Pain Management

Pain is a subjective, unpleasant, sensory, and emotional experience associated with actual or potential tissue damage or described in terms of such damage.
It may be classified as acute, chronic or cancer pain.

Nociceptive pain (Adaptive pain)

- Nociception (also nocioception or nociperception) is the sensory nervous system's response to certain harmful or potentially harmful stimuli.
- Nociceptive pain or ***acute pain*** is either somatic (arising from skin, bone, joint, muscle, or connective tissue) or visceral (arising from internal organs, e.g., the large intestine).
- Stimulation of free nerve endings (nociceptors) leads to the sensation of pain. Release of bradykinins, prostaglandins, histamine, interleukins, tumor necrosis factor α (TNF-α), serotonin, and substance P may sensitize and/or activate nociceptors.
- A descending CNS system also controls pain transmission. This system originates in the brain and can inhibit synaptic pain transmission at the dorsal horn. Important neurotransmitters here include endogenous opioids, serotonin, norepinephrine, and γ-aminobutyric acid.

Maladaptive pain (Pathophysiologic pain)

Pathophysiologic pain is often described in terms of ***chronic pain***. It results from damage or abnormal functioning of nerves in the CNS or PNS.
Pain circuits sometimes rewire themselves anatomically and biochemically, resulting in chronic pain, hyperalgesia or allodynia.
Examples: postherpetic neuralgia, diabetic neuropathy, fibromyalgia, irritable bowel syndrome, chronic headaches, and some non-cardiac chest pain.

Treatment

- Goals of treatment are to minimize pain, maximize functioning, and provide reasonable comfort and quality of life at the lowest effective analgesic dose.
- With chronic pain, goals may include rehabilitation and resolution of psychosocial issues.
- The elderly and the young are at higher risk for under-treatment of pain because of communication limitations.

Nonopioid agents

- Treatment is initiated with the most effective analgesic with the fewest side effects. So, nonopioids are often preferred over the opioids for mild to

moderate pain. The ***salicylates*** and ***NSAIDs*** reduce prostaglandins, thereby decreasing the number of pain impulses received by the CNS.

- NSAIDs may be particularly useful for cancer-related bone pain and chronic low back pain.
- NSAIDs examples: ibuprofen, ketoprofen, naproxen, etodolac, mefenamic acid, diclofenac (Na^+ and K^+), ketorolac. Selective COX-2 inhibitors include meloxicam (at low dose) and celecoxib.
- Salicylates include aspirin, diflunisal, lysine acetylsalicylate, etc.
- The *salicylate salts* cause fewer gastrointestinal side effects than *aspirin* and do not inhibit platelet aggregation. Aspirin-like compounds should not be given to children or teenagers with viral illnesses (e.g., influenza or chickenpox), as Reye syndrome may result.
- **Paracetamol** has analgesic and antipyretic activity but little anti-inflammatory action. It is highly hepatotoxic on overdose.

Opioid agents

- ***Addiction*** is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving.
- In case of acute pain, analgesics are given initially around the clock. As the painful state subsides, as-needed schedules can be used.
- Around-the-clock administration is useful for management of chronic pain.
- Patients with severe pain may receive high doses of opioids with no unwanted side effects, but as pain subsides, patients may not tolerate even low doses.
- Most opioid-related itching or rash is due to histamine release and mast cell degranulation, and is not a true allergic response. When opioid allergies occur, an opioid from a different structural class may be cautiously tried.
- With ***patient-controlled analgesia*** (PCA), patients self-administer preset amounts of IV opioids via a syringe pump electronically interfaced with a timing device; thus patients can balance pain control with sedation.
- Administration of opioids directly into the CNS (epidural and intrathecal/ subarachnoid routes) is common for acute pain, chronic non-cancer pain, and cancer pain.
- Intrathecal and epidural opioids are often administered by continuous infusion or patient-controlled analgesia. They are safe and effective when given simultaneously with intrathecal or epidural local anesthetics such as *bupivacaine*. All agents administered directly into the CNS should be preservative-free.
- *Naloxone* is used to reverse respiratory depression, but continuous infusion may be required.

Morphine and Congeners (Phenanthrenes)

- Morphine is a first-line agent for moderate to severe pain. Morphine is often considered the opioid of choice to treat pain associated with myocardial infarction, as it decreases myocardial oxygen demand.
- Respiratory depression often manifests as decreased respiratory rate. The cough reflex is also depressed. Patients with underlying pulmonary dysfunction are at risk for increased respiratory compromise. Respiratory depression can be reversed by naloxone.
- Combining opioid analgesics with alcohol or other CNS depressants amplifies CNS depression and is potentially lethal.
- Morphine may cause orthostatic hypotension, and hypovolemic patients are at particular risk.

Meperidine and Congeners (Phenylpiperidines)

- ***Meperidine*** is less potent and has a shorter duration of action than morphine. It is not for long-term use. Its use should be avoided in the elderly and in those with renal dysfunction.
- ***Fentanyl*** is often used as an adjunct to general anesthesia. It is more potent and faster acting than meperidine. Transdermal fentanyl can be used for chronic pain requiring opioid analgesics.

Methadone and Congeners (Diphenylheptanes)

- Methadone has extended duration of action and ability to suppress withdrawal symptoms in ***heroin addicts***.
- With repeated doses, its analgesic duration of action is prolonged, but excessive sedation may result. Although effective for acute pain, it is used for chronic cancer pain and increasingly for chronic non-cancer pain.
- There are a growing number of methadone-related deaths, and cardiac arrhythmias may occur, especially with higher doses.

Opioid Agonist-Antagonist Derivatives

- Partial agonists and antagonists (e.g., pentazocine and nalorphine) compete with agonists for opioid receptor sites and exhibit mixed agonist–antagonist activity.
- They may have selectivity for analgesic receptor sites and cause less respiratory depression than opioids and have lower abuse potential than morphine. However, psychotomimetic responses (hallucinations and dysphoria), limited analgesic effect, and propensity to initiate withdrawal in opioid-dependent patients have limited their use.

Opioid Antagonists

Naloxone, ***naltrexone*** and ***nalmefene*** are pure opioid antagonist that binds competitively to opioid receptors, does not produce an analgesic response or opioid side effects. It is used to reverse the toxic effects of agonist and agonist–antagonist opioids.

Central Analgesic

Tramadol is indicated for moderate to moderately severe pain. It may be useful for treating chronic pain, especially neuropathic pain.

Tapentadol is indicated for moderate to severe acute pain and diabetic peripheral neuropathy.

They have side-effect profiles similar to those of other opioid analgesics. They may also increase the risk of seizures.

Adjuvant analgesics (Coanalgesics)

Chronic pain with a neuropathic component such as diabetic neuropathy often requires adjuvant analgesic therapy (coanalgesics), such as antidepressants (TCAs: ***nortriptyline***, SNRIs: ***duloxetine*** and ***venlafaxine***), anticonvulsants (***pregabalin*** and ***gapabentin***), or topically applied local anesthetics.

For cancer bone pain, strontium-89, samarium, corticosteroids, and bisphosphonates are useful adjuvants.

Regional analgesia

- Regional analgesia with ***local anesthetics*** (e.g. lidocaine, bupivacaine, tetracaine, mepivacaine) is useful for both acute and chronic pain.
- Anesthetics can be positioned by injection (i.e., in the joints, epidural or intrathecal space, nerve plexus, or along nerve roots) or applied topically.
- High plasma concentrations of local anesthetics can cause dizziness, tinnitus, drowsiness, disorientation, muscle twitching, seizures, and respiratory arrest. Cardiovascular effects include myocardial depression, heart block and hypotension.