

PART I: PRINCIPLES OF PAIN MANAGEMENT

General Principles of Pain Assessment

- The process of pain management starts with adequate assessment of the pain
- The absence of appropriate assessment is the leading reason for poor pain management
- A comprehensive pain assessment addresses the pain's:
 - Nature
 - Cause
 - Underlying pathophysiology
 - Personal context:
 - Psychological
 - Social
 - Spiritual
 - Practical issues

General Principles of Pain Management. A comprehensive pain management strategy includes:

- Use of appropriate interventions
 - Pharmacologic
 - Nonpharmacologic
- Education of the patient, family, and all caregivers about the plan
- Ongoing assessment of treatment outcomes
- Regular review of the plan of care
- Use of other members of the interdisciplinary team, including:
 - Nurses
 - Social workers
 - Pharmacists
 - Chaplains
 - Physiotherapists
 - Occupational therapists
 - Child life specialists
- Flexibility is essential—successful plans are tailored to the individual patient and family
- Willingness to ask for help from colleagues with more expertise when the plan is not effective at controlling the patient's pain

Pain Pathophysiology. Acute vs. Chronic Pain

- Acute pain
 - Is usually related to an easily identified event or condition.
 - Usually resolves within a period of days or weeks
 - Is usually nociceptive
- Chronic pain
 - May or may not be related to an easily identified pathophysiologic phenomenon
 - May be multifactorial
 - May be present for an indeterminate period

Nociceptive Pain

Nociceptive pain is thought to be related to either direct stimulation of intact mechanical, chemical, or thermal nociceptors or the transmission of electrical signal along normally functioning nerves

- Nociceptive pain is presumed to involve:
 - Direct stimulation of intact mechanical, chemical, or thermal nociceptors

- Transmission of electrical signals along normally functioning nerves
- It can be subdivided into 2 subgroups:
 - Somatic pain
 - Involves skin, soft tissue, muscle, and bone
 - Due to stimulation of the somatic nervous system
 - Patients may describe this as sharp, aching, and/or throbbing pain that is easily localized
 - Visceral pain
 - Involves cardiac, lung, GI and GU tracts
 - Results from stimulation of the autonomic nervous system
 - Patients may find this pain difficult to describe or localize
- Nociceptive pain generally responds well to opioids and/or coanalgesics

Neuropathic Pain

- Neuropathic pain is presumed to result from disordered function of the peripheral or central nervous system (CNS) due to any of many potential causes, including:
 - Compression
 - Transection
 - Infiltration
 - Ischemia
 - Metabolic injury
- There are varied subtypes, including:
 - Those sustained by peripheral processes (eg, painful neuroma)
 - Those sustained by CNS processes (e.g., phantom pain)
 - Complex regional pain syndromes (previously referred to as causalgia or reflex sympathetic dystrophies)
- These pains can also be classified by syndrome (e.g., malignant plexopathy, painful polyneuropathy, phantom pain, postherpetic neuropathy, etc)
- Patients tend to describe neuropathic pain with words like burning, tingling, numbness, shooting, stabbing, or electric-like feelings
- The intensity of pain involved may exceed observable injury
- Although neuropathic pain may respond well to opioids, adjuvant analgesics (tricyclic antidepressants, anticonvulsants, antiarrhythmics, etc) are often required in combination with opioids to achieve adequate relief

Additional Information about Pain Pathophysiology

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

Pharmacologic Approaches to Pain Management: General Guidelines and Considerations

- Do not delay use of analgesics
 - While the diagnosis and treatment of the underlying cause of any pain is an important part of the medical treatment plan, there is no reason to delay the use of analgesics
 - It is not appropriate to withhold pain management until the investigations and treatment of the underlying disease are complete, or other criteria are met.
 - Although research is not yet conclusive, unmanaged pain may lead to changes in the nervous system that could reduce its responsiveness to treatment
 - Equally important, unrelieved pain can have a devastating psychological effect on the individual and family
- If possible, treat the source of the pain as well as the pain itself. Consider the use of primary therapies directed against the source of pain (e.g., radiation for a neoplasm), if it is:
 - Feasible
 - Consistent with the goals of care
- Do NOT use placebos

- Some physicians have advocated the use of placebos to see if patients are really in pain
- While 30% to 70% of patients will appear to experience some response, ***there is no ethical or scientific basis for the use of placebos to assess or treat pain***
- Agencies and organizations that have issued position statements to this effect include:
 - Agency for Health Care Policy and Research (AHCPR)
 - American Pain Society (APS)
 - Joint Commission on Accreditation of Healthcare Organizations (JCAHO)
 - American Nursing Association (ANA)

The WHO 3-Step Model for Pharmacological Approaches to Pain Management

History and Overview of the WHO Conceptual Model

- In 1986, the World Health Organization (WHO) developed a 3-step conceptual model to guide the management of cancer pain
- This model provides a simple, well-tested approach for the rational selection, administration, and titration of a myriad of analgesics
- Today, there is worldwide consensus favoring its use for the medical management of all pain associated with serious illness
- Depending on the severity of the pain, start management at the corresponding step:
 - For mild pain (1–3/10 on a numerical analogue scale), start at step 1
 - For moderate pain (4–6/10), start at step 2
 - For severe pain (7–10/10), start at step 3
- It is not necessary to traverse each step sequentially; a patient with severe pain may need to have step 3 opioids right away
- Effective treatment requires a clear understanding of the pharmacology, potential impact, and adverse effects associated with each of the analgesics prescribed, and how these may vary from patient to patient. Information about the prescribing of individual analgesics are summarized in the Medication Tables

Step 1: Nonopioid Analgesics. Ceiling Effects of Nonopioid Analgesics

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

Acetaminophen Uses:

- Acetaminophen is an effective step 1 analgesic
- It may also be a useful coanalgesic in many situations, including headache

Acetaminophen Mechanism of Action:

- 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

Acetaminophen Risks/Adverse Effects:

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

Nonsteroidal Anti-inflammatory Drugs

Uses

- Nonsteroidal anti-inflammatory drugs (NSAIDs, including aspirin) are effective step 1 analgesics

- They may also be useful coanalgesics
- Effective for bone and inflammatory pain

Mechanism of Action

- NSAIDs work, at least in part, by inhibiting cyclo-oxygenase, the enzyme that converts arachidonic acid to prostaglandins
- All NSAIDs inhibit cyclo-oxygenase (COX) but vary in COX-2 selectivity

Classes of NSAIDs

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

Risks/Adverse Effects

- NSAIDs can have significant adverse effects
 - There are substantial differences among NSAID classes as to the likelihood of adverse effects.
 - This may in part be due to their relative COX-2 selectivity
- Potential adverse effects that can occur with any of the nonselective medications, irrespective of the route of administration, include:
 - Gastropathy
 - Renal failure
 - Inhibition of platelet aggregation
- Some drugs, however, such as ibuprofen, nabumetone, and others appear to be relatively safer
- Gastric cytoprotection with misoprostol or omeprazole may be needed in patients with significant risk factors, particularly those with:
 - A history of gastric ulcers or bleeding
 - Current nausea/vomiting
 - Protein wasting (cachexia)
 - The elderly
- To minimize the risk of renal failure, including papillary necrosis, ensure adequate hydration and good urine output in all patients on NSAIDs
- The nonselective medications are relatively contraindicated in the setting of significant preexisting renal insufficiency
- If bleeding is a problem, or coagulation or platelet function is impaired, NSAIDs may be contraindicated
- The new COX-2 selective inhibitors lack these toxicities and may be indicated in high-risk patients

Steps 2 and 3: Opioid Analgesics

Opioid Pharmacology

- Opioids (codeine, hydrocodone, hydromorphone, morphine, oxycodone, etc.) all follow first-order kinetics and pharmacologically behave very similarly
- They reach their peak plasma concentration (C_{max}) approximately:
 - 60 to 90 minutes after oral (including enteral feeding tube) or rectal administration
 - 30 minutes after subcutaneous or intramuscular injection
 - 6 minutes after intravenous injection
- They are eliminated from the body in a direct and predictable way, irrespective of the dose
 - The liver first conjugates them
 - Then the kidney excretes 90% to 95% of the metabolites
 - Their metabolic pathways do not become saturated

- Each opioid metabolite has a half-life ($t_{1/2}$) that depends on its rate of renal clearance
- When renal clearance is normal, codeine, hydrocodone, hydromorphone, morphine, oxycodone, and their metabolites, all have effective half-lives of approximately 3 to 4 hours
- When dosed repeatedly, their plasma concentrations approach a steady state after 4 to 5 half-lives.
- Thus, steady-state plasma concentrations are usually attained within a day

Routine Oral Dosing—Immediate-Release Preparations

- If an immediate-release oral opioid is selected and the pain is continuous, or nearly so, give the medication q 4h
- The best possible pain control **for the dose** will be achieved within a day (once steady state has been reached)
- Provide the patient with access to prn doses of the same medication that can be used should breakthrough pain occur (**rescue dose**: the term “rescue” dose refers to an extra dose of analgesics that is given for additional relief when transitory flares of pain occur (“breakthrough” pain) and last more than several minutes)
- If pain remains uncontrolled after 24 hours:
 - Increase the routine dose by:
 - 25% to 50% for mild to moderate pain
 - 50% to 100% for severe to uncontrolled pain
 - Or by an amount at least equal to the total dose of rescue medication used during the previous 24 hours
 - Do not wait any longer. Delays only prolong the patient’s pain unnecessarily
- If pain is severe and uncontrolled after 1 or 2 doses (e.g., crescendo pain), increase the dose more quickly. Follow the patient closely until the pain is better controlled
- Guidelines for initial dosing of morphine are given in the Resources section

Routine Oral Dosing—Extended-Release and Long-Half-life Opioid Preparations

- Increasingly, oral extended- or sustained-release formulations of the commonly used opioids are becoming widely available for routine usage
- Less frequent dosing with either these preparations or opioids with long half-lives (e.g., methadone, $t_{1/2}$ » 12–24 hours, sometimes longer) is likely to improve patient compliance and adherence
- Extended- or sustained-release opioid tablets:
 - Are specifically formulated to release medication in a controlled fashion over 8, 12, or 24 hours (depending on the product)
 - Must be ingested whole, not crushed or chewed
- Extended-release capsules containing time-release granules can be either:
 - Swallowed whole
 - Or the granules can be mixed with fluid and flushed down a feeding or other tube into the upper GI tract
- Best possible pain control for the dose will be achieved within 2 to 4 days (once steady state has been reached)
- Doses should not be adjusted any more frequently than once every 2 to 4 days
- Methadone has a long and variable half-life
 - Although the half-life usually approaches a day (sometimes longer), the effective dosing interval for analgesia is usually at least q 8h; it is often q 6h and sometimes even q 4h
 - Given the variability of methadone’s half-life and the unexpected potency that this medication often demonstrates, it is prudent to increase the dose only q 4 to 7 days, or less often, if possible

Breakthrough Dosing

- Transitory flares of pain, called “breakthrough pain,” can be expected both at rest and during movement
- When such pain lasts for longer than a few minutes, extra doses of analgesics (“breakthrough” or “rescue” doses) will likely provide additional relief
- To be effective and to minimize the risk of adverse effects:
 - Consider an immediate-release preparation of the same opioid that is in use for routine dosing
 - Do not use extended-release opioids for rescue dosing. When methadone or transdermal fentanyl is used, it is best to use an alternative short-acting opioid, eg, morphine or hydromorphone, as the rescue dose. Oral immediate-acting fentanyl is also available
- For each breakthrough dose, offer 5% to 15% of the 24-hour dose

- As peak analgesic effect correlates with peak plasma concentration (C_{max}), a breakthrough dose can be offered once C_{max} has been reached
- As noted, codeine, hydrocodone, morphine, oxycodone, and hydromorphone all behave similarly
- An extra breakthrough dose can be offered once every:
 - 1 hour if administered orally (possibly less frequently for frail patients)
 - 30 minutes if administered subcutaneously (or intramuscularly)
 - 10 to 15 minutes if administered intravenously
- Longer intervals between breakthrough doses only prolong a patient's pain unnecessarily

Opioid Clearance Concerns: Renal Concerns

- Opioids and their metabolites are primarily excreted renally (90%–95%)
- Morphine has two principal metabolites:
 - Morphine-3-glucuronide
 - Morphine-6-glucuronide
 - Morphine-6-glucuronide is active and has a longer half-life than the parent drug morphine
- Consequently, when dehydration or acute or chronic renal failure impairs renal clearance, excessive accumulation of active drug must be avoided by either:
 - Increasing the dosing interval for morphine, or
 - Decreasing the dosage size
- If urine output is minimal (oliguria) or none (anuria):
 - Stop routine dosing and
 - Administer morphine only "as needed"
- This is particularly important when patients are dying
- This may not be as important for other opioids such as hydromorphone or fentanyl

Opioid Clearance Concerns: Hepatic Concerns

- Opioid metabolism is not as sensitive to hepatic compromise
- However, if hepatic function becomes severely impaired:
 - Increase the dosing interval or
 - Decrease the dose

Analgesics Not Recommended. Not all analgesics available today are recommended for acute or chronic dosing. The following are not recommended:

Meperidine

- Poor oral absorption
- 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
 - Produces significant adverse effects when it accumulates (eg, tremulousness, dysphoria, myoclonus, and seizures)
- The routine dosing of meperidine q 3h for analgesia:
 - Leads to unavoidable accumulation of normeperidine
 - Exposes the patient to unnecessary risk of adverse effects, particularly if renal clearance is impaired

Propoxyphene

- Propoxyphene is typically administered at doses that produce relatively little analgesia
 - No better than placebo
 - Low efficacy at commercially available doses
- Dose escalation could lead to accumulation of a toxic metabolite

Mixed Agonist-Antagonists

- The mixed opioid agonist-antagonists include:
 - Pentazocine
 - Butorphanol
 - Nalbuphine
 - Dezocine
- These should not be used in the patient already taking a pure agonist opioid such as:
 - Codeine
 - Hydrocodone
 - Hydromorphone
 - Methadone
 - Morphine
 - Oxycodone
- If used together, competition for the opioid receptors may cause a withdrawal reaction
- Further, agonist-antagonists are not recommended as routine analgesics, as their dosing is limited by a ceiling effect
- The use of pentazocine and butorphanol is associated with relatively high risk of psychotomimetic adverse effects

Special Concerns in Pain Management: Addiction

- The perception that the administration of opioid analgesics for pain management causes addiction is a prevalent myth that inhibits adequate pain control
- Confusion about the differences between addiction, tolerance, and physical dependence is in part responsible
- Addiction, as the term is now used, is a complex phenomenon involving:
 - Psychological dependence on drugs
 - Behavioral syndrome characterized by:
 - Compulsive drug use
 - Continued use, despite harm
 - Care must be taken to differentiate a true addiction (substance use disorder) from:
 - Pseudo addiction due to under treatment of pain
 - Behavioural/family/psychological dysfunction
 - Drug diversion with criminal intent
- To manage pain effectively, physicians will need to educate patients, families, and other professionals about the inappropriate fear of addiction
 - Opioids by themselves do not cause psychological dependence
 - Addiction is a rare outcome of pain management when there is no history of substance abuse

Pharmacologic Tolerance

- Pharmacologic tolerance is the reduced effectiveness of a given dose of medication over time
- Tolerance to side effects is observed commonly and is favorable
- Tolerance to analgesia is rarely significant clinically when opioids are used routinely
- Doses may remain stable for long periods if the pain stimulus remains unchanged
- When increasing doses are required, suspect worsening disease rather than pharmacologic tolerance

Physical Dependence

- Physical dependence is the result of neurophysiological changes that occur in the presence of exogenous opioids
- Similar outcomes occur in the presence of exogenous hormones and other medications (beta-blockers, alpha-2 agonists, etc)
- Abrupt opioid withdrawal may result in an abstinence syndrome characterized by:
 - Tachycardia
 - Hypertension
 - Diaphoresis
 - Piloerection
 - Nausea and vomiting

- Diarrhea
- Body aches
- Abdominal pain
- Psychosis and/or hallucinations
- Physical dependence is NOT:
 - The same as addiction
 - Evidence for addiction
- Its presence does not mean that opioids cannot be discontinued
 - If the pain stimulus decreases or disappears, opioid doses usually can be reduced in decrements of 50% or more every 2 to 3 days, and finally stopped
 - If the dose is lowered too quickly and abstinence symptoms occur distressing symptoms may be settled with:
 - A transient increase in the opioid dose,
 - Treatment with clonidine, or
 - A small dose of a benzodiazepine (e.g., lorazepam)

Pain Management among Patients with Substance Abuse Histories

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

Pain That Responds Poorly to Routine Opioid Therapy

- More sophisticated adverse effect therapy, such as a psychostimulant, may help sedation
- An alternate route of administration (e.g., intraspinal opioid)
- Switch to an alternative opioid ("opioid rotation")
- An adjuvant analgesic (e.g., NSAID) may help reduce the amount of opioid required
- Nonpharmacologic approaches

Ongoing Assessment in Pain Management

- If pain control is inadequate, the dose of analgesics should be increased until either:
 - Pain relief is achieved, or
 - Unacceptable adverse effects occur
- In contrast with acetaminophen and the NSAIDs, there is no maximum dose of a pure agonist opioid
- If adverse effects become intolerable, effective pain control without the same adverse effects may be achieved through:
 - An alternative analgesic
 - An alternative route of administration
- Some patients will also experience less pain spontaneously or with changes in their underlying cause
- If the pain decreases or disappears, analgesic doses may need to be reduced or discontinued
- Driving is safe for patients who:
 - Have good pain control on stable doses of an opioid
 - Are not experiencing any adverse effects (especially drowsiness)

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