PAIN AND ITS MANAGEMENT

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Pain

Definition:

- An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.
Types of Pain

- Acute pain
- Cancer pain
- Chronic non-malignant pain
Pain

- **Acute pain:** lasts less than 6 months, subsides once the healing process is accomplished.

- **Chronic pain is constant and prolonged,** lasting longer than 6 months, and sometimes, for life.
Major Categories of Pain

Classified by inferred pathophysiology:

1. **Nociceptive pain** (stimuli from somatic (arising from skin, bone, joint, muscle or connective tissue) and visceral structures (Arising from internal organs such as large intestine or pancreas))

2. **Neuropathic pain** (stimuli abnormally processed by the nervous system)
Pathophysiology of Pain

- 4 Basic Processes
  1. Transduction
  2. Transmission
  3. Perception
  4. Modulation
Ascending and Descending pain pathway
Pain receptors (nociceptors) in the skin are activated by tissue damage.

A signal travels up the peripheral nerve to the spinal cord.

Within the spinal cord, chemical messengers (neurotransmitters) are released. These activate other nerves that pass signals to the brain.

The thalamus relays the signals on to the somatosensory cortex (sensation), frontal cortex (thinking) and limbic system (emotional response).
Transduction

Sensation of Pain

Stimulation of free nerve endings known as nociceptors

Nociceptors with the capacity to distinguish between noxious and innocuous stimuli

Nociceptors, when exposed to mechanical (incision or tumor growth), thermal (burn), or chemical (toxic substance) stimuli, tissue damage occurs
Substances released by the damaged tissue facilitates the movement of pain impulse to the spinal cord.

The substances released from the traumatized tissue are:
- Prostaglandins
- Bradykinin
- Serotonin
- Substance P
- Histamine

Sensitize or activate the nociceptor
Sufficient amounts of noxious stimulation cause the cell membrane of the neuron (nervous system cell) to become permeable to sodium ions, allowing the ions to rush into the cell and creating a temporary positive charge.

Then potassium transfers back into the cell, thus changing the charge back to a negative one. With this depolarization and repolarization, the noxious stimuli is converted to an impulse. This impulse takes just milliseconds to occur.
Transmission

Receptor Activation

 Leads to action potential

 Transmitted along afferent nerve fibres to the spinal cord
- Afferent nerve fibre classified into A, B, C fibre
- Afferent A fibre further subdivided into alpha, beta, gamma and delta subfibres
- Nociceptive transmission takes place in A-delta and C fibre
- Stimulation of Myelinated A-delta fibre
  - Release Excitatory aminoacid, glutamate
  - Activate AMPA receptor (alpha amino 3 hydroxy 5 methylisoxazole 4 propionic acid)
  - Produce Bright, Well localised pain
- Stimulation of unmyelinated C fibre

- Release glutamate, glutamate, substance P, neurokinin A, somastatin, galanin and calcitonin gene related peptides (cGRP)

- Substance P activate neurokinin -1- receptor

- Increase excitability of spinal cord neuron

Dull, Poorly localized and persistent pain
Transmission

**Impulse**

- **Spinal cord**

- **Brain stem**

- **Thalamus**

- **Central structures of brain (cerebral cortex)**

  **Pain is processed.**
Perception of Pain

- End result of the neural activity of pain transmission

- Pain perception occurs in the cortical structures thalamus relays the signals onto
  
  Somatosensory Cortex (Sensation)
  Frontal Cortex (Thinking)
  Limbic system (Emotional response)
Modulation of Pain

- Placebo, Exercise, Comfort, Stress
- Nucleus Raphe Magnus
- Corticospinal Tract
- Vagal Stimulation
- Sympathetic Stimulation
- Dorsal Horn (B)
- Spinal Ganglion
- Substantia Gelatinosa (C)
- Spinothalamic Tract
- Spinal Cord

- Endorphins, Enkephalins, Clonidine, Opioids
- GABA
- Serotonin
- Midostalum
- Citalopram

- Dorsal Horn Cell

- Nociceptor
- Dynorphin
- Receptor
- GABA
- Inhibition
Modulation of Pain

- Changing or inhibiting pain impulses in the descending tract (brain ➔ spinal cord)

- Descending fibers also release inhibitory neurotransmitters such as norepinephrine, GABA, glycine, endorphin and enkephalins which have the capability of inhibiting the transmission of noxious stimuli by blocking substance P and other excitatory neurotransmitter activity on primary afferent fibres
Neuropathic Pain

- Abnormal processing of the impulses either by the peripheral or central nervous system

- May be caused by injury (amputation and subsequent phantom limb pain), scar tissue from surgery (back surgery high risk), nerve entrapment, or damaged nerves (diabetic neuropathy)
Management of Pain

Pharmacological treatment
Non-Pharmacological treatment
Pharmacological treatment

• Non Opioid Analgesics
• Opioid Analgesics
• Analgesic Adjuvants
Pharmacological treatment

- Acetaminophen
- NSAIDs
  - Non-selective COX inhibitors
  - Selective COX-2 inhibitors
- Opioids

- Analgesic Adjuvants
  - Antidepressants
  - Anticonvulsants
  - Corticosteroids
  - Antihistamine
  - Benzodiazepine
  - Substance P inhibitors
  - NMDA inhibitors
  - Amphetamine
Non-Pharmacological Therapy

- Exercise
- Physical methods
  - ice, heat, massage
- Cognitive-behavioral therapy
- Acupuncture
- TENS (Transcutaneous electrical nerve stimulation)
- Alternative therapies
  - relaxation, imagery
### NSAID’s

- **Salicylates:**
  - Acetylsalicylic acid
  - Diflunisal

- **Paraaminophenol:**
  - Acetaminophen

- **Fenamates:**
  - Meclofenamate
  - Mefenamic acid

- **Pyranocarboxylic acid:**
  - Etodolac

- **Acetic acid:**
  - Diclofenac

- **Propionic acid:**
  - Ibuprofen
  - Ketoprofen
  - Fenoprofen
  - Naproxen

- **Pyrrolizine Carboxylic acid:**
  - Ketorolac

- **COX-2- inhibitors:**
  - Celecoxib
  - Valdecoxib
Opioid Analgesics

- **Morphine like agonist:**
  - Morphine
  - Hydromorphone
  - Oxymorphone
  - Levorphanol
  - Codeine
  - Hydrocodone
  - Oxycodone
  - Meperidine like agonist:
    - Meperidine
    - Fentanyl

- **Agonist-Antagonist derivatives:**
  - Pentazocine
  - Butorphenol
  - Nalbuphine
  - Buprenorphine
  - Dezocine

- **Central Analgesics:**
  - Tramadol
## Analgesic adjuvants

<table>
<thead>
<tr>
<th>Classes</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic antidepressants</td>
<td>Amitriptyline, Desipramine, doxepin, imipramine</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine, phenytoin, clonazepam, valproate</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Alprazolam, lorazepam</td>
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<tr>
<td>Amphetamine</td>
<td>Dextroamphetamine</td>
</tr>
<tr>
<td>Antihistamine</td>
<td>Methylphenindate</td>
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<tr>
<td></td>
<td>hydroxyzine and promethazine</td>
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NSAID’s

• Except Acetaminophen, all the drugs prevent the formation of prostaglandins peripherally produced in response to noxious stimuli. Thereby decreasing the number of pain impulses received by CNS.
Acetaminophen

- Acetaminophen may scavenge hydroperoxides generated during arachidonic metabolism, and thus quench prostaglandin formation in the CNS (The hydroperoxides normally stimulate COX, causing positive feedback)
Opioid Analgesics

- Act by depressing pain impulse transmission at the spinal cord level by interacting with opioid receptors
  - Binding of opioids with its receptor cause decrease in calcium entry to the cell and allows for increased time of channels to remain closed and decreases the release of neurotransmitters
- Neurotransmitters are needed to continue the pain impulse from the spinal cord to the brain—opioids (narcotics) are effective analgesics because they block the release of neurotransmitters
Adjuvant Analgesics

- Local anesthetics, anticonvulsants relieve pain primarily by decreasing the sodium and potassium transfers at the neuron level, thereby slowing or stopping pain transmission.

- Corticosteroids, such as dexamethasone used for cancer pain, also interferes with the production of prostaglandins.
Antidepressants:
Cancer pain responds to antidepressants which interfere with the reuptake of serotonin and norepinephrine which increases their availability to inhibit noxious stimuli.

Substance P:
Substance P is involved in nociception, transmitting information about tissue damage from peripheral receptors to the central nervous system to be converted to the sensation of pain. It has been theorized that it plays a part in fibromyalgia. Capsaicin has been shown to reduce the levels of Substance P probably by reducing the number of C-fibre nerves or causing these nerves to be more tolerant. Thus, Capsaicin is clinically used as an analgesic and an inflammatory agent to induce pain associated with arthritis and many types of neuralgia. A role of substance P and Neurokinin A in nociception is suggested by the reduction in response thresholds to noxious stimuli by central administration of K2 and K3 agonists.
- **Detroampetamine** – used for cancer pain to overcome sedation of opioids
- **Antihistamine** - hydroxyzine and promethazine – to augment sedative or anxiolytic effect and reduce itching associated with opioids.
- **Benzodiazepine** – skeletal muscle relaxation and anxiolysis in the treatment of acute pain
Antidepressants

Antidepressants that work upon 5-HT or NE receptors--such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)—block the reuptake of serotonin and norepineprine, thus enhancing pain transmission.
Gate control theory

Gate control theory suggests that the spinal cord contains a neurological “gate” that either block pain signals or allows them to continue on to the brain. Unlike an actual gate, which opens and closes to allow things to pass through, the "gate" in the spinal cord operates by differentiating between the types of fibers carrying pain signals. Pain signals traveling via small nerve fibers are allowed to pass through, while signals sent by large nerve fibers are blocked. Gate control theory is often used to explain phantom or chronic pain.
How Pain Works  The Melzack-Wall Pain Gate

NO INPUT  = GATE CLOSED

LARGE FIBER INPUT  = GATE CLOSED

SMALL FIBER INPUT  = GATE OPEN

S Small Nerve Fibers  i Inhibitory Neuron
L Large Nerve Fibers  P Projection Cells
The interplay among these connections determines when painful stimuli go to the brain:

- When no input comes in, the inhibitory neuron prevents the projection neuron from sending signals to the brain (gate is closed).
- Normal somatosensory input happens when there is more large-fiber stimulation (or only large-fiber stimulation). Both the inhibitory neuron and the projection neuron are stimulated, but the inhibitory neuron prevents the projection neuron from sending signals to the brain (gate is closed).
- Nociception (pain reception) happens when there is more small-fiber stimulation or only small-fiber stimulation. This inactivates the inhibitory neuron, and the projection neuron sends signals to the brain informing it of pain (gate is open). Descending pathways from the brain close the gate by inhibiting the projector neurons and diminishing pain perception.