

EPEEC for Veterans

Education in **P**alliative and **E**nd-of-life Care for Veterans

Trainer's Guide

Module 4

Pain

Management

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Module 4 trainer's notes

Principal message

Pain management is one of the most prominent and important symptom control skills that clinicians possess. It requires a sophisticated knowledge of pathophysiology, pharmacology, and therapeutics.

Module overview

Many Veterans with chronic and advanced illnesses experience pain. Adequate assessment by knowledgeable clinicians 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. Non-pharmacologic approaches may significantly increase the relief achieved. Adequate pain control is possible in more than 90% of Veterans if the therapeutic approaches that are within the purview of all clinicians are applied. It is important to identify and address Veteran-related, profession-related, and system-related barriers to good pain control.

Preparing for a presentation

1. Assess the needs of your audience

Choose from the material provided in the syllabus according to the needs of your expected participants. It is better for participants to come away with a few new pieces of information, well learned, than to come away with a deluge of information, but remembering nothing.

2. Presentation timing

Allow sufficient time to have participants introduce themselves.

The suggested timing for a one-hour session would be:

Introduction	2-3 minutes
Trigger tape & discussion	5-7 minutes
Presentation	40 minutes
<u>Summary</u>	<u>2-3 minutes</u>
Total	49-53 minutes

3. Number of slides: 63

4. Preparing your presentation

The text in the syllabus was not designed to be used as a prepared speech. Nor are all the slides appropriate to use in the course of a 50-60 minute presentation. Instead, the slides have been designed to trigger your presentation. Although the slides closely follow the text of the syllabus, they do not contain all of the content. Their use presumes that you have mastered the content. You may want to make notes on the slide summary pages to help you prepare your talk in more detail and provide you with notes to follow during your presentation.

Practice your presentation using the slides you have chosen, and speaking to yourself in the kind of language you expect to use, until it is smooth and interesting and takes the right amount of time. As with other EPEC for Veterans modules this module has more material than a 50-60 minute presentation. Choose the most important objectives.

5. Preparing a handout for participants

The syllabus text and slides in the **Trainer's Guide** were designed to be reproduced and provided to participants as a handout, either in its entirety, or module by module. If the entire curriculum is not being offered, please include the following in each handout:

- **EPEC for Veterans Front Cover Page**
- **EPEC for Veterans Acknowledgment Pages** (to acknowledge the source of the material)
- Relevant sections of the syllabus and slides for **Module 4**

6. Equipment needs

- computer with DVD capability or separate DVD player
- flipchart and markers for recording discussion points

Making the presentation

1. Introduce yourself

If you have not already done so, introduce yourself. Include your name, title, and the organization(s) you work for. Briefly describe your clinical experience related to the information you will be presenting.

2. Introduce the topic

Show the title slide for the part of the module you will present. To establish the context for the session, make a few broad statements about the importance of pain management

as a clinical skill. Tell participants the format and time you will take to present the session. Identify any teaching styles other than lecture that you intend to use.

3. Review the session objectives

Show the slide with the session objectives listed. Read each objective and indicate those that you are planning to emphasize.

4. Show the trigger tape or present the clinical case

After reviewing the objectives for the session, show the trigger tape or present the clinical case below. It has been designed to engage the audience and provide an appropriate clinical context for the session. It was not designed to demonstrate an ideal interaction, but to ‘trigger’ discussion.

Clinical case

H.G. is a 67-year-old Veteran. Fourteen months ago, H.G. 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. 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 H.G. learned the news of the cancer’s recurrence.

Discussion

If the discussion is slow to start, you may want to ask more direct questions, like:

- Have they had similar patients?
- How did the patient react to the clinician’s questions?
- How did the clinician start? What was well done? What was missing?
- What did the clinician do to foster a comfortable atmosphere?
- How did the physician address the patient’s concerns?

Use the discussion to set the stage for the material to follow. Don’t let the discussion focus on a critique of the technical quality of the trigger tape or how ‘real’ the players seemed. If the participants don’t like something that was said or done in the trigger tape, ask them how they would do it themselves.

Setting limits to discussion time

Limit discussion of each scene of the trigger tape to no more than 5 minutes, then move on to the presentation. To help move on if the discussion is very engaged, try saying something like:

- Let's hear two last points before we move on.
- Now that you have raised many of the tough questions, let's see how many practical answers we can find.

5. Present the material

Recommended style: Interactive lecture

Module 4 is particularly dense with critical material that all clinicians need to know in order to manage pain effectively. An interactive lecture will permit you to engage your audience, yet cover some of the key take-home points within 45 to 60 minutes.

Alternative style: Case-based

If you have mastered the material and the method, a case-based approach to teaching pain management can be very effective. Use and expand on the case of H.G. to illustrate pathophysiology, pharmacology, and decision making appropriate to pain management. Refer to the issues raised in the trigger tape to discuss the topics of addiction, tolerance, and physical dependence.

Alternative style: Case-based problem solving

People generally learn skills best if they practice doing them. For example, initial information about changing routes of administration and changing opioids can be covered briefly in a slide-based lecture format. Then, turn off the projector, turn up the lights, and ask the participants to solve the problems in the appendix.

Have the cases and the equianalgesic dosing table reproduced so that each participant has a copy and can write directly below the case. Ask a participant to read the problem aloud. Ask different members of the audience how to figure it out. Orient them to the equianalgesic dosing table at the time they need to use it to solve the problem. Do the mathematics at the flipchart. Avoid letting participants who know how to do this just shout out the answer.

6. 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 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 Veteran'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. 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 (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

7. In general, the oral route is the least invasive, most convenient route for administering opioids on a routine basis.
8. If the pain is continuous, or nearly so, start with an appropriate dose of an immediate-release opioid routinely q 4 hr around the clock.
9. 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, 50-100% for severe to uncontrolled pain.
10. Once the continuous pain is controlled, switch to an extended-release preparation to simplify routine dosing and increase the chance of Veteran adherence.

Addiction, dependence and tolerance

11. 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.
12. 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.
13. 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 of administration and changing opioids

14. Incomplete cross-tolerance is likely caused by subtle differences in the molecular structure of each opioid and the way each interacts with the Veteran'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 Veteran. Start with 50-75% of the published equianalgesic dose of the new opioid if pain is otherwise well controlled.

Neuropathic pain

15. For burning, tingling pain with or without numbness, tricyclic antidepressants or gabapentin are the most widely used adjuvant medications.
16. Desipramine has fewer anticholinergic adverse effects and is the tricyclic antidepressant of choice, particularly in elderly and frail Veterans. 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.

Bone pain

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

Steroids

18. 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.

7. Summarize the Discussion

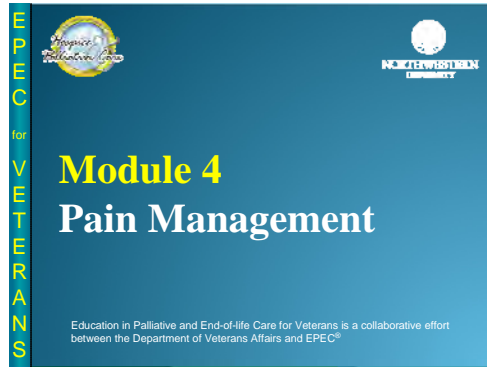
Briefly review each part of the presentation. Recap 2 or 3 of the most important ideas that were discussed.

8. Post-test/evaluation

Ask the participants to evaluate the session.

Abstract

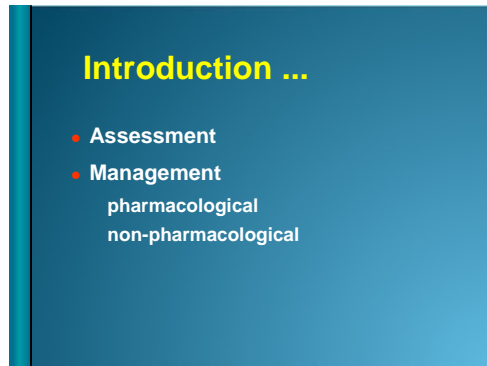
Slide 1



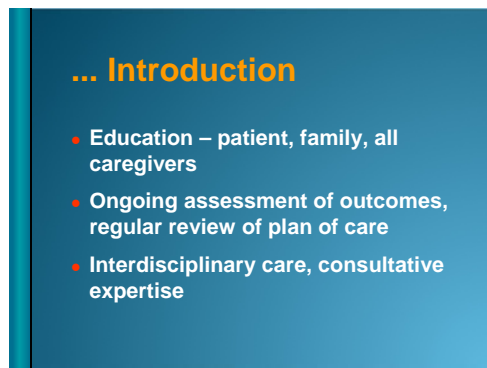
Many Veterans with chronic and advanced illnesses experience pain. Adequate assessment and treatment can almost always relieve and control pain effectively. Pharmacologic management of nociceptive and neuropathic pain can be conceptualized along the 3 steps of the World Health Organization (WHO) analgesic ladder. Non-pharmacologic approaches may significantly increase the relief achieved. Adequate pain control is possible in most Veterans if consistent therapeutic approaches are applied. It is important to identify and address Veteran-related, profession-related, and system-related barriers to good pain control.

Introduction

Slide 2



Slide 3



Pain is a frequent problem in any medical practice, whether associated with advanced illness, such as cancer, or other acute or chronic conditions.^{1,2} Although clinicians now have effective treatments at their disposal, pain remains poorly assessed and treated. Lack of knowledgeable and experienced clinicians and myths about addiction continue to be significant barriers to good pain management and contribute unnecessarily to Veteran and family suffering.

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 less important. Management principles include appropriate pharmacologic and non-pharmacologic interventions; education of the Veteran and family about the plan; ongoing assessment of treatment; and regular review of the plan of care.

This module is divided into three sections:

- Section 1.** Pain policy, including barriers, and addiction. This section is relevant for all members for the interdisciplinary team.
- Section 2.** Basic assessment and management including equianalgesic conversions; including adverse effects. This section is relevant for all clinicians, but especially physicians and nurses.
- Section 3.** Specific types of pain, adjuvants and interventional pain management techniques. This section is meant for advanced clinicians.

Objectives

Slide 4

A blue rectangular slide with a white border. The title "Objectives ..." is in yellow. Below it is a bulleted list of four objectives in white text.

- Explain pain policy at VA
- Describe nociceptive and neuropathic pain
- Demonstrate equianalgesic conversion
- Calculate the conversion between different opioids

Slide 5



... Objectives

- Discuss adjuvant analgesic agents
- Recognize the adverse effects of analgesics and their management
- Identify barriers to appropriate pain management

After studying this module, clinicians will be able to:

- explain pain policy at VA;
- describe nociceptive and neuropathic pain;
- demonstrate equianalgesic conversion;
- calculate the conversion between different opioids;
- discuss adjuvant analgesic agents;
- recognize the adverse effects of analgesics and their management; and
- identify barriers to appropriate pain management.

Clinical case

Slide 6



Clinical case

H.G. is a 67-year-old Veteran. Fourteen months ago, H.G. 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. 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 H.G. learned the news of the cancer's recurrence.

Section 1: Pain policy, barriers and addiction

Pain policy at VA

The overall goal of the Veterans Health Administration (VHA) Directive on Pain Management is to develop “a comprehensive, multicultural, integrated, system-wide approach to pain management.” Its specific objectives include prompt pain assessment, as well as management, monitoring, and educational approaches.

The current VHA Directive can be found in the appendix or accessed at www.va.gov/pain_management/docs/VHAPainDirective.pdf. In addition to VHA Directive, multiple resources concerning pain activities at VA are available at VHA Pain Management website (<http://www.va.gov/painmanagement/>). This website includes clinical, educational, and administrative resources. It also includes instructions for accessing a pain management listserv for VA clinicians involved in pain management.

Barriers

Slide 7

Barriers ...

- Not important
- Poor assessment
- Lack of knowledge
- Fear of
 - addiction
 - tolerance
 - adverse effects

Slide 8

... Barriers

- Regulatory oversight
- Veterans unwilling to report pain
- Veterans unwilling to take medication

In 1998, Veterans Health Administration (VHA) established a pain management strategy. Despite this, there remain barriers to full implementation of comprehensive pain management. Overall, challenges in pain management are not from lack of effective

treatments, but rather from systemic problems with delivering effective treatments.^{3,4,5} Specific examples of barriers include:

- beliefs by clinicians that pain management is not important;
- poor assessment techniques;
- inadequate dissemination of available knowledge;
- fears of addiction, tolerance, and adverse effects; and
- inappropriate regulatory oversight.

Individual care plans should encourage Veterans to report their pain and take into account each Veteran’s willingness to take medication. In addition to adequate knowledge, health care systems and institutions may need to change in order to facilitate the implementation of the knowledge.

One specific barrier, the fear of addiction, is discussed in the section below.

Addiction, tolerance and physical dependence

The perception that the administration of opioids 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. Below, we describe some of these distinctions.⁶

Slide 9

Addiction

- Psychological dependence
- Compulsive use
- Continued use in spite of harm
- Consider
 - true addiction vs. under-treatment of pain
 - behavioral/family/psychological disorder
 - drug diversion

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. Care must be taken to differentiate a true addiction (also known as substance use disorder) from pseudoaddiction due to undertreatment of pain, behavioral/family/psychological dysfunction, and drug diversion with criminal intent.

Slide 10

Tolerance

- Reduced effectiveness of a given dose over time
- More medication to get the same effect
- Not clinically significant with chronic dosing
- If dose is increasing, suspect disease progression

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 not the most common cause clinically of worsening pain if opioids are used routinely. When increasing doses are required of opioids are required for pain relief, suspect worsening disease rather than pharmacologic tolerance. Doses may remain stable for long periods if the pain stimulus remains unchanged.

Slide 11

Physical dependence

- A process of neuro adaptation
- Abrupt withdrawal may → abstinence syndrome
- If dose reduction required, reduce by 50% q 2–3 days
avoid antagonists

Physical dependence results from neurophysiologic changes that occur in the presence of 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, psychosis, and/or hallucinations.

Physical dependence is not the same as addiction nor is it necessarily evidence of addiction. Its presence does not mean that opioids cannot be discontinued. If the pain stimulus decreases or disappears, opioid doses can usually be reduced by 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 may be necessary to treat distressing symptoms.⁷

Substance abuse and pain

Slide 12

Substance users

- Can have pain too
- Treat with compassion
- Protocols, contracting
- Consultation with pain or addiction specialists

Since Veterans 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.⁸

Veterans who have a history of, or who are currently engaged in substance abuse will need special care to ensure that they receive effective pain control in a way that is safe for both the Veteran and caregivers. This can be a daunting task and is best accomplished by using the skills of the interdisciplinary team, supplemented with assistance from the mental health, substance abuse and palliative care specialists. Substance abuse is not an excuse for inadequate pain control. In addition, the concept of suffering includes psychosocial and existential issues that are almost always at the root of the problem of substance abuse. A holistic approach to treatment is more like to adequately relieve physical pain by improving adherence to the treatment plan at the same time addressing the totality of suffering.

Ethical issues and pain

Slide 13

Ethical issues and pain

- The duty to treat pain
- Placebos

Two major ethical issues in pain treatment are: 1) the duty to treat pain and 2) the use of placebos.

The duty to treat pain

A number of commentators and professional societies have recognized the treatment of pain as a fundamental human right.⁹ In 1998, the bioethicist and physician Edmund Pellegrino recognized, “The availability, accessibility, and effectiveness of modern methods of pain control make it morally mandatory for every physician to be knowledgeable in the use of analgesics.”¹⁰ We would expand Pellegrino's point to include all clinicians, not only physicians.

While this module focuses on physical pain, pain happens to a whole person. The concept of ‘total pain’ first conceptualized by Dame Cicely Saunders, emphasizes that there may be non-physical causes of pain as well. Psychological factors (e.g., depression, PTSD), social factors (e.g., familial estrangement), and spiritual or existential factors (e.g., loss of meaning in life) can all exacerbate pain.¹¹ Pain is more likely to be treated successfully when these sources of suffering are also addressed.

Placebos

In the past, some clinicians have advocated the use of placebos to see if patients are “really in pain.” While 30% or more of patients may experience some response to placebos,^{12,13} there is no ethical basis for the use of placebos to assess or treat pain. Examples of groups that have issued statements to this effect include: The American Pain Society (APS),¹⁴ and the American Nursing Association (ANA).¹⁵

Section 2: Pathophysiology, assessment and management

Pathophysiology

Slide 14

Pathophysiology

- **Acute pain**
identified event, resolves days–weeks
usually nociceptive
- **Chronic pain**
cause often not easily identified,
multifactorial
indeterminate duration
nociceptive and / or neuropathic

Wolf C.J. Ann Intern Med. 2004.

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.¹⁶

Acute and chronic pain may be conceptualized as either **nociceptive** or **neuropathic**. The type of predominating pain can usually be inferred through the description, and physical findings. The International Association for the Study of Pain (IASP) has published definitions and made them available on their website.¹⁷

Nociceptive pain

Slide 15

Nociceptive pain

- Direct stimulation of intact nociceptor
- Transmission along normal nerves
somatic or visceral
- Tissue injury apparent
- Management
opioids
adjuvant / coanalgesics

Wolf C.J. Ann Intern Med. 2004.

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 divided into somatic and visceral pain.

Somatic pain, mediated by the somatic nervous system, innervates skin, bone, and muscle. Pain localization is usually precise and is often described as sharp, aching, or throbbing.

Visceral pain, mediated by the autonomic nervous system, generally involves internal structures such as the gastrointestinal tract. It may be difficult to localize and is sometimes characterized as crampy.

Neuropathic pain

Slide 16

Neuropathic pain ...

- Disordered peripheral or central nerves
- Compression, transection, infiltration, ischemia, metabolic injury
- Varied types
 - peripheral, deafferentation, complex regional syndromes

Zhuo, 2007.

Slide 17

... Neuropathic pain

- Pain may exceed observable injury
- Described as burning, tingling, shooting, stabbing, electrical
- Management
 - opioids
 - adjuvant / coanalgesics often required

Neuropathic pain is defined as *a primary lesion or dysfunction of the nervous system*. It can be peripheral or central. The nerves themselves may be damaged by ischemia, compression, infiltration, metabolic injury, medication effects or transection. Neuropathic pain may be due to disease such as diabetic neuropathy or post-herpetic neuralgia. Or it may be due to an injury such as chemotherapy or other toxin-induced neuropathy.

Neuropathic pain also involves 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 “facilitation.”¹⁸ Although the nerves themselves are undamaged, abnormal signaling 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 sensory state partially explains the clinical phenomenon of allodynia, 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.¹⁹ Thus, some neuropathic pain can develop from repetitive nociceptive pain

without structural damage to the nerves themselves. Veterans' descriptors are helpful clues to neuropathic pain and many include such terms as: burning, tingling, numbness, shooting, or electric-like.

Although neuropathic pain may respond well to opioids, adjuvant analgesics (serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, anticonvulsants, antiarrhythmics) may be required in combination with opioids to achieve relief.

Assessment

The gold standard of assessing pain is to believe the Veteran. For cognitively intact Veterans assess location, radiation, quality, intensity, factors that exacerbate or relieve the pain, and temporal aspects such as whether it is continuous or paroxysmal, as well as its duration and meaning to the Veteran. Whether the pain is directly or indirectly related to illness, therapy, or unrelated should be assessed. These insights may help elucidate the pathophysiology that underlies the pain and may also direct the therapy.^{20,21}

Quantify pain severity by asking the Veteran to rate the pain. Examples of scales to quantify pain experience include:

- a 0-10 scale where 10 is the worst pain someone has ever felt and 0 is no pain at all, or
- a visual analog scale where a Veteran indicates pain with a mark on a 100 mm line delimited by descriptors such as “no pain” and “worst possible pain” at either end.

The important concept in pain assessment is that for an individual Veteran a consistent scale be used so that the response to therapy can be monitored. Whereas acute pain is accompanied by signs of adrenergic stimulation such as tachycardia and hypertension, chronic pain is usually not associated with these autonomic responses. Thus, lack of observable vital sign changes does not rule out pain or indicate a Veteran is malingering.

There has been an effort to incorporate pain as the “Fifth Vital Sign at VA and elsewhere.” This recognizes the importance of pain management in daily care, however measurement and documentation may not change clinician behavior and change patient outcomes.²² Nonverbal and cognitively-impaired Veterans often cannot use the visual analog scales to report their pain levels.²³ Pain assessment in nonverbal patients is challenging, but tools and scales have been developed to help assess and record pain behaviors in this population.²⁴

Slide 18

Pain assessment

- Location
- Radiation
- Quality
- Severity
- Timing

Management

Slide 19

Management

- Don't delay for investigations or disease treatment
- Unmanaged pain → nervous system changes
 amplify pain
- Treat underlying cause (e.g., radiation for a neoplasm)

While the diagnosis and treatment of the underlying cause of any pain is important, there is no reason to delay the use of analgesics until a definitive diagnosis is found. It is not appropriate to withhold pain management until investigations and treatment of the underlying disease are complete, or other criteria are met. Unrelieved pain can have a devastating psychological effect on the individual and family. It can also lead to changes in the nervous system that may amplify pain.²⁵

Pharmacologic approaches to pain management

In 1986, the World Health Organization (WHO) developed a 3-step conceptual model to guide the management of cancer pain.^{26,27,28} The WHO pain ladder is used as a guide for the development of pain policy in many countries. Depending on the severity of the pain, start management at the corresponding step. For mild pain (1–3/10 on a numerical 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 Veteran with severe pain may need to have step 3 opioids right away.



WHO Pain Ladder

Step 1 analgesics

The non-opioid 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 adjuvant 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.²⁹ Chronic doses greater than 3 g in 24 hr or acute doses greater than 4 g in 24 hr are not recommended for this reason. Hepatic disease or heavy alcohol use increases the risk of hepatic toxicity further which may warrant further reduction in dose.³⁰

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs, including aspirin) are effective step 1 analgesics. They may also be useful adjuvants. They work, at least in part, by inhibiting cyclo-oxygenase (COX), the enzyme that converts arachidonic acid to inflammatory prostaglandins. COX has also been found in spinal cord neurons where it appears to play a role in setting up the dysfunctional signaling pattern involved in neuropathic pain.³¹

There are several classes of NSAIDs. Some Veterans respond better to one class than to another and serial trials of different agents may be needed to find one that is efficacious. Extended-release products may enhance adherence. Intravenous formulations are also available for one NSAID (ketorolac).

NSAIDs can have significant adverse effects that include gastropathy, renal insufficiency, and platelet inhibition.³² These may be explained, in part, by the fact that cyclo-oxygenase exists in 2 forms a constitutive form, COX-1, and a form that is inducible

under conditions of inflammation, COX-2. There are COX-2 selective NSAIDs, e.g., celecoxib, and non-selective NSAIDs, e.g., ibuprofen. Whereas renal insufficiency is a risk of both non-selective and COX-2 selective NSAIDs, the risk of gastropathy and platelet inhibition is decreased with COX-2 selective NSAIDs.³³ It is possible to ameliorate the gastropathy associated with non-selective NSAIDs by using protective agents such as proton pump inhibitors.³³ In addition, the COX-2 selective agents may provide less analgesia than nonspecific NSAIDs and there have been concerns related to increased cardiac complications.³⁴ While NSAIDs can be effective analgesics, their potential side effects (including GI toxicity and renal toxicity) should be monitored closely in frail and debilitated Veterans with multiple comorbidities. The American Geriatrics Society recently issued a position statement discouraging the use of NSAIDs in the elderly due to adverse effects.³⁵

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 pain control. Opioid receptors affect the intracellular levels of potassium and calcium modifying a nerve's threshold for firing and propensity to release neurotransmitters.³⁶

Opioids are the first-line therapy for moderate to severe pain in nociceptive, neuropathic, and mixed pain syndromes. However, for severe neuropathic pain, opioids alone are often insufficient³⁷ and are most often combined with adjuvant analgesics as will be discussed later.

Step 2 opioids available as combination medications include codeine, oxycodone and hydrocodone. The opioids combined with acetaminophen or ibuprofen are limited in dosage due to their non-opioid components. For example, combinations containing acetaminophen 500 mg should be limited to 6-8 tablets per day due to the risk of hepatotoxicity.

The step 2 medications also include tramadol. Tramadol, in addition to having weak activity at opioid receptors, also affects norepinephrine and serotonin levels.³⁸ Although the exact mechanism is unknown, the non-opioid effects of tramadol may mediate its efficacy for neuropathic pain.³⁹ 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.⁴⁰ However, there is a greater potential for precipitating seizures even at therapeutic dosages. Although this risk is likely only 1%, it is increased among people with multiple comorbidities.⁴¹ Tramadol has a ceiling effect at 300 mg/day for its analgesic effect. In general cost, side effects and the ceiling effect make tramadol a less attractive option for pain management in the palliative care setting.

The step 3 pure opioids (morphine, hydromorphone, oxycodone) do not share this limitation, and in fact they have no theoretical ceiling for efficacy or end-organ toxicity.^{42,43} They can be titrated to effect limited only by adverse effects.

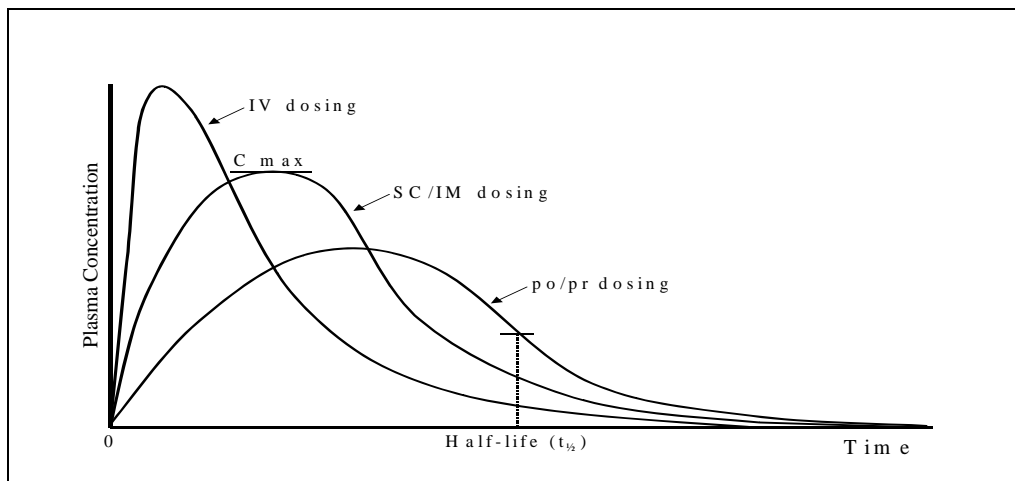
Overall, you do not need to go up pain ladder in a stepwise fashion: if a Veteran is having moderate or severe pain, you should go directly to steps 2 or 3 for analgesic relief.

Opioid pharmacology

Opioids all follow first-order pharmacokinetics, reaching peak plasma concentration (C_{max}) approximately 60 to 90 minutes after oral, enteral feeding tube, or rectal administration; 30 minutes after subcutaneous or intramuscular injection (IM injections are not recommended due to the pain related to the injection and the existence of effective routes such as subcutaneous with similar efficacy); and 6 minutes after intravenous injection.^{44,45}

The analgesia associated with each opioid has a half-life ($t_{1/2}$) that depends both on the rate of liver metabolism and renal clearance. Except for methadone, which has a half-life that ranges from 15 to 40 hours, opioids (codeine, hydrocodone, hydromorphone, morphine, and oxycodone) have effective half-lives of approximately 3 to 4 hours when renal clearance is normal.⁴⁶ 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.

Diagram: pharmacologic dosing curves after a single opioid dose (curves vary based on the route of administration)



Routine oral dosing: Immediate-release opioid preparations

For immediate-release oral opioids, give the medication q 3- 4 hours. For example, an opioid-naïve Veteran who is in significant pain could be started on morphine 10-15 mg orally scheduled every 4 hours. Given this dosing, the total 24-hour dose of morphine a Veteran would receive is 90 mg. The best possible pain control for the dose will be

achieved within a day (once steady state has been reached). Provide the Veteran with access to PRN doses of the same medication should breakthrough pain occur.

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 breakthrough (rescue) medication used during the previous 24 hours. If pain is severe and uncontrolled after 1 or 2 doses, increase the dose more quickly. While it is important to adequately control pain as quickly as possible in elderly Veterans with debility and /or co-morbid conditions, careful assessment of side effects is also important. Observe the Veteran closely until the pain is better controlled.

Extended-release opioid preparations

Extended-release oral opioids are formulated to release medication 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 is usually achieved within 2 to 4 days (once steady state has been reached). Doses should not be adjusted more frequently than once every 2 to 4 days. Fentanyl patches are a unique extended release opioid applied topically with exchange of patches every 72 hours.

To convert from an immediate-release to an extended-release formulation, calculate the total 24 hour dose of an opioid and then divide evenly into q 8, q 12 or q 24 hrs. For example, a Veteran receiving 10 mg of immediate-release morphine every 4 hours would receive 30 mg extended-release morphine q 12 hrs.

Bolus effect

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Bolus effect

- Swings in plasma concentration
 - drowsiness 1/2-1 hr post ingestion
 - pain before next dose due
- Move to
 - extended-release preparation
 - continuous SC, IV infusion

As opioid levels in the bloodstream change, some Veterans may experience drowsiness 1/2 to 1 hour after a dose of medication as the plasma level peaks followed by pain before the next dose as the plasma level falls. This ‘bolus effect’ can usually be resolved by switching to an extended-release formulation or a continuous parenteral infusion to reduce the swings in the plasma concentration after each dose. The bolus effect 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 generally avoid these pitfalls by smoothing out peak and trough extremes.

Breakthrough dosing

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Breakthrough dosing

- Use immediate-release opioids
 - 10% of 24 hr dose
 - offer after C_{max} reached
 - PO / PR ≈ q 1 h
 - SC, IM ≈ q 30min
 - IV ≈ q 10–15min
- Do not use extended-release opioids

Transitory flares of pain, called ‘breakthrough pain,’ can occur both at rest and with 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 used 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.

For each breakthrough dose, offer 10% 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. Therefore, morphine, oxycodone, codeine, and hydromorphone can be administered every 1 hour if administered orally, or possibly less frequently for frail Veterans, every 30 minutes if administered subcutaneously, and every 15 minutes if administered intravenously.

As an example, in the Veteran 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.

Initial dosing for constant pain

Initial dosing varies depending whether the Veteran is opioid-naïve or is already receiving opioids.

For a Veteran who is opioid naive and in significant pain, start dosing with 5 to 20 mg of immediate-release oral morphine liquid concentrate or tablet q 2 hrs. 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 hr dose of extended-release morphine to prescribe routinely, or give the total dose once daily (depending on the product). When an extended release dose is determined, prescribe a breakthrough

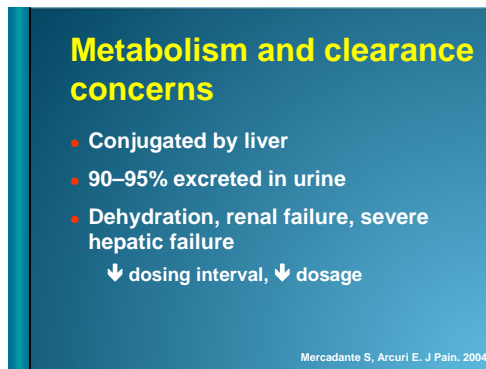
dose of immediate-release morphine using liquid concentrate or tablet. The breakthrough dose should be 10% of the 24-hour dose q 1 hr po prn.

For a Veteran who is currently receiving an opioid and is in pain, the dose can be increased 50-100%.

If a Veteran requires more than 2 to 4 breakthrough doses in a 24-hour period on a routine basis in addition to an extended-release formulation, consider increasing the dose of the extended-release preparation. Determine the total amount of morphine used (routine + breakthrough) and administer the total in divided doses q 12 hr or q 24 hr (depending on the product). Recalculate the breakthrough dose so that it is always 10% of the total daily dose and offer it q 1 hr PO.

Metabolism and clearance concerns

Slide 23



Metabolism and clearance concerns

- Conjugated by liver
- 90–95% excreted in urine
- Dehydration, renal failure, severe hepatic failure
 - ↓ dosing interval, ↓ dosage

Mercadante S, Arcuri E. J Pain. 2004.

Opioids are hepatically metabolized and renally excreted. For example, the liver conjugates morphine to metabolites, morphine-6-glucuronide and morphine-3-glucuronide that can still cause toxic side effects, and that must be cleared renally.⁴² There is evidence that other opioids such as codeine, hydrocodone, hydromorphone, and fentanyl also have active metabolites.

When dehydration or acute or chronic renal failure occurs, the dosing interval for morphine should be increased or the dosage size decreased to avoid excessive accumulation of active drug.

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

Not recommended

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Not recommended

- **Meperidine**
poor oral absorption
normeperidine is a toxic metabolite
- **Propoxyphene**
no better than placebo
toxic metabolite at high doses

There are a number of available analgesics that are not recommended because of limited efficacy and adverse effects.

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, myoclonus, and seizures.⁴⁷ Consequently, meperidine is to be avoided in a palliative care setting. The one setting in which it may still have a role is in the treatment of rigors.

Propoxyphene is typically administered at doses that produce relatively little analgesia. Dose escalation can lead to accumulation of a toxic metabolite.⁴⁸ It was taken off the US market in November, of 2010, but there may still be patients taking it. They should be switched to one of the opioids discussed earlier in this module.

Pain poorly responsive to opioids

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Pain poorly responsive to opioids

- **If dose escalation → adverse effects**
alternative
route of administration
opioid ('opioid rotation')
adjuvants
use a non-pharmacological approach

If dose escalation does not lead to analgesia and results in adverse effects, there are a few options. Opioid rotation, in which a different opioid is used, may be effective. For reasons that are not clear, some patients are more sensitive to one opioid over another.⁴⁹ A psychostimulant such as methylphenidate, may help counter act sedation. An adjuvant analgesic may help reduce the amount of opioid required. Finally, consider a non-pharmacologic approach.

One rare adverse effect that is increasingly recognized is the possibility of opioid-induced hyperalgesia. This almost always occurs in patients who are receiving very high level doses of opioids. When this occurs increased opioid dosage results in paradoxical hyperalgesia. It is usually manifest as intense allodynia. Its mechanism is thought to be abnormal responses of NMDA receptors. Its treatment involves tapering of the opioid and consideration of methadone which has NMDA blocking properties.^{50,51} Opioid-induced hyperalgesia is a clinical syndrome and the diagnosis can only be made retrospectively when there is improvement with dose reduction or more commonly opioids rotation.

Ongoing assessment

Slide 26

Ongoing assessment

- Increase analgesics until pain relieved or adverse effects unacceptable
- Be prepared for sudden changes in pain
- Driving is safe if
pain controlled, dose stable, no adverse effects

If pain control is inadequate, the analgesic dose 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 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 Veterans will also experience less pain spontaneously or with changes in the underlying cause of pain. If the pain decreases or disappears, analgesic doses can be reduced or discontinued.

Although evidence is limited, if Veterans 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.⁵²

Alternative routes of administration

Slide 27

Alternative routes of administration

- Enteral feeding tubes
- Transmucosal
- Rectal
- Transdermal
- Parenteral
- Intraspinal

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

Slide 28

Enteral feeding tube

- Provides alternative for bypassing gastroesophageal obstructions
- Delivers medications to stomach or upper intestine

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.

Slide 29

Transmucosal

- Allows administration of more concentrated immediate-release liquid preparations

particularly effective in Veterans unable to swallow or who are dying

Transmucosal (buccal mucosal) administration of more concentrated immediate-release liquid preparations provides a similar alternative, particularly in the Veteran who is unable to swallow, although transmucosal absorption is variable. This route is particularly effective for Veterans who are dying.

Oral transmucosal fentanyl citrate is a formulation of fentanyl in a candy matrix on a stick as well as a transmucosal lozenge, which is approved for the treatment of breakthrough pain.⁵³ More recently, intranasal fentanyl has shown even more rapid onset than oral.⁵⁴ This formulation is expensive however, and is not part of the formulary for VA. Almost all Veterans could use one of the more cost-effective formulations, such as morphine concentrate 20 mg/ml, with the same effect.⁵⁵ Although morphine concentrate may not be absorbed directly from the sublingual region, is only partially absorbed from the sublingual region. This may also result in some GI absorption.

Slide 30

Rectal administration

- Immediate or extended release behave pharmacologically like related oral preparations
- May be effective if oral intake suddenly not possible
- Many Veterans and families do not like

Rectal administration of immediate or extended-release rectal preparations behave pharmacologically like related oral preparations.⁵⁶ This route may be effective if oral intake is suddenly not possible, although many Veterans and families do not like this route for continuous administration.

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Transdermal patch

- Fentanyl
 - peak effect after application \approx 24 hrs
 - patch lasts 48–72 hrs
 - ensure adherence to skin

Gourlay GK, et al. Pain. 1989.

Transdermal patches are an effective route of administration for Veterans receiving stable opioid dosing. Currently, transdermal patches are only manufactured for fentanyl. Transdermal patches behave 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 and do not lift off with bathing or sweating.

Slide 32

Topical analgesic creams

- Even simple procedures may be painful

Topical analgesic creams should always be considered as even simple procedures such as venipuncture may be painful. Open wounds may also be a source of considerable pain, particularly during dressing changes, and topical analgesia with morphine has been shown to be effective.⁵⁷

Slide 33

Parenteral administration

- SC, IV, IM
 - bolus dosing q 3–4 h
 - continuous infusion
 - easier to administer
 - more even pain control

Parenteral administration is useful in selected Veterans, especially as inpatients. When renal function is normal, provide routine parenteral doses every 1-2 hours and adjust the dose every 12 to 24 hours once steady state is reached. In situations of an acute pain crisis, such as pathologic fracture, a Veteran may need IV pain medication administered every 10-15 minutes for several doses to achieve adequate analgesia. If the IV route is going to be used for any length of time, and the Veteran is cognitively intact, a patient controlled analgesia (PCA) system can be effective. A PCA can be programmed to deliver both a continuous infusion and a breakthrough dose. Doses are effectively the same for subcutaneous or intravenous delivery. If a parenteral route will be used for some time, continuous infusions produce a more constant plasma level, reduce the risk of adverse effects and are better tolerated by the patient.

While intravenous infusions may be preferable if intravenous access is already established, 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 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.

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

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Intraspinal opioids

- Epidural
- Intrathecal

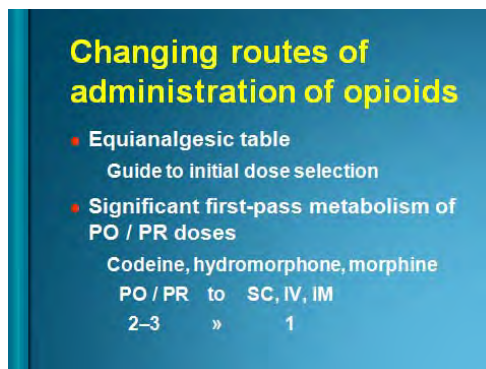
Intraspinal opioids (epidural or intrathecal) may be useful in selected Veterans who have pain in the lower part of their body, or pain that is poorly responsive to routine systemic opioid therapy. Intraspinal delivery allows much lower doses of opioids to be used and consequently reduces systemic side 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. A specialist who is knowledgeable about their specific indications and pharmacology, and who is skilled in their delivery, is usually required to administer them. This topic is addressed in **Section 3** of this module.

It is important that all staff be familiar with VA formulary as it relates to available analgesics. While not all opioid formulations on the market will be available in VA, there are a wide range of opioid formulations to meet the Veterans' need for pain control. Consultation with your pharmacist, palliative care specialist, pain specialist as needed ensures the best pain management for the Veteran. If required the clinician can request non-formulary medication or contract services outside of VA for Veterans who have particularly difficult to control pain syndromes.

Equianalgesic conversions

Changing routes of administration of opioids

Slide 35



Changing routes of administration of opioids

- Equianalgesic table
Guide to initial dose selection
- Significant first-pass metabolism of PO / PR doses

Codeine, hydromorphone, morphine

PO / PR	to	SC, IV, IM
2-3	»	1

PO / PR (mg)	Analgesic	SC / IV / IM (mg)
15	Hydrocodone	-
3	Hydromorphone	1
15	Morphine	5
10	Oxycodone	-
150	Meperidine	50

When changing routes of administration, an equianalgesic table is a useful guide for initial dose selection. Equivalent dosing recommendations represent consensus from limited available evidence, so they are guides only, and individual Veterans may require doses to be adjusted. Tables, such as the one indicated here, are clinically convenient and easy to use. Large inter-patient variability makes firm ratios elusive. A clinical guide for changing opioid analgesics such as this one, adapted with permission from Levy, can be used: on the horizontal axis are routes of administration and on the vertical axis are different opioids.⁵⁸ 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, 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 50 mg of oral morphine per 24 hours.^{59,60}

Meperidine is not recommended for pain control. However, clinicians may be consulted to assist with pain management for a Veteran who is receiving meperidine, the conversion is provided to assist the clinician in converting the Veteran to an appropriate opioid. Codeine is an inactive pro-drug and must be converted to the active form before it has its analgesic effect. Since up to 5% of the population lack the enzyme to convert codeine to the effective form it is not recommended for routine use.

Table 1: Equianalgesic dosing

ORAL/RECTAL DOSE (MG)	ANALGESIC	PARENTERAL DOSE (MG)
15	Hydrocodone	–
15	Morphine	5
10	Oxycodone	–
3	Hydromorphone	1
–	Fentanyl	0.05
150	Meperidine	50

Methadone has a long and variable half-life.^{61,62,63} Although the half-life usually approaches a day or longer, the effective dosing interval for analgesia is usually as frequently as q 8 hr or q 6 hr. However, given that it may have significant and delayed respiratory depressive side effects, monitor carefully for side effects. Given the variability of methadone’s half-life and its unexpected potency, it is prudent to increase the maintenance dose only every 4 to 7 days, or less often, if possible. Recently, concern regarding drug-drug interactions and the potential of methadone to cause prolonged QT interval with possible cardiac complications have increased the need for careful monitoring.^{64,65} Although the majority of these cases are not in the palliative care setting, caution should be used, especially in patients with prognoses of months or years. However, methadone still has unique benefits, such as NMDA receptor activity, that may outweigh the risk. Methadone should not be abandoned since the use of this agent can have significant positive impact on some Veteran's quality of life that is not achieved with other opioids. Since equianalgesic ratios are variable, experts recommend starting at 5-10 mg tid and increasing every 4-7 days.

Opioid cross-tolerance

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Changing opioids

- **Cross-tolerance**
start with 50–75% of published equianalgesic dose
more if pain, less if adverse effects
- **Methadone**
start with 10–25% of published equianalgesic dose

Ripamonti C, Zecca E, Bruera E. Pain. 1997.

In some Veterans, pharmacologic tolerance to an opioid may reduce the analgesic effect. Opioid rotation may be appropriate to improve analgesia. This should be done with care since tolerance to the opioid in use, will often be marked relative to other opioids.⁶⁶ 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 Veteran.⁶⁷ Incomplete cross-tolerance is likely due to differences in the molecular structure of each opioid and the way each interacts with the Veteran’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 Veteran. Start 50-75% of the published equianalgesic dose of the new opioid to compensate for incomplete cross-tolerance and individual variation, particularly if the Veteran has controlled pain. If the Veteran has moderate to severe pain, do not reduce the dose as much. If the Veteran has had adverse effects, reduce the dose more.

Adverse effects of opioids

Slide 38

Opioid adverse effects

<ul style="list-style-type: none">• Common <ul style="list-style-type: none">ConstipationDry mouthNausea / vomitingSedationSweats	<ul style="list-style-type: none">• Uncommon <ul style="list-style-type: none">Bad dreams / hallucinationsDysphoria / deliriumMyoclonus / seizuresPruritus / urticariaRespiratory depressionUrinary retention
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Opioids have many possible adverse effects; some are common, and some are not.^{68,69,70,71,72} If unmanaged, they may be a reason for non-adherence.⁷³

Opioid allergy

Slide 39

Opioid allergy

- Nausea / vomiting, constipation, drowsiness, confusion
adverse effects, not allergic reactions
- Anaphylactic reactions are the only true allergies
bronchospasm
- Urticaria, bronchospasm can be allergies; need careful assessment

Many people believe that opioid-induced nausea/vomiting, constipation, drowsiness, or even confusion are allergic reactions. However, these are not allergic reactions; they are adverse effects. Anaphylactic or true allergic reactions to opioids are rare.⁷⁴ Urticaria and bronchospasm could be direct opioid effects or signs of allergy. Sudden onset of breathlessness or other signs of anaphylaxis should be taken seriously, and the offending opioid replaced with another from a different class. As a life-threatening emergency, anaphylaxis should be treated rapidly with epinephrine and steroids.

Urticaria/pruritus

Slide 40

Urticaria/pruritus

- Mast cell destabilization by morphine, hydromorphone
- Treat with routine long-acting, non-sedating antihistamines
 - fexofenadine 60 mg PO bid or higher
 - diphenhydramine, loratadine or doxepin

In some patients, opioids produce urticaria or pruritus.⁷⁵ 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; loratadine 10 mg PO qd or doxepin 10–30 mg PO nightly. If pruritus persists despite treatment, opioid rotation should be considered.

Constipation

Slide 41

Constipation ...

- Common to all opioids
- Opioid effects on CNS, spinal cord, myenteric plexus of gut
- Easier to prevent than treat
- Diet usually insufficient
- Bulk forming agents not recommended

Slide 42

... Constipation

- Stimulant laxative
- Combine with a stool softener
- Prokinetic agent
- Osmotic laxative
- Other measures

Constipation secondary to opioid administration is common. It is primarily the result of opioid effects on the central nervous system, spinal cord, and myenteric plexus of the gut that, in turn, reduce gut motor activity and increase stool transit time. The colon has more time to desiccate its contents, leaving hard stools that are difficult to pass. Other factors,

such as dehydration, poor food intake and other medications, may make the problem worse.

Tolerance to constipation may develop very slowly, if at all.^{62,63} It requires anticipatory and ongoing management. Dietary interventions alone, e.g., increase 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 may also counteract opioid-induced constipation. If constipation persists, some Veterans will benefit from the addition of an osmotic agent, such as milk of magnesia, polyethylene glycol, lactulose, or sorbitol, to increase the stool's moisture content.

Nausea/vomiting

Slide 43

Nausea/vomiting ...

- Onset with start of opioids
tolerance develops within days
- Prevent or treat with dopamine-blocking antiemetics
prochlorperazine 10 mg q 6 h
haloperidol 1 mg 6 h
metoclopramide 10 mg q 6 h

Slide 44

... Nausea/vomiting

- Other antiemetics may also be effective
- Alternative opioid if refractory

Many Veterans 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. Opioid-induced nausea may be related to stimulation of the chemoreceptor trigger zone, the vestibular apparatus, and to delayed gastric emptying. Nausea typically responds well to antiemetics that target the chemoreceptor trigger zone

(anti-dopaminergic agents), the vestibular apparatus (antihistamines) and that target gastric motility (metoclopramide).

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. Metoclopramide is often a good first choice since it works at both the chemoreceptor trigger zone and stimulates gastric emptying.

In elderly Veterans, care is necessary in the use of the dopamine blocking agents in populations with Parkinson's disease, Parkinson-like syndrome and Lewy body dementia as these agents can result in severe reactions with worsening of stiffness, delirium and hallucinations.⁷⁶ Many older Veterans may have relatively mild symptoms and not have a formal diagnosis, but may have a reaction when the problem is uncovered by dopamine-blocking agents.

Sedation

Slide 45

Sedation ...

- Onset with start of opioids
distinguish from exhaustion due to pain
tolerance develops within days
- Complex in advanced disease

Slide 46

... Sedation

- If persistent, alternative opioid or route of administration
- Psychostimulants may be useful
methylphenidate 5 mg q am and q noon,
titrate

Veterans sometimes complain of feeling sedated or mentally clouded after beginning an opioid. 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.

For Veterans with advanced disease, mental clouding and excessive somnolence are often issues even in the absence of opioids, particularly when they have multiple comorbid medical conditions, medications, and declining function. Pain may, in fact, be the

primary stimulant keeping them alert. Once pain is managed, the Veteran's 'natural' level of sedation may become apparent.

If sedation occurs, encourage Veterans and families to clearly articulate their goals (see EPEC for Veterans Module 1: Goals of Care) and develop a pain management plan that balances alertness and pain control to suit the individual. Some Veterans 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, e.g., methylphenidate 5 mg q am and q noon and titrate, particularly if the opioid is providing effective analgesia.⁶¹

Delirium

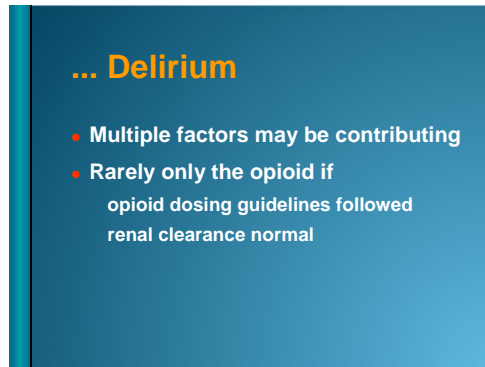
Slide 47



Delirium ...

- **Presentation**
 - confusion, bad dreams, hallucinations
 - restlessness, agitation
 - myoclonic jerks, seizures
 - depressed level of consciousness
 - respiratory depression

Slide 48



... Delirium

- **Multiple factors may be contributing**
- **Rarely only the opioid if**
 - opioid dosing guidelines followed
 - renal clearance normal

The onset of confusion, bad dreams, hallucinations, restlessness, agitation, myoclonic jerks, a depressed level of consciousness, or seizures suggests delirium. One or more of these adverse effects may present gradually, e.g., in the Veteran who is not passing much urine and is accumulating opioid due to decreased intake, dehydration, or rapidly developing sepsis. Delirium is almost always multi-factorial. Stopping an opioid abruptly may induce a pain crisis and/or withdrawal symptoms with worsening of the delirium. Review for the reversible cause of delirium in addition to opioids, treatment of the delirium and discussion of goals of care with patient and family such that if a terminal delirium had developed such that control of both pain and delirium symptoms in the last hours of living are accomplished (see EPEC for Veterans Module 5: Psychological Symptoms).

Respiratory depression

Slide 49

Respiratory depression

- Opioid effects differ for patients treated for pain
 - loss of consciousness precedes respiratory depression
- Management
 - identify, treat contributing causes
 - if unstable vital signs, naloxone 0.1-0.2 mg IV q 1-2 min

Many clinicians have an exaggerated view of the risk of respiratory depression when using opioids to relieve pain.⁶¹

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 Veteran 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 Veteran who takes too many extra doses of opioid will fall asleep and stop pushing the button before respiratory depression occurs.

If respirations are compromised (respiratory rate is < 6/min), naloxone may be necessary if it is the goal of care to keep the Veteran 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 Veteran is alert. As the effective plasma half-life is short (10 to 15 minutes) because of naloxone’s higher affinity for lipids, monitor the Veteran closely every few minutes for recurrent drowsiness. If drowsiness recurs, repeat dosing as required until the Veteran is no longer compromised.

Adjuvant analgesics

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Adjuvant analgesics

- Medications that supplement primary analgesics may themselves be primary analgesics use at any step of WHO ladder

Adjuvant analgesics are *medications that, when added to primary analgesics, further improve pain control*. They may also be primary analgesics, e.g., tricyclic antidepressants for postherpetic neuralgia. They can be added at any step in the WHO ladder.

The medications 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.

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Gabapentin

- Anticonvulsant
 - 100 mg PO daily to tid, titrate increase dose q 1–3 d
 - usual effective dose 900–1800 mg / day; max may be > 3600 mg / day
 - minimal adverse effects
 - drowsiness, tolerance develops within days
 - starting dose in frail elderly can be as low as 100 mg Qhs for three days

Backonja, et al. JAMA. 1998.

Gabapentin has emerged as the most common initial therapy for neuropathic pain. Studies have shown it to be efficacious in the control of post herpetic neuralgia and diabetic neuropathic pain.^{77,78} The most troublesome side effect is fatigue.^{77,78} This symptom can usually be controlled by careful titration. Doses as low as 300 mg per day may be effective, but often 900 mg per day is the typically effective dose. If necessary, doses can be gradually increased to a level of 3600 mg/day (dosed tid). Other anticonvulsants such as carbamazepine and valproic acid are effective but require monitoring of levels and monitoring for signs of organ toxicity.⁷⁹ Newer anticonvulsants

such as lamotrigine also seem to be effective in early clinical studies.⁸⁰ If one anticonvulsant is not effective, it is rational to try another one.

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Pregabalin

- Newer anticonvulsant approved for the treatment of neuropathic pain
- Turned to when gabapentin is not effective / has intolerable side effects

Pregabalin is a newer anticonvulsant that is approved for the treatment of neuropathic pain.^{81,82} It is often turned to when gabapentin is not effective or has intolerable side effects. Pregabalin is usually started at 75 mg po tid and can be increased to 150 mg tid if not effective.⁸³

Antidepressants

Slide 53

Tricyclic antidepressants ...

- Amitriptyline
10–25 mg PO nightly, titrate (escalate q 4–7 d)
analgesia in days to weeks
- Desipramine
10–25 mg PO q hs, titrate
tricyclic of choice in seriously ill

Max, et al. N Engl J Med. 1992.

Slide 54

... Tricyclic antidepressants

- Amitriptyline
monitor plasma drug levels
> 100 mg / 24h for risk of toxicity
anticholinergic adverse effects prominent, cardiac toxicity
sedating limited usefulness in frail, elderly
- Avoid tricyclics in older adults

The tricyclic antidepressants (TCAs) are the best studied antidepressant class that show efficacy in neuropathic pain. The pain effect has been separated from the antidepressant effect and doses effective for neuropathic pain are usually lower than doses needed for depression.⁸⁴ Amitriptyline has been most extensively studied. It blocks reuptake of serotonin and norepinephrine and appears to also block the NMDA receptor.⁸⁵ However,

amitriptyline also has the most anticholinergic side effects of the TCAs. This fact can be used advantageously if younger Veterans have trouble sleeping at night. Often, however, the anticholinergic effects of dry mouth, sedation, constipation, and urinary retention are obstacles to use and thus great caution should be used with older adults. It is prudent to avoid amitriptyline in older adults and instead use desipramine and nortriptyline as these two are effective for neuropathic pain and have less anticholinergic activity.⁸⁶ 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 and duloxetine) show some evidence of efficacy for neuropathic pain but they have not been well studied.⁸⁷ Studies have shown selective serotonin reuptake inhibitors (SSRIs) to be much less effective.⁷²

Corticosteroids

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Corticosteroids

- **Dexamethasone**
 - long half-life (>36 hrs), dose once / day
 - minimal mineralocorticoid effect
 - doses of 2-20 + mg / day
- **Adverse effects**
 - steroid psychosis
 - proximal myopathy
 - other long-term adverse effects

Corticosteroids are potent anti-inflammatory agents useful in both nociceptive and neuropathic pain. Reducing inflammation and peritumor edema can relieve 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 the corticosteroid of choice because of its minimal mineralocorticoid effects and thus decreased risk of salt and fluid retention.^{88,89} Corticosteroids may also enhance pain control through the creation of a sense of euphoria. Most of the complications (proximal muscle weakness, osteoporosis and immunosuppression of steroid use are long-term sequelae 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.⁹⁰ 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.⁹¹

NMDA-receptor antagonists: Ketamine, dextromethorphan, and methadone

The N-methyl-D-aspartate (NMDA) receptor may be involved in the spinal neural circuitry that leads to a neuropathic pain state resistant to higher 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.⁹²

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 and thus methadone is generally started at 5-10 mg tid and titrated slowly every 4-7 days. There is very little consistency in ratios of methadone to morphine.⁹³ In general, these medications should be used in consultation with a pain or palliative care specialist.

Anesthetics

Anesthetics that are nonselective inhibitors of sodium channels have also been utilized to treat neuropathic pain. Parenteral lidocaine has been found to have efficacy in diabetic neuropathy, trigeminal neuralgia, and other severe neuropathic pain syndromes.^{94,95}

Typically effective serum levels range from 2-5 mg/liter. However, there are little data in the palliative care population. Oral anesthetics/antiarrhythmics such as mexiletine have also been used with success in neuropathic pain.⁹⁴ Monitoring for cardiac toxicity may be necessary in patients with longer life expectancies. Topical lidocaine patches have been approved for use in postherpetic neuralgia.⁹⁶ They have also been shown to have efficacy in the treatment of low back pain.⁹⁷

Alpha-2-adrenergic agonists

Alpha-2-adrenergic agonists such as clonidine can also be effective adjuvant analgesics for both nociceptive and neuropathic pain.⁹⁸ They act at the spinal cord in two ways.

First, they act on the same neurons as opioids in the cord and lead to the same intracellular events but act through a different receptor.⁹⁹ Thus, it is likely that they can enhance the nociceptive effects of opioids. Second, alpha-2-adrenergic agonists decrease sympathetic outflow involved with neuropathic pain.¹⁰⁰ For the same reason, clonidine is thought to alleviate PTSD symptoms and may be an effective medication in patients with hyperarousal and neuropathic pain.¹⁰¹ Clonidine can be given orally or transdermally or delivered intraspinally. Systemic delivery may be limited by side effects of lethargy, dry mouth, and hypotension.

Section 3: Specific types of pain and their management

Specific pain types: Bone pain

Slide 56

Bone pain ...

- Constant, worse with movement
- Metastases, compression or pathological fractures
- Prostaglandins from inflammation, metastases
- Rule out cord compression

Blum, et al. Oncology. 2003.

Slide 57

... Bone pain ...

- Management
 - opioids
 - NSAIDs
 - corticosteroids
 - bisphosphonates

Slide 58

... Bone pain

- Management
 - radiopharmaceuticals
 - external beam radiation
 - orthopedic interventions
 - external bracing

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. Cord compression should always be considered when there is new-onset significant back pain in the Veteran with metastatic cancer (especially in breast, prostate or lung cancer). Approaches to bone pain include medications, radiation, and radiopharmaceuticals.

Bone pain is associated with inflammation. NSAIDs and/or corticosteroids are important components of the treatment of this pain syndrome. Bisphosphonates have also been used for bone pain in the setting of cancer, although they take 1-2 weeks to take effect.

Bisphosphonates, like pamidronate, inhibit osteoclast activity, thus stabilizing bone and through an unknown mechanism can also relieve bone pain. They are effective for both lytic and sclerotic bone lesions.¹⁰² Typical dosing of pamidronate is 90 mg intravenously over 2 hours every month. Although calcitonin is sometimes advocated for bone pain, the most recent Cochrane review did not support its use.¹⁰³

Treatment for an isolated bone lesion is radiation therapy.¹⁰⁴ Near 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. Radiopharmaceuticals such as strontium-89 and samarium 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.¹⁰⁵

Specific pain types: Pain from bowel obstruction

Slide 59

Pain from bowel obstruction ...

- Constipation
- External compression
- Bowel wall stretch, inflammation
- Definitive intervention
 - relief of constipation
 - surgical removal or bypass

Slide 60

... Pain from bowel obstruction

- Management
 - opioids
 - corticosteroids
 - NSAIDs
 - anticholinergic medications
 - e.g., scopolamine
 - octreotide

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. Malignant bowel obstruction is most commonly seen in colon and ovarian cancers. The pain due to bowel obstruction is frequently described as constant, sharp, and cramping. It may be associated with considerable bloating,

distention, gas, or even nausea/vomiting. Relief of constipation or surgical removal or bypass of external blockages may be definitive; in some Veterans, the obstruction will be irreversible (see EPEC for Veterans Module 6a: GI Symptoms).

Most Veterans 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. These include corticosteroids to reduce inflammation and anticholinergic medications, e.g., scopolamine, or somatostatin analogs like octreotide to reduce the volume of fluid entering the intestine, thus relieving the bowel wall stretch and the pain.¹⁰⁶

Interventional pain management

Interventional approaches to pain management can help the subgroup of Veterans who have pain that is refractory to medical interventions or for whom medical interventions result in intolerable side effects. They include intraspinal therapy, nerve blocks, and celiac plexus blocks. Other nerve blocks are also available for specific nerve involvement.¹⁰⁷

Intraspinal therapy

The two most common ways of giving intraspinal therapy are by the epidural or intrathecal route.^{108,109,110,111,112,113} The reduced systemic exposure to opioids can help relieve refractory effects such as constipation, nausea, and sedation. Epidural catheters are commonly used to produce mostly a regional effect 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.¹¹⁴

Epidural therapy provides pain relief in the small number of Veterans in whom it is appropriate.^{115,116} However, complications such as dislodged catheters, pain on injection, bruising, bleeding, and infection can occur.

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 connected to a small catheter tunneled to the site of spinal entry, usually the L1-2 interspace. Veterans 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 infusion.

Relative contraindications to intraspinal therapy include active infection, coagulopathy or heparin, or spinal cord compression that would prevent diffusion of the drugs. Veterans

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 blocks

A celiac plexus block (CPB) is used to treat the severe, progressive pain of upper abdominal cancers (most commonly pancreas, stomach, liver, gallbladder, and colon) that fails to respond to conventional treatment. A satisfactory response is seen in up to 87% of pancreas cancer patients, with relief of pain as well as of anorexia and constipation.¹¹⁷

The celiac plexus partly innervates all the abdominal structures including the diaphragm, stomach, adrenal glands, liver, spleen and intestines. 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 CT or fluoroscopic guidance, via ultrasound guidance during endoscopy or intraoperatively. Serious complications are rare with experienced hands.^{118,119} More common and predictable complications such as hypotension and postural hypotension, require careful postop observation, and transient post block diarrhea (due to sympathetic block) which remits in several days.

CPB should be considered early in the course of the disease, as the data shows a high success rate with CPB when done earlier in the disease course. CPB success is operator-dependent. This means that clinicians with more experience and skill are more likely to be successful in the relief of pain. CPB is underutilized and should be considered in almost all Veterans at the time of diagnosis of pancreas cancer.

Non-pharmacologic pain management techniques

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Non-pharmacologic ...

- Neurostimulation
TENS, acupuncture
- Physical therapy
exercise, heat, cold

Slide 62

... Non-pharmacologic

- **Psychological approaches**
 - cognitive therapies (relaxation, imagery, hypnosis)
 - biofeedback
 - behavior therapy, psychotherapy
- **Complementary therapies**
 - massage
 - art, music, aroma therapy

While pharmacologic approaches may be the mainstay of pain management, clinicians 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.¹²⁰ Members of the interdisciplinary team (IDT), who may be more familiar with non-pharmacologic interventions, can frequently assist the clinicians to identify and refer Veterans appropriately. An engaged IDT will best serve the needs of the Veteran and their family in the palliative care setting. This is particularly true of those Veterans with the most severe and refractory pain syndromes.

Summary

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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 Veterans. 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 Veterans’ 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 basis for the use of placebos to assess or treat pain.

WHO pain ladder

4. A 3-step model to guide analgesic choice depending on the severity of the Veteran'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. 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 (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

7. In general, the oral route is the least invasive, most convenient route for administering opioids on a routine basis.
8. If the pain is continuous, or nearly so, start with an appropriate dose of an immediate-release opioid routinely q 4 hr around the clock.
9. 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, 50-100% for severe to uncontrolled pain.
10. Once the continuous pain is controlled, switch to an extended-release preparation to simplify routine dosing and increase the chance of Veteran adherence.

Addiction, tolerance and physical dependence

11. 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.
12. Pharmacologic tolerance is defined as the reduced effectiveness of a given dose of medication over time. When increasing doses are required, suspect worsening disease rather than pharmacologic tolerance.
13. 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 of administration and changing opioids

14. Incomplete cross-tolerance is likely caused by subtle differences in the molecular structure of each opioid and the way each interacts with the Veteran'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 Veteran. Start with 50-75% of the published equianalgesic dose of the new opioid if pain is otherwise well controlled.

Neuropathic pain

15. For burning, tingling pain with or without numbness, tricyclic antidepressants or gabapentin are the most widely used adjuvant medications.
16. Desipramine has fewer anticholinergic adverse effects and is the tricyclic antidepressant of choice, particularly in elderly and frail Veterans. 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.

Bone pain

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

Steroids

18. 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.

Appendices

Appendix 1: VHA Pain Directive 2003-021

Pain management

Purpose: The Veterans Health Administration (VHA) Directive provides policy and implementation guidance for the improvement of pain management consistent with VHA National Pain Management Strategy and compliance with generally accepted Pain Management Standards of Care.

Background: VHA National Pain Management Strategy was initiated November 12, 1998, and established Pain Management as a national priority. The overall objective of the national strategy is to develop a comprehensive, multicultural, integrated, system-wide approach pain management that reduces pain and suffering and improves quality of life for Veterans experiencing acute and chronic pain associated with a wide range of injuries and illnesses, including terminal illness.

Implications: It is VHA policy that VHA's National Pain Management Strategy and the ongoing work of VHA National Pain Management Program office and Coordinating Committee will be used to guide the development of local policies related to pain management.

Specific Objectives:

The updated VHA National Pain Management Strategy aims to:

1. Establish expectations for attitudes, knowledge and skills in pain management in primary, secondary and tertiary care.
2. Create system-wide VHA care standards for pain management, appropriate to setting and professional role that reduce suffering and improves quality of life.
3. Ensure that pain assessment is performed in an appropriately timely, regular, and consistent manner along the continuum of care from acute to chronic pain in all VHA settings.
4. Ensure that pain treatment is prompt and strives to achieve pain management objectives along the continuum of care from acute to chronic pain in all VHA settings.
5. Include patients and families as active participants in pain management.
6. Provide for appropriate level and frequency of monitoring for improvement in outcomes of pain management including pain control, physical and psychosocial function, quality of life and complications.
7. Provide for an interdisciplinary, multimodal approach to pain management that emphasizes optimal pain control and improved function and quality of life.

Appendix 2: Problem solving cases

The following cases illustrate common issues in pain management. 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/hr 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?

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?

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

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 extended-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?

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/hr 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
 $6 \text{ mg/hr} \times 24 \text{ hours} = 144 \text{ mg/d IV morphine}$
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 hr 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 hr PRN

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: extended-release morphine, 45 mg PO bid

Remember breakthrough dose

Sig: 5–15 mg PO immediate-release morphine q 1 hr PRN

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 hr RTC

6. Don't forget breakthrough

Sig: Hydromorphone, 1–2 mg PO q 1 hr PRN

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

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

$$\frac{960 \text{ mg/d IM meperidine}}{X \text{ mg/d oral hydromorphone}} = \frac{50 \text{ mg IM meperidine}}{3 \text{ mg oral hydromorphone}}$$

3. Solve for X

$$X = 57.6 \text{ mg/d PO hydromorphone}$$

4. Decide on schedule (divide by 6 for q 4hr 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

30 mg PO q 4 h

Calculating the answer

1. Figure out total daily dose of opioid

3 tablets x 5 mg oxycodone/tablet x 8 = 120 mg/d oxycodone

2. Set up ratio from the table

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

3. Solve for X

$$X = 180 \text{ mg/d oral morphine}$$

4. Decide on schedule

Sig: Morphine, 30 mg PO q 4 hr 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, 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

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 extended-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 0.6mg/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 two 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.

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