

EPEEC

Education for Physicians on End-of-life Care

Participant's Handbook

Module 4

Pain

Management

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Abstract

Most patients with advanced life-threatening illness experience pain. Adequate assessment by a knowledgeable physician, often working closely with an interdisciplinary team, can relieve and control pain effectively.

Pharmacologic management of nociceptive and neuropathic pain can be conceptualized along the 3 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.

Nonpharmacologic 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.

Key words

addiction, adjuvant analgesics, adverse effects, barriers, cross-tolerance, equal analgesia, myths, neuropathic, nociceptive, nonopioid, opioid, opioid allergy, opioid excess, opioid overdose, pain, physical dependence, somatic, tolerance, visceral

Introduction

Pain is a frequent problem in any medical practice, whether associated with advanced illness or other acute or chronic conditions. It is the physical symptom that patients and families fear most. Although physicians now have very effective treatments at their disposal, pain remains one of the most poorly assessed and treated physical symptoms. Lack of knowledgeable and experienced physicians and myths about addiction continue to be significant barriers to good pain management and contribute unnecessarily to patient and family debilitation and suffering.

This module is divided into 3 parts:

- part 1 discusses assessment, pathophysiology, and pain management, including the WHO 3-step ladder, NSAIDs and acetaminophen, opioid pharmacology, dosing guidelines, opioids that are not recommended, and addiction
- part 2 discusses alternate routes of administration, alternate opioids, and equianalgesic dosing
- part 3 discusses adjuvant analgesics for neuropathic pain, bone pain, bowel obstruction, corticosteroids, topical analgesia, anesthesia/neurosurgery, opioid adverse effects, nonpharmacologic approaches, and barriers to pain management

Module 4, Part 1: Principles of pain management

Objectives

The objectives of part 1 of this module are to:

- compare and contrast nociceptive and neuropathic pain
- know steps of analgesic management

Clinical case on trigger tape

Mr Gonzales is a 67-year-old mechanic who immigrated to the United States from Mexico 10 years ago. His primary care physician is Dr O'Brien. Fourteen months ago, Mr Gonzales presented with microcytic anemia, which soon led to a diagnosis of adenocarcinoma of the colon, Duke stage C. Treatment included bowel resection and adjuvant chemotherapy. During his treatment, Mr Gonzales was relatively asymptomatic. Subsequently, he noted pain in his leg. Imaging studies revealed lesions in the liver and right femur. A bone biopsy confirmed the diagnosis of metastatic adenocarcinoma. It has been 6 weeks since Mr Gonzales learned the news of the cancer's recurrence.

General principles

This module focuses on the assessment and management of physical pain, an important area of competency for physicians. This is not to imply that the other components of suffering (other physical, psychological, social, spiritual, or practical issues) are diminished in their importance. Those factors are covered in part in Module 3: Whole Patient Assessment and elsewhere throughout the EPEC curriculum. Regulatory and legal issues related to the prescribing of controlled substances are covered in Plenary 2: Legal Issues in End-of-life Care.

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 nonpharmacologic 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.

Use of other members of the interdisciplinary team perhaps including the nurse, social worker, pharmacist, chaplain, physiotherapist, occupational therapist, child life specialist, etc, is often key to 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, ask for help from colleagues with more expertise.

Comprehensive pain assessment

Pain management requires adequate assessment. Its absence is the leading reason for poor pain management. Pain assessment is discussed in Module 3: Whole Patient Assessment.

Pain pathophysiology

Pain can be acute or chronic. Acute pain is usually related to an easily identified event or condition. 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. A broad description of the predominating pain pathophysiology can usually be inferred through the description, physical findings, and the 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, www.pslgroup.com.

Nociceptive pain

Nociceptive pain is presumed to involve direct stimulation of intact mechanical, chemical, or thermal nociceptors and transmission of electrical signals along normally functioning nerves. It can be subdivided into 2 subgroups: somatic and visceral pain. Somatic pain (eg, skin, soft tissue, muscle, and bone) is due to stimulation of the somatic nervous system. Patients may describe this as sharp, aching, and/or throbbing pain that is easily localized. Visceral pain (eg, cardiac, lung, GI and GU tracts) results from stimulation of the autonomic nervous system. Patients may find this pain difficult to describe or localize. Nociceptive pain generally responds well to opioids and/or coanalgesics.

Neuropathic pain

Neuropathic pain is presumed to result from disordered function of the peripheral or central nervous system due to any of many potential causes. There are varied subtypes, including those sustained by peripheral processes (eg, painful neuroma), those sustained by CNS processes (eg, phantom pain), and complex regional pain syndromes (previously referred to as causalgia or reflex sympathetic dystrophies). These pains can also be classified by syndrome (eg, malignant plexopathy, painful polyneuropathy, phantom pain, postherpetic neuropathy, etc).

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.

Pain management

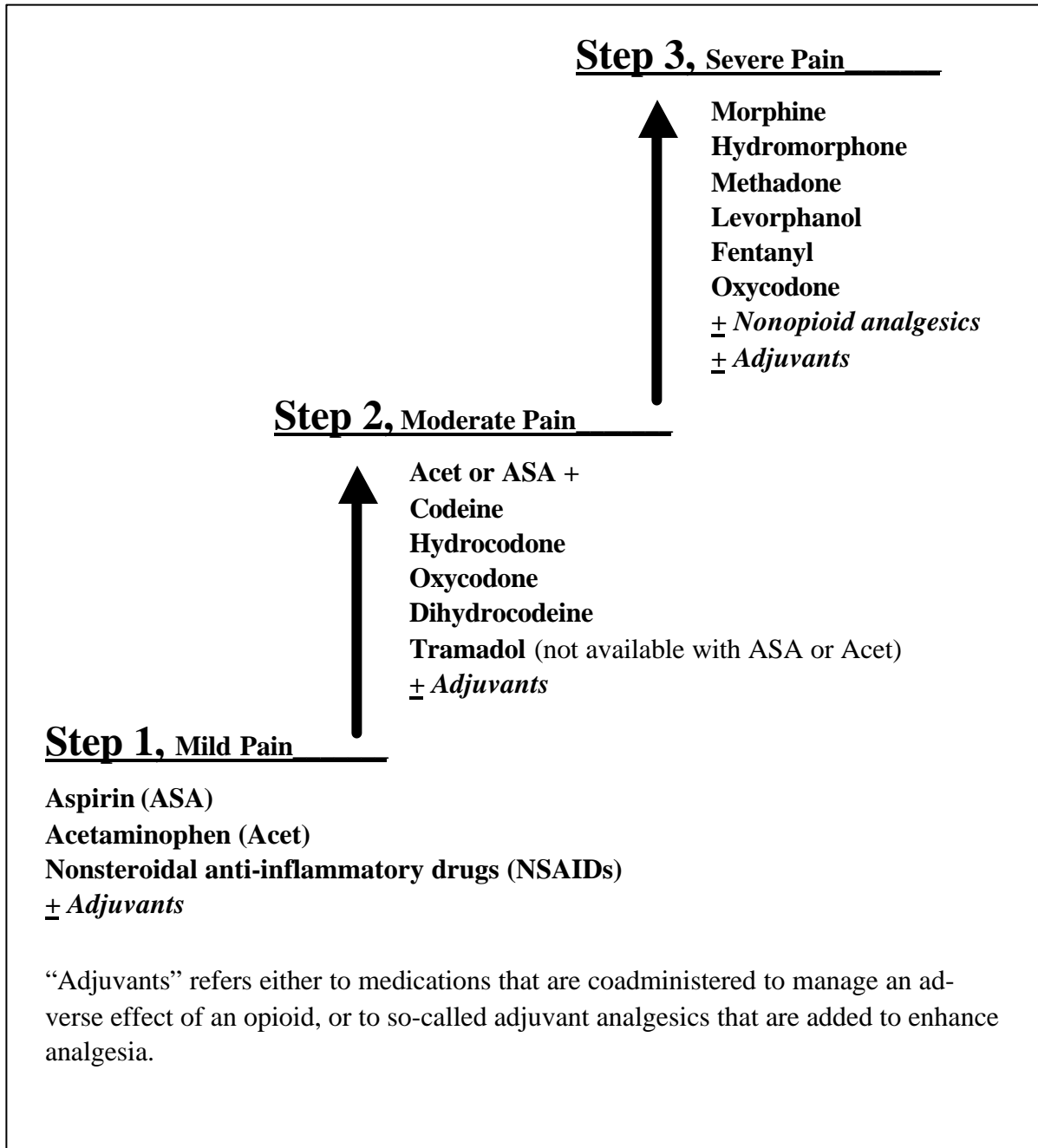
While the diagnosis and treatment of the underlying cause of any pain is an important part of the medical treatment plan, there is no reason to delay the use of analgesics. It is not appropriate to withhold pain management until the investigations and treatment of the underlying disease are complete, or other criteria are met. 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 individual and family. Consider the use of primary therapies directed against the source of pain (eg, radiation for a neoplasm), if it is feasible and consistent with the goals of care.

Placebos

Some physicians have advocated the use of placebos to see if patients are really in pain. While 30% to 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), American Pain Society (APS), Joint Commission on Accreditation of Healthcare Organizations (JCAHO), and the American Nursing Association (ANA) have all issued position statements to this effect.

Pharmacologic approaches to pain management

WHO 3-Step Ladder



In 1986, the World Health Organization (WHO) developed a 3-step conceptual model to guide the management of cancer pain. It provides a simple, well-tested approach for the rational selection, administration, and titration of a myriad of analgesics. Today, there is worldwide consensus favoring its use for the medical management of all pain associated with serious illness.

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 are summarized in the Medication Tables at the end of the EPEC materials.

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. Chronic doses > 4.0 g/24 h or acute doses > 6.0 g/24 h are not recommended as they may cause hepatotoxicity. Hepatic disease or heavy alcohol use increases the risk further.

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs, including aspirin) are effective step 1 analgesics. They may also be useful coanalgesics. They work, at least in part, by inhibiting cyclo-oxygenase, the enzyme that converts arachidonic acid to prostaglandins.

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 the Medication Tables at the end of the EPEC materials.

NSAIDs can have significant adverse effects. There are substantial differences among NSAID classes as to the likelihood of adverse effects. This may in part be due to their relative COX-2 selectivity. Gastropathy, renal failure, and inhibition of platelet aggregation can occur, irrespective of the route of administration, with any of the nonselective medications. Some drugs, however, such as ibuprofen, nabumetone, and others appear to be relatively safer. Gastric cytoprotection with misoprostol or omeprazole may be needed in patients with significant risk factors, particularly those with a history of gastric ulcers or bleeding, current nausea/vomiting, or protein wasting, cachexia, and for the elderly. To

minimize the risk of renal failure, including papillary necrosis, ensure adequate hydration and good urine output in all patients on NSAIDs. The nonselective medications are relatively contraindicated in the setting of significant preexisting renal insufficiency. If bleeding is a problem, or coagulation or platelet function is impaired, NSAIDs may be contraindicated. The new COX-2 selective inhibitors lack these toxicities and may be indicated in high-risk patients.

Step 2 and 3 analgesics

Step 2 and 3 analgesics involve opioid use.

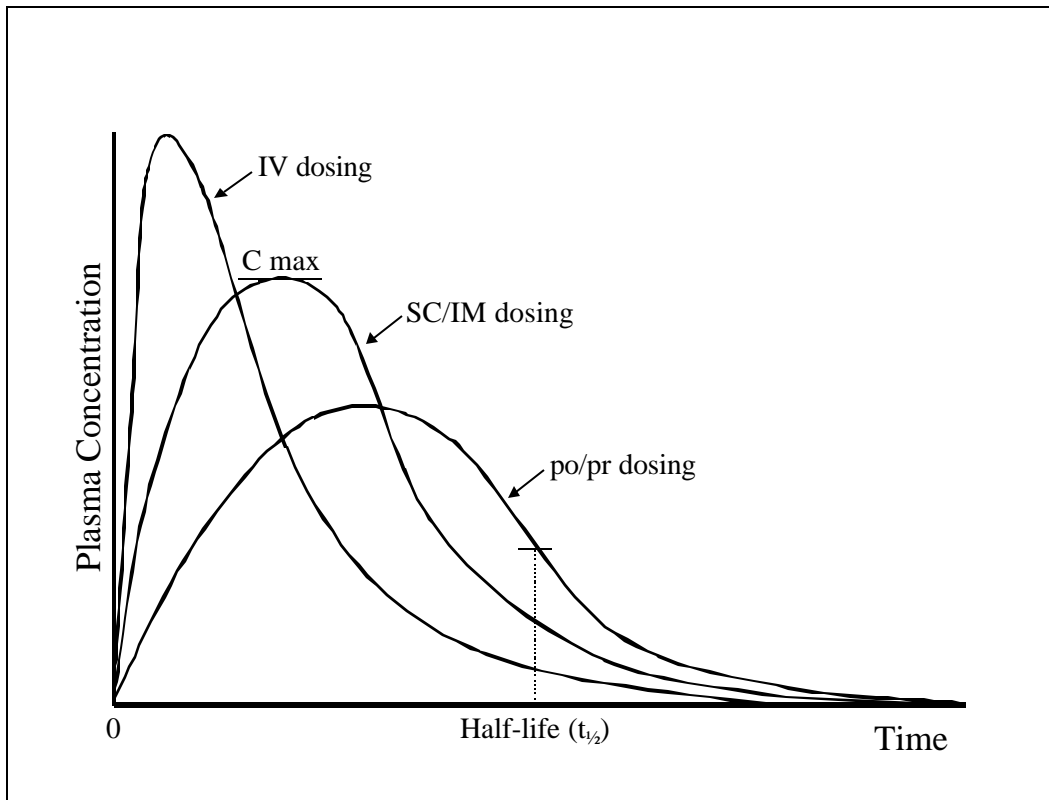
Opioid pharmacology

Opioids, codeine, hydrocodone, hydromorphone, morphine, oxycodone, etc, all follow first-order kinetics and pharmacologically behave very similarly. They reach their peak plasma concentration (C_{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. They are eliminated from the body in a direct and predictable way, irrespective of the dose. The liver first conjugates them. Then the kidney excretes 90% to 95% of the metabolites. Their metabolic pathways do not become saturated.

Each opioid metabolite has a half-life ($t_{1/2}$) that depends on its rate of renal clearance. When renal clearance is normal, codeine, hydrocodone, hydromorphone, morphine, oxycodone, and their metabolites all have effective half-lives of approximately 3 to 4 hours. 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 a day.

Pharmacologic Dosing Curves After a Single Opioid Dose

Curves vary based on the route of administration



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. The best possible pain control for the dose will be achieved within a 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 the next section but one.

If pain remains uncontrolled after 24 hours, increase the routine dose by 25% to 50% for mild to moderate pain, by 50% to 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 1 or 2 doses (eg, 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 the appendix to Module 4.

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 (eg, methadone, $t_{1/2} \approx 12\text{--}24$ 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.

Methadone has a long and variable half-life. Although the half-life usually approaches a day or longer, the effective dosing interval for analgesia is usually as frequently 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 dose only every 4 to 7 days, or less often, if possible.

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, ie, 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, eg, morphine or hydromorphone, as the rescue dose. Oral immediate-acting fentanyl is also available.

For each breakthrough dose, offer 5% to 15% of the 24-hour dose. As peak analgesic effect correlates with peak plasma concentration (C_{max}), a breakthrough dose can be offered once C_{max} has been reached. As noted, codeine, hydrocodone, morphine, oxycodone, and hydromorphone all behave similarly. An extra breakthrough dose can be offered once 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.

Clearance concerns

Opioids and their metabolites are primarily excreted renally (90%–95%). Morphine has two principal metabolites: morphine-3-glucuronide and morphine-6-glucuronide. Morphine-6-glucuronide is active and has a longer half-life than the parent drug morphine. Consequently, 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. This may not be as important for other opioids such as hydromorphone or fentanyl.

Opioid metabolism is not as sensitive to hepatic compromise. However, if hepatic function becomes severely impaired, increase the dosing interval or decrease the dose.

Not recommended

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 the 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 the 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 drug use and continued use, despite harm. Care must be taken to differentiate a true addiction (substance use disorder) from pseudoaddiction due to 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 side effects is observed commonly and is favorable. 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, suspect worsening disease rather than pharmacologic tolerance.

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. Physical dependence is not evidence of addiction. Its presence does not mean that opioids cannot be discontinued. 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 (eg, 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.

Since patients with histories of substance abuse can also develop significant pain, they deserve compassionate treatment of their pain when it occurs. Most will need to adhere to strict dosing protocols, and contracting may become necessary. Physicians who are unfamiliar with these situations may need the help of specialists in pain management and/or addiction medicine.

Pain poorly responsive to opioids

If dose escalation results in adverse effects, consider one of the following options. More sophisticated adverse effect therapy, such as a psychostimulant, may help sedation. An alternate route of administration or a different opioid may be effective, without some of the side effects. An adjuvant analgesic may help reduce the amount of opioid required. Finally, consider a nonpharmacologic approach. These possibilities are discussed in parts 2 and 3, which follow.

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 to drive a car.

Module 4, Part 2: Equianalgesic dosing

Objectives

The objectives of part 2 of this module are to:

- know alternative routes of delivery
- demonstrate ability to convert between opioids while maintaining analgesia

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 very limited (US only).

Rectal administration of immediate or extended-release rectal preparations behave pharmacologically like related oral preparations. 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 only manufactured containing fentanyl, they 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 (ie, 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 same 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. 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 the 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.

EQUIANALGESIC DOSES OF OPIOID ANALGESICS		
ORAL/RECTAL DOSE (MG)	ANALGESIC	PARENTERAL DOSE (MG)
100	Codeine	60
–	Fentanyl	0.1
15	Hydrocodone	–
4	Hydromorphone	1.5
2	Levorphanol	1
150	Meperidine	50
10	Methadone	5
15	Morphine	5
10	Oxycodone	–

An equianalgesic table 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 between opioids.

Changing opioids

When converting to or from transdermal fentanyl patches, published data suggest that a 25- μ g patch is equivalent to 45 to 135 mg of oral morphine per 24 hours. However, clinical experience suggests that most patients will use the lower end of the range of morphine doses (ie, for most patients, 25 μ g is about equivalent to 45 to 60 mg of oral morphine per 24 hours).

Opioid cross-tolerance

While pharmacologic tolerance may develop to the opioid in use, tolerance may not be as marked relative to other opioids. 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% to 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. Start with 10% to 25% of the published equianalgesic dose and titrate appropriately to achieve pain control.

Problem solving

The following cases demonstrate common dosing conversions. Answers can be found at the end of the Appendix.

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?

- a. 2 mg po q 4 h
- b. 4 mg po q 4 h
- c. 8 mg po q 4 h
- d. 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?

- a. 5 mg po q 4 h
- b. 10 mg po q 4 h
- c. 20 mg po q 4 h
- d. 30 mg po q 4 h

Case 6

Mrs C has been taking codeine, 60 mg by mouth every 4 hours, and methadone, 40 mg orally every 6 hours, to adequately control abdominal pain from bulky retroperitoneal metastases. She is now admitted with a chemotherapy-induced stomatitis. Your attending physician suggests that you place her on a constant infusion of intravenous morphine. Without adjusting for partial cross-tolerance, what hourly rate of intravenous morphine will you choose to continue to keep her pain well controlled?

- a. 1 mg/h
- b. 2 mg/h
- c. 4 mg/h
- d. 8 mg/h

Module 4, Part 3: Adjuvants, adverse effects, barriers

Objectives

The objectives of part 3 of this module are to:

- know use of adjuvant analgesic agents
- know adverse effects of analgesics and their management
- list barriers to pain management

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 (eg, tricyclic antidepressant medications for postherpetic neuralgia). They can be added into the pain management plan at any step in the WHO ladder.

Neuropathic pain management

Burning, tingling neuropathic pain

Neuropathic pain often requires an adjuvant analgesic in addition to an opioid to adequately manage the pain. For patients who describe their neuropathic pain as “burning” or “tingling” with or without associated numbness, the first choice is usually a tricyclic antidepressant or gabapentin. The selective serotonin reuptake inhibitors (SSRIs) have shown disappointing clinical efficacy as analgesics and are less effective as adjuvants to manage neuropathic pain than the tricyclic antidepressants.

Amitriptyline is the most extensively studied of the tricyclic antidepressants. In contrast to its antidepressant effects, low doses beginning at 10 to 25 mg orally at bedtime may be effective in only a few days. The dose may be escalated every 4 to 7 days until pain relief or adverse effects intervene. It may take high doses and a few weeks to control the pain. Plasma drug levels can be monitored to watch for an increased risk of toxicity at doses greater than 100 mg/24 h. Although it is the most studied medication of this type, amitriptyline has the most adverse effects because of its prominent anticholinergic activity and risk of cardiac toxicity. Although the sedating effect may be helpful to the patient who is also having difficulty sleeping, this adverse effect profile limits its use in many frail and elderly patients.

In contrast, the tricyclic desipramine has minimal anticholinergic or sedating adverse effects. Dosing is the same as for amitriptyline. Its adverse effect profile may make it the tricyclic of choice, particularly in the frail and seriously ill. Nortriptyline may also be effective and has less adverse effects than amitriptyline.

Gabapentin, a new anticonvulsant, appears to be quite effective as an adjuvant for all types of neuropathic pain. Its site and mode of action are not clear. Most clinicians begin at low doses (100 mg po q d to tid) and dose escalate every 1 to 2 days by 100 mg po tid to effect. Some patients require doses of more than 3600 mg/d. Adverse effects appear to be minimal. While some patients experience drowsiness with dose escalation, tolerance appears to develop within a few days if the dose remains stable.

Shooting, stabbing neuropathic pain

For episodic shooting, stabbing, electrical pain, the anticonvulsants gabapentin, carbamazepine, and valproic acid are the most widely used adjuvant medications.

Gabapentin is dose escalated as noted above. Carbamazepine is started at 100 mg po bid to tid and increased by 100 to 200 mg every 5 to 7 days to effect. Valproic acid is started at 250 mg po q hs and increased by 250 mg every 7 days in divided doses to effect. As doses escalate, monitoring carbamazepine or valproic acid plasma levels may help to predict increasing risk of adverse effects.

Complex neuropathic pain

As nerve damage evolves, the resulting pain can become mixed and very complex to manage. Nerve damage and chronic pain can lead to primary neuronal death, loss of myelin sheath, central sensitization, changes in the effective neurotransmitters and neuroreceptors, and even sensory neuronal death. Over time, opioid receptors may be down-regulated, making opioids much less effective, and NMDA (N-methyl-d-aspartate) receptors may become much more important as glutamate becomes a significant neurotransmitter. Opioids may cease to be or continue to be only partially effective.

Combinations of adjuvant analgesic medications may be required, including oral antiarrhythmics, alpha-2 adrenergic agonists, NMDA receptor antagonists, corticosteroids, etc. Consider consulting with a pain management expert early to minimize patient suffering and the risk of further damage from pain itself.

Case 7

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?

Answers for cases 7-9 are indicated in the appendix of this module.

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, 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.

Opioids remain the mainstay of bone pain management. NSAIDs, corticosteroids, bisphosphonates (eg, alendronate, pamidronate), calcitonin, radiopharmaceuticals (eg, strontium, samarium), an external beam radiation may all provide significant additional relief. When definitive orthopedic interventions are not possible, external mechanical supports (splints, braces, etc) may provide relief from movement-related pain. Consultation with a pain management expert may be necessary to achieve adequate relief.

Case 8

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?

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 Module 10: Common Physical Symptoms) 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 to be 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 (eg, 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.

Corticosteroids

Corticosteroids are frequently helpful and commonly used in advanced illness. They may be useful for acute nerve compression, increased intracranial pressure, bone pain, visceral pain (obstruction and/or capsular distention), anorexia, nausea, and depressed mood. Dexamethasone, with its long half-life (>36 hours) and minimal mineralocorticoid effect,

is the drug of choice. It can be administered once a day in doses of 2 to 20 mg or more. Steroid psychosis should be considered if an agitated delirium ensues. Proximal myopathy, oral candidiasis, bone loss, and other toxicities are possible with long-term use but are seldom a problem in the setting of advanced disease.

Case 9

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?

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.

Anesthesia, neurosurgery

For difficult to manage, persistent pain, anesthesia or neurosurgical colleagues may be able to provide considerable pain relief through nerve blocks, unilateral cordotomies, or other selective procedures. Consider referring patients with upper abdominal pain caused by pancreatic disease, lower body pain, pain localized to 1 limb, unilateral pain, etc.

Adverse effects

Opioids have many possible adverse effects; some are common, some not (see Module 10: Common Physical Symptoms). 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 is discussed in Module 10: Common Physical 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 (eg, fexofenadine, 60 mg po bid; diphenhydramine, loratadine, or doxepin, 10–30 mg po q hs).

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. It requires anticipatory and ongoing management. Dietary interventions alone (eg, increase fluid and fiber) are often insufficient. Bulk-forming agents (eg, 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 (eg, senna, bisacodyl, glycerine, casanthranol, etc) and escalate the dose to effect. While stool softeners (eg, docusate sodium) are not usually effective by themselves, combination stimulant/softeners (eg, senna + docusate sodium or calcium) can be useful. Prokinetic agents (eg, 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 Module 10: Common Physical 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.

Dopamine-blocking agents (eg, 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 an alternative opioid may become necessary (see Module 10: Common Physical 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 Module 7: 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. Also, consider the use of a psychostimulant (eg, methylphenidate, 5 mg q am and q noon and titrate), particularly if the opioid is providing effective analgesia.

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 (eg, in the patient who is not passing much urine and is accumulating opioid due to decreased intake or dehydration) or rapidly (eg, in the patient who is developing sepsis) (see Module 6: Depression, Anxiety, Delirium).

Respiratory depression

Many physicians have an exaggerated view of the risk of respiratory depression when using opioids to relieve pain. 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 are quite different from those experienced by a patient who is not in pain and receives similar doses. As doses increase, respiratory depression does not occur suddenly in the absence of overdose. Somnolence always precedes respiratory depression. Adequate ongoing assessment and appropriate titration

of opioids based on pharmacologic principles will prevent misadventures. 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 ($> 6/\text{min}$), the routine opioids may be stopped and the patient appropriately hydrated or sepsis managed until the adverse effects abate.

If respirations are compromised ($< 6/\text{min}$), naloxone may be necessary if it is the goal of care to keep the patient alert while treating the underlying cause. Dilute 0.4 mg of naloxone to 10 mL with sterile water. Administer 0.1 to 0.2 mg IV q 1 to 2 min until the patient is alert. As the effective plasma half-life is short (10 to 15 minutes) because of naloxone's high affinity for lipids, monitor the patient closely every few minutes for recurrent drowsiness. If drowsiness recurs, repeat dosing as required until the patient is no longer compromised.

Nonpharmacologic 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 nonpharmacologic interventions, can frequently assist the physician to identify and refer patients appropriately.

Barriers

Today, pain management remains inadequate in spite of the fact that we have possessed information discussed in this module for more than 20 years. While this inadequacy may reflect inadequate knowledge, it also reflects barriers to pain relief that are pervasive and (in some cases) institutional. To become effective, we need to overcome real or perceived barriers, including beliefs by physicians and other professionals that pain management is not important; poor assessment techniques; inadequate dissemination of the 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 the knowledge.

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 patients. Careful assessment and appropriate use of opioids as outlined in the WHO 3-step ladder approach will go a long way toward improving the quality of our patients' lives.

Key take-home points

Part 1

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. A 3-step model to guide analgesic choice depending on 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 (eg, codeine, hydrocodone, hydromorphone, morphine, oxycodone) follow first-order kinetics. They reach their peak effect and plasma concentration (C_{max}) 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% to 50% for mild to moderate pain, 50% to 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% to 15% of the total 24-hour dose of opioid at a frequency equal to C_{max} 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 (eg, 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. Its hallmark is psychological dependence on drugs and a behavioral syndrome characterized by compulsive drug use and continued use despite harm. Distinguish between true addiction, 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. Clinical importance is rare. When increasing doses are required, suspect worsening disease rather than pharmacologic tolerance.
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.

Part 2

1. 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.
2. Intramuscular injections are not recommended.
3. When changing routes of administration, or switching between opioids, an equianalgesic table is a useful guide for initial dose selection.
4. 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% to 75% of the published equianalgesic dose of the new opioid if pain is otherwise well controlled.

Part 3

Neuropathic pain

1. Opioids may contribute significantly to the management of neuropathic pain.
2. For burning, tingling pain with or without numbness, tricyclic antidepressants or gabapentin are the most widely used adjuvant medications.

3. 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.
4. 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

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

Steroids

6. 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

7. Addiction (psychological dependence), tolerance, and physical dependence are not considered adverse effects of opioid analgesics.
8. Concerns about the double effect 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.
9. Many people believe that opioid-induced nausea/vomiting, constipation, drowsiness, or even confusion are allergic reactions. They are in fact adverse effects, not allergic reactions.
10. 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 nonsedating antihistamines or mast cell stabilizers.
11. Adverse effects of opioids can be managed. Patients generally develop pharmacologic tolerance to all but constipation within a relatively brief period.

12. 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.
13. Many patients starting opioids (up to 30%) experience nausea with or without vomiting. Tolerance develops. Treat with antiemetics or change to a different opioid.
14. 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.
15. 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.
16. Physicians often have an inordinate fear of respiratory depression caused by opioids. Pain is a potent stimulus to breathe. Pharmacologic tolerance to respiratory depression develops quickly. Somnolence always precedes respiratory depression.

Nonpharmacologic approaches

17. Nonpharmacologic approaches to pain management may have a significant adjunct effect on pain management.

Barriers

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

Pearls

1. Believe the patient.
2. Be the physician you would want if you were in pain.
3. Dehydration may present as confusion caused by opioid accumulation.
4. Opioids 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. Dehydration may present as delirium caused by opioid accumulation.
10. Sepsis may present as delirium caused by effective opioid excess.

Potential pitfalls

1. Using extended-release preparations for initial dose titration.
2. Mixing opioids.
3. Detergent stool softeners alone (eg, docusate) at conventional doses do not counteract the constipation 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.

Resources

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Appendix

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% to 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% to 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 so that it is always 5% to 15% of the total daily dose and offer it q 1 h po.

NB: 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 nonpharmacologic 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
 $144 \text{ mg/d IV morphine} = 1 \text{ mg IV morphine}$
 $X \text{ mg/d oral morphine} = 3 \text{ mg oral morphine}$
3. Solve for X
 $X = 442 \text{ mg/d oral morphine}$
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

$$300 \text{ mg/d IM meperidine} = 50 \text{ mg IM meperidine}$$

$$X \text{ mg/d po morphine} = 15 \text{ mg po morphine}$$

3. Solve for X

$$X = 90 \text{ mg/d po morphine}$$

4. Decide on schedule and formulation

Sig: sustained-release morphine, 45 mg po bid

Remember breakthrough dose

Sig: 5–15 mg po immediate-release morphine q 1 h prn

5. Remember the stimulant laxative

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?

Answer

1. Figure out total daily dose of each opioid

$$2 \text{ tablets} \times 5 \text{ mg hydrocodone/tablet} \times 6 = 60 \text{ mg/d hydrocodone}$$

$$1 \text{ tablet} \times 5 \text{ mg oxycodone/tablet} \times 4 = 20 \text{ mg/d oxycodone}$$

2. Set up ratios from the table

$$60 \text{ mg/d oral hydrocodone} = 15 \text{ mg oral hydrocodone}$$

$$X \text{ mg/d oral hydromorphone} = 4 \text{ mg oral hydromorphone}$$

$$20 \text{ mg/d oral oxycodone} = 10 \text{ mg oral oxycodone}$$

$$X \text{ mg/d oral hydromorphone} = 4 \text{ mg oral hydromorphone}$$

3. Solve for X in each case

$$X = 16 \text{ mg/d po hydromorphone}$$

$$X = 8 \text{ mg/d oral hydromorphone}$$

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

5. Decide on schedule

Sig: Hydromorphone, 4 mg po q 4 h RTC

6. Don't forget breakthrough

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

c. 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

$$\frac{960 \text{ mg/d IM meperidine}}{X \text{ mg/d oral hydromorphone}} = \frac{50 \text{ mg IM meperidine}}{4 \text{ mg oral hydromorphone}}$$

3. Solve for X

$$X = 76.8 \text{ mg/d po hydromorphone}$$

4. Decide on schedule

$$12 \text{ mg po q 4 h}$$

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

d. 30 mg po q 4 h

Calculating the Answer

1. Figure out total daily dose of opioid

$$3 \text{ tablets} \times 5 \text{ mg oxycodone/tablet} \times 8 = 120 \text{ mg/d oxycodone}$$

2. Set up ratio from the table

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

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

Mrs C has been taking codeine, 60 mg by mouth every 4 hours, and methadone, 40 mg orally every 6 hours, to adequately control abdominal pain from bulky retroperitoneal metastases. She is now admitted with a chemotherapy-induced stomatitis. Your attending physician suggests that you place her on a constant infusion of intravenous morphine. Without adjusting for partial cross-tolerance, what hourly rate of intravenous morphine will you choose to continue to keep her pain well controlled?

Answer

c. 4 mg/h

Calculating the Answer

Methadone, 40 mg po = 20 mg IV = morphine, 20 mg IV

Codeine, 60 mg po = 40 mg IV = morphine, 3 mg IV

Total daily dose:

Methadone, 40 mg po X 4 = morphine, 80 mg IV

Codeine, 60 mg po X 6 = 18 mg IV

Total morphine/24 h = 98 mg

$98 \text{ mg} \div 24 \text{ h} = 4 \text{ mg/h}$

Case 7

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, 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 8

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 9

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.