory activity of the various synthetic analogues of cortisol is not dissociated from the expected catabolic actions of glucocorticoid hormones. With improvement of the underlying disorder, the steroid dosage can be rapidly tapered and then discontinued over a 2- to 3-day period. After more than 2 weeks of treatment, suppression of the hypothalamic-pituitary-adrenal axis may persist for as long as 9 to 12 months. The steroid dosage should also be given as a single morning dose if possible.

The available data on glucocorticoids for the treatment of asthma are reviewed.

Several serious psychiatric syndromes can be rarely caused by corticosteroids: substance-induced mood disorders (with depressive, manic, and mixed features), substance-induced psychotic disorders, and delirium. A variety of pharmacologic strategies for treatment and prevention have been proposed.

The article describes a randomized, single-blind trial of high-dose dexamethasone as an adjunct to radiotherapy in 57 patients with metastatic spinal cord compression from solid tumors. Dexamethasone was administered as a bolus of 96 mg intravenously, followed by 96 mg orally for 3 days and then tapered in 10 days. A successful treatment result defined as gait function after treatment was obtained in 81% of patients treated with dexamethasone compared with 63% of patients receiving no dexamethasone therapy. Six months after treatment, 59% of patients in the dexamethasone group were still ambulatory compared with 33% in the no-dexamethasone group. Median survival was identical in the two treatment groups.
External beam radiotherapy and systemic endocrine and cytotoxic treatments are the mainstay of treatment in advanced cancers. Bisphosphonates provide an additional treatment strategy.

The authors describe a comprehensive review of the multimodality treatment available for patients with bone mets. Pain management, including the adjuvant modalities of bisphosphonates, corticosteroids, calcitonin, radiopharmaceuticals, and NSAIDs, is discussed.

A systematic review was conducted of 67 trials to assess the management of opioid side effects-constipation, pruritus, nausea and vomiting, myoclonus, sedation, respiratory depression, and delirium. Opioid rotation to manage side effects was also studied. The lack of well-designed, randomized controlled trials and the heterogeneity of populations and study designs made the drawing of firm conclusions difficult and precluded performance of meta-analysis.

The article describes a survey of symptom prevalence, etiology, and severity in 593 cancer patients treated by a pain service. Efficacy of pain treatment was good in 70%, satisfactory in 16%, and inadequate in 14% of patients. Prevalence and severity of anorexia, impaired activity, confusion, mood changes, insomnia, constipation, dyspepsia, dyspnea, coughing, dysphagia, and urinary symptoms were significantly reduced; those of sedation, other neuropsychiatric symptoms, and dry mouth were significantly increased; and those of coma, vertigo, diarrhea, nausea, vomiting, intestinal obstruction, erythema, pruritus, and sweating remained unchanged. The most frequent symptoms were impaired activity (74% of days), mood changes (22%), constipation (23%), nausea (23%), and dry mouth (20%). Of all 23 symptoms, only constipation, erythema, and dry mouth were assessed as being most frequently caused by the analgesic regimen.

A random sample of 65 adult oncology outpatients with a Karnofsky performance status score of ≥50, an average pain intensity score of ≥2.5, and radiographic evidence of bone metastasis were recruited for this longitudinal study from 7 outpatient settings. Adherence rates for opioid analgesics prescribed on an around-the-clock basis ranged from 84.5% to 90.8% and on an as-needed basis, from 22.2% to 26.6%.


This article reviews the current optimal management of opioid-related nausea and vomiting, constipation, cognitive side effects, myoclonus, and respiratory depression.


Eighty-one cancer patients, aged 37 to 76 years, were enrolled onto a prospective, longitudinal, randomized controlled study from the outpatient clinic settings of 26 western Washington-area medical oncologists. Patients randomized to the pain algorithm group achieved a statistically significant reduction in usual pain intensity, measured as slope scores, when compared with standard community practice (P<.02).


In a randomized clinical trial of 202 patients with unrelieved pain (visual analog scale (VAS) pain scores ≥5 on a 0-10 scale) on at least 200 mg or morphine oral equivalent daily, implanted intrathecal therapy reduced pain, relieved common drug toxicities, and was associated with improved survival in patients with refractory cancer pain. Reductions in fatigue, confusion, sedation, personality changes, constipation, vomiting, and urticaria were noted. Survival was also improved, with 17 more patients of every 100 estimated to be alive at 6 months.


The article summarizes evidence that pain of sufficient magnitude can, directly or indirectly, suppress immune mechanisms normally serving to defend the body against tumors, and can thereby cause a marked increase in tumor growth.


Morphine, in a concentration typical of that observed in patients' blood, stimulates human microvascular endothelial cell proliferation and angiogenesis in vitro and in vivo.


One hundred-thirty patients with histologically proven, unresectable pancreatic cancer received either an alcohol or a saline block. The neurolytic block, as compared with medical management alone, improved pain, elevated mood, reduced pain interference with activity, and was associated with an increase in life expectancy.


In a population of 92 cancer patients, 13 received intrathecal morphine. The generally accepted indications for the technique appeared to be justified. Three patients developed meningitis.


Twenty-six cases of chronic intrathecal morphine administration are described. The average duration was 132 days. The efficacy of the method was excellent: 23 of 26 patients used no other analgesics or only minor ones such as aspirin, paracetamol, or dextropropoxyphene. There were no infections and only four catheter blockages (one by tumor).

The median postimplant survival time in this study was 4 months.


Forty-three patients with intractable pain received intrathecal morphine delivered by implanted continuous-infusion devices. In 35 patients the pain was due to cancer, and 8 patients had chronic nonmalignant pain. Twenty-eight (80%) of the patients with cancer-related pain experienced excellent or good relief. Side effects were rare.


Fifty patients with refractory cancer pain were treated with a continuous intrathecal infusion of morphine using an external pump with patient-controlled boluses. In this retrospective study, the average duration of intrathecal infusion was 142 (7-584) days. The mean starting dose, 2.5 (0.4-8.3) mg/day, increased to a mean final dose of 9.2 (1-94) mg/day, the average dose being 5.4 (1-23) mg/day. During the treatment period, no clinically detectable infections and no respiratory depression occurred. Leakage of cerebrospinal fluid followed by postspinal headache occurred in only six patients.


Three distinct levels of pain severity can be defined on a 0-10-point numerical scale. Based on the degree of interference with cancer patients' function, ratings of 1-4 correspond to mild pain, 5-6 to moderate pain, and 7-10 to severe pain. The authors' analysis illustrates that the pain severity-interference relationship is nonlinear.


In this study, 16 of 1,205 cancer patients received epidural therapy. Although analgesia was obtained in all 16, complications occurred in 11 of the 16 patients, including dislodged or broken catheters, pain on injection, bleeding/bruising, or infection.

Epidural analgesia gave adequate pain relief in 76% of 91 patients who received it, but complications occurred in 43% of patients, such that the authors did not recommend it for patients with more than 3 months to live.


The article describes a prospective, cohort, nonrandomized, consecutive trial of 90 patients, 40 men and 50 women, 20 to 96 years old (median, 70 years), with various nonmalignant "refractory" pain conditions lasting for 0.3 to 50 years (median, 3 years). During the intrathecal period (range, 3-1,706 days; median, 60 days; total 14,686 days, 7,460 [50% of which were spent at home]), 86 patients (approximately 95%) obtained acceptable (60-100%) pain relief.


The authors reviewed 15 published series since 1964. A total of 480 patients with cancer of the pancreas were reported; at least a satisfactory response to NCPB was reported in 418 (87%). Major deficiencies were found in these reports.


Twenty-four patients were divided into 2 groups: 12 patients underwent NCPB (group 1) and 12 were treated with pharmacologic therapy (group 2). Immediately after the block, patients in group 1 reported significant pain relief compared with those in group 2 (P<0.05), but long-term results did not differ between the groups. Mean analgesic consumption was lower in group 1.

CPB is a relatively safe procedure, and although it is associated with common adverse effects such as diarrhea, hypotension, and local pain, these are mostly transient. However, severe complications, including paraplegia, have been reported.


Chemical splanchnicectomy with alcohol was performed in 65 patients, and 72 patients received a placebo. No differences in hospital mortality or complications, return to oral intake, or length of hospital stay were observed. Mean pain scores were significantly lower in the alcohol group at 2-, 4-, and 6-month follow-up and at the final assessment (p<0.05). Furthermore, patients with preexisting pain who received alcohol showed a significant improvement in survival when compared with controls (p<0.0001).


When orally administered medications fail to control pain or cause excessive side effects, patients should be referred to an appropriate specialist or medical center for consideration of other pain-relieving techniques.


Physicians tend to treat pain as a completely somatic disorder, but chronic pain states are always biopsychosocial in nature. Anesthesiological and neurosurgical procedures are only a part of the possible and necessary treatment options.


Neurolytic procedures should be performed prior to initiation of high-dose narcotic therapy, radiation, chemotherapy, and surgery when possible.
Self-Assessment

Module 2: Cancer Pain Management

1. Neuropathic pain is:
   - a). usually treated with anti-inflammatory agents
   - b). a result of disordered nerve function
   - c). due to direct stimulation of intact nociceptors
   - d). rarely responsive to opioid analgesics

2. Mrs. Martinez is a 42-year-old woman who has breast cancer metastatic to bone and liver. Her pain has been well controlled on sustained-release morphine, 120 mg PO bid, for 3 months. Which of the following is most likely to occur as a result of this treatment?
   - a). psychological dependence
   - b). physical dependence
   - c). pharmacologic tolerance
   - d). respiratory depression

3. Mr. Martin has locally advanced transitional cell cancer of the bladder with chronic pelvic and abdominal pain. Which of the following is most important in determining the maximum dose of oral morphine during dose titration?
   - a). pain relief
   - b). respiratory depression
   - c). risk of overstepping regulatory limits
   - d). strength of pill

4. Pharmacologic tolerance develops to all of the following side effects of opioid analgesics except:
   - a). constipation
b). nausea

c). respiratory depression

d). sedation
Self-Assessment Answers

Question 1. The correct answer is: b)

This question concerns understanding pain pathophysiology. Neuropathic pain is a result of disordered nerve function. It does not result from inflammatory processes and does not relate to ongoing stimulation of intact nociceptors. Opioids are effective in managing neuropathic pain. However, relief is usually incomplete without the addition of adjuvant or coanalgesics.

Question 2. The correct answer is: b)

This question is aimed at understanding the pharmacology of opioids. Physical dependence (the appearance of a withdrawal syndrome if the drug is stopped suddenly) should be expected. Now that she is on a stable dose, it is unlikely the dose needs to be escalated unless her disease worsens. Progressive pharmacologic tolerance is unlikely. There is no evidence that opioids cause psychological dependence. Respiratory depression on a stable dose of morphine is unlikely.

Question 3. The correct answer is: a)

This question is aimed at understanding the pharmacology of opioids. There is no upper limit to pure agonist opioid analgesics. The dose is limited by side effects. Respiratory depression is exceedingly uncommon when doses are titrated to pain relief. There are no a priori limits to morphine dose escalation. Pill strength is not an issue—patients may need to take many pills to achieve the desired dose.

Question 4. The correct answer is: a)

This question is aimed at understanding adverse effects of opioids. Constipation is nearly universal and does not get better with repeated dosing. Pharmacologic tolerance develops within days to weeks to the common adverse effects such as nausea and sedation, as well as to the uncommon effect of respiratory depression.