Chronic Pain Management

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Chronic Pain

- Chronic pain is pain that persists beyond the usual course of an acute disease or after a reasonable time for healing to occur; healing period typically can vary from 1 to 6 months
- May be nociceptive, neuropathic, or mixed
- Psychological mechanisms or environmental factors play a major role
- Absent or attenuated neuroendocrine stress responses
  - Prominent sleep and affective mood disturbances

Chronic Pain Pathophysiology

- Spontaneous self-sustaining neuronal activity in the primary afferent neuron
- Mechanosensitivity associated with chronic nerve compression
- Ephaptic transmission: short-circuits between pain fibers and other fibers following demyelination, resulting in activation of nociceptive fibers by non-noxious stimuli at the site of injury
- Functional reorganization of receptive fields in dorsal horn neurons→ sensory input from surrounding intact nerves→ intensifies any input from the area of injury
- Loss of descending inhibitory influences that are dependent on normal sensory input
- Lesions of the thalamus or other supraspinal structures
- Accumulation of substances such as bradykinin, serotonin, IL-6, IL-1beta, and prostaglandins→ sensitization of second-order neurons in the dorsal horn

Nociceptive Pain

- Caused by activation or sensitization of peripheral nociceptors or nerve endings
  - Specialized receptors that transduce noxious stimuli

Neuropathic Pain

- **T**he result of injury or acquired abnormalities of peripheral or central neural structures
  - Involves peripheral-central and central neural mechanisms
    - Associated with partial or complete lesions of peripheral nerves, dorsal root ganglia, nerve roots, and central structures
- Peripheral mechanisms include spontaneous discharges; sensitization of receptors to mechanical, thermal, and chemical stimuli; and up-regulation of adrenergic receptors
- Central mechanisms include loss of segmental inhibition, wind-up of WDR neurons, spontaneous discharges in deafferentated neurons, and reorganization of neural connections
- Typically associated with diabetic neuropathy, causalgia, phantom limbs, postherpetic neuralgia, stroke, spinal cord injury, and multiple sclerosis
  - Pain tends to be paroxysmal and sometimes lancinating with a burning quality, usually associated with hyperpathia

Neuropathic Pain Treatment

- Anticonvulsants (gabapentin or pregabalin)
- Antidepressants (tricyclic's or serotonin-norepinephrine reuptake inhibitors)
- Antiarrhythmic (mexiletine)
- Alpha 2 adrenergic agonists (clonidine and dexmedetomidine)
- Topical agents (lidocaine or capsaicin)
- Analgesics (NSAIDs and opioids)

Central Sensitization

- Three mechanisms responsible for central sensitization in the spinal cord:
  - "Wind up" and sensitization of second-order neurons
    - Wide dynamic range (WDR) neurons, increase their frequency of discharge with the same repetitive stimuli and exhibit prolonged discharge, even after afferent C fiber input has stopped
    - Glutamate, excitatory neurotransmitter, release increased contributing to "wind up" phenomenon
  - Receptor field expansion
    - Dorsal horn neurons increase their receptive fields such that adjacent neurons become responsive to stimuli (whether noxious or not) to which they were previously unresponsive
  - Hyperexcitability of flexion reflexes
    - Enhancement of flexion reflexes is observed both ipsilaterally and contralaterally

Central Sensitization Continued

- Can be associated in patients with:
  - Fibromyalgia, osteoarthritis, musculoskeletal disorders, generalized pain hypersensitivity, headaches, temporomandibular joint disorders, dental pain, neuropathic pain, visceral pain hypersensitivity disorders and postsurgical pain

Systemic Responses to Pain

- Neuroendocrine response of leukocytosis and depression of the reticuloendothelial system
  - Can lead to infection, especially in patients with severe recurring pain due to:
    - Peripheral nociceptive mechanisms
    - Prominent central mechanisms, ex. paraplegia

Psychological Responses to Pain

- Somatization disorder: physical symptoms of a medical condition that cannot be explained→ involuntary distress and physical impairment
- Conversion disorder: symptoms of voluntary motor or sensory deficits that suggest a medical condition; symptoms cannot be medically explained but are associated with psychological factors
- Hypochondriasis: prolonged >6 months preoccupation with the fear of having a serious illness despite adequate medical evaluation and reassurance
- Malingering: intentional production of physical or psychological symptoms that are motivated by external incentives (ex. avoiding work)
- Substance-related disorders: habitual misuse of prescribed or illicit substances that often precedes and drives complaints of pain and drug-seeking behavior

Acetaminophen

- Available as PO, IV and rectal routes
- Analgesic and antipyretic
- Inhibits prostaglandin synthesis but lacks significant anti-inflammatory activity
- Hepatotoxic at high doses
- Recommended adult maximum daily limit: 3000 mg/d (FDA 4,000 mg/d)
- Onset: 0.5 h Dose: 500-1000 mg Dosing interval: q4h

NSAIDs

- Inhibit prostaglandin synthesis (COX 1&2)
- COX-1: responsible for platelet dysfunction from inhibition
- COX-2: expressed primarily with inflammation
- Antiplatelet effect of NSAIDs is reversible and lasts approximately five elimination half-lives (24-96 h)
- Most common side effects: stomach upset, heartburn, nausea, and dyspepsia
  - Proprionic acid: Ibuprofen- Onset: 0.5h Dose: 400 mg PO Dosing: q4-6h Maximum daily dose: 3200 mg PO
  - Indole: Ketorolac (Toradol)- Onset: 0.5-1h Dose: 10 mg PO Dosing interval: q4-6h Maximum daily dose: 40 mg PO
    - Recommended adult IV single dose is 15-60 mg. Multiple IV doses of 15 or 30 mg q6h, not to exceed 60 or 120 mg daily
  - Cox-2 inhibitor: Celecoxib (Celebrex)- Onset: 3 h Dose: 100-200 mg PO Dosing interval: 12h Maximum Daily Dose: 400 mg PO

Antidepressants

- Most useful for neuropathic pain, typically at a dose lower than what is needed for antidepressant activity
- Analgesic activity result of blockade of presynaptic reuptake of serotonin, norepinephrine, or both
- Undergo extensive first-pass hepatic metabolism, highly protein bound, highly lipophilic with large volumes of distribution
- Side effects: antimuscarinic effects (dry mouth, impaired visual accommodation, urinary retention, and constipation), antihistaminic effects (sedation and increased gastric pH), alpha blockade (orthostatic hypotension), and quinidine-like effects (AV block, QT prolongation, torsades de pointes) * Tricyclic antidepressants such as amitriptyline and nortriptyline

Antidepressants Continued

- Citalopram (Celexa)- SSRI- low sedation, low antimuscarinic activity, low orthostatic hypotension, half-life 35h, daily dose 20-40 mg PO
- Duloxetine (Cymbalta)- SNRI- very useful in treatment of neuropathic pain- half-life of 12h, typically end with dose of 60 mg PO, but usually need to titrate over 13 week period to reach 60 mg PO
- Bupropion (Wellbutrin)- aminoketone class- low sedation, low antimuscarinic activity, low orthostatic hypotension, half-life 11-14h, daily dose 300-450 mg PO
- Fluoxetine (Prozac)- SSRI- low sedation, low antimuscarinic activity, low orthostatic hypotension, half-life 160-200h, daily dose 20-80 mg PO
- Paroxetine (Paxil)- SSRI- low sedation, low antimuscarinic activity, low orthostatic hypotension, half-life 31h, daily dose 20-40 mg PO
- Sertraline (Zoloft)- SSRI- low sedation, low antimuscarinic activity, low orthostatic hypotension, half-life 26h, daily dose 50-200 mg PO
- Venlafaxine (Effexor)- SNRI- low sedation, low antimuscarinic activity, low orthostatic hypotension, half-life 5-11h, daily dose 75-375 mg PO

Antispasmodics & Muscle Relaxants

- Cyclobenzaprine (Flexeril)- MOA unknown- helpful in treatment of muscle spasm in conditions such as multiple sclerosis, low back pain, and spastic diplegia
  - Flexeril recommended daily dose: 5 mg PO
  - Contraindications with MAOIs when taken within 2 weeks of Flexeril→ serious life-threatening side effects
  - Serotonin syndrome when taken with duloxetine or phenelzine
- Baclofen (Gablofen, Lioresal)- GABA agonist- very effective when administered by continuous intrathecal drug infusion
  - Typically initiated at 5-10 mg 2 or 3 times/day, increasing the dose by 5-10 mg/day every 2-3 days
  - Typical effective range dose: 50-60 mg PO
  - Abrupt discontinuation has been associated with fever, altered mental status, pronounced muscle spasticity or rigidity, rhabdomyolysis, and death

Corticosteroids

- **Anti-inflammatory**, autoimmune, anti-allergic
- Prevent the release of arachidonic acid→inhibiting phospholipase A2 on cell membranes→ decrease inflammatory cytokines and prostaglandins
- Administration routes: PO, IV, epidural, caudal, and intra-articular
- Large doses or prolonged administration can result in significant side effects such as: hypertension, hyperglycemia, immunosuppression, peptic ulcers, osteoporosis, aseptic necrosis of the femoral head, proximal myopathy, sodium and water retention, gastritis, hypothalamic-pituitary-adrenal axis suppression, insomnia, cataracts, and psychosis
- Typical doses:
  - Hydrocortisone- glucocorticoid and mineralocorticoid activity- 20 mg PO daily- half-life 8-12h
  - Prednisone- glucocorticoid activity- 5 mg PO daily, half-life 12-36h
  - Methylprednisolone- glucocorticoid activity- 125 mg IV- single preoperative dose, half-life 12-36h
  - Dexamethasone- glucocorticoid activity- 10-15 mg IV before induction, half-life 36-72h

Anticonvulsants

- MOA: block voltage-gated calcium or sodium channels, inhibit neuronal excitation and stabilize nerve membranes in an effort to decrease repetitive neural ectopic firing
- Recommended to begin prior to surgery, typically a one time dose for prevention of postoperative pain
  - Carbamazepine (Tegretol)- half-life 10-20h, daily dose: 200-1200 mg PO, therapeutic level: 4-12 mcg/ml
  - Clonazepam (Klonopin)- half-life 30-40h, daily dose: 1-40 mg PO, therapeutic level: 0.001-0.08 mcg/ml
  - **Gabapentin (Neurontin)- half-life 5-7h, daily dose: 900-4000 mg PO, therapeutic level: >2 mcg/ml**
  - Lamotrigine (Lamictal)- half-life 24h, daily dose: 25-400 mg PO, therapeutic level: 2-20 mcg/ml
  - **Pregabalin (Lyrica)- half-life 6h, daily dose: 150-600 mg PO, therapeutic level: 2.8-8.2 mcg/ml**

Alpha 2 Adrenergic Agonists

- Clonidine (Catapres)- centrally acting direct alpha 2 agonist→resulting in inhibition of adenylyl cyclase and decreased cAMP
- Activates postsynaptic potassium channels while inhibiting presynaptic voltage-gated calcium channels→ reducing the neurotransmitter
  - 220:1 alpha 2 to alpha 1 receptors→sedation, hypotension, and bradycardia
  - PO dose: 0.1-0.3 mg BID, a transdermal patch also avail (0.1-0.3 mg/d) applied for 7 days
- Dexmedetomidine (Precedex)- highly selective alpha 2 agonist
  - 1,620:1 alpha 2 to alpha 1 receptors
  - Rapid onset: 5 minutes, short DOA, half-life 3h
  - Typical analgesic dose: 0.5-1 mcg/kg IV bolus given over 10 minutes prior to induction

Ketamine

- Noncompetitive NMDA antagonist
- Useful in neuropathic and phantom limb pain→ effective in reducing hyperalgesia and allodynia
- Typical dose: 0.1-0.5 mg/kg IV
- Preserves airway patency, ventilation and cardiovascular stability

Botulinum Toxin

- Onabotulinumtoxin A (Botox)- injection has been useful for treatment of involuntary muscle contractions (focal dystonia and spasticity)
- Approved by the FDA for prophylactic treatment of chronic migraine headaches
- MOA- blocks acetylcholine released at the synapse in motor nerve endings, but not sensory nerve fibers
- Proposed mechanisms of analgesia include: improved local blood flow, relief of muscle spasms, and release of muscular compression of nerve fibers

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