Rational Pharmacology in Chronic Pain Therapy
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Objectives
At the end of this presentation, you should be able to...
1) Summarize four chronic pain pathologies
2) Employ the rationale for which medications are most appropriate for which chronic pain pathology
3) Compose a treatment plan for a chronic pain test case using the presented rationales

Pre-test
1) List as many types of chronic pain as you can.
2) List as many descriptive words about pain that you can.

Pre-test
3) Which of the medication is inappropriate for chronic musculoskeletal pain?
   a. Short-acting opioids
   b. Long-acting opioids
   c. SNRI (e.g. duloxetine)
   d. NSAIDs
   e. None of the above

Pre-test
4) Inflammatory pain happens in which stage of pain transmission?
   a. Transduction
   b. Conduction
   c. Transmission
   d. Perception

Patient Case
• Think about this case and determine if the current treatment plan is appropriate – think about possible alternatives.
• I.P. is a 55 y/o woman with chronic low back pain. Recent MRI reveals mild left sided radiculopathy in the L5 nerve root, attributed by the radiologist to a L5-S1 disk herniation and subsequent repair in 2010. She is physically functional and is able to work; however, she reports increased difficulty performing daily tasks. She presents to clinic asking for pain evaluation.
**Patient Case**

- Her pain picture includes descriptors like dull aching in the lower back, lancinating left sided pain, some feelings of numbness in left buttock. She reports reduced physical activity this last year due to pain and fear of injury. She reports feeling depressed and of having low energy.
- Ht: 156 cm (5’1”) Wt: 88 kg (BMI: 38.2) Pain Level: 6/10
- Pain medications (relatively unchanged in 3 years):
  - IBU 800 mg 1 TID with food
  - APAP/hydrocodone 325/5 mg 1-2 up to TID PRN pain

**Patient Case**

- In addition to counseling about diet and exercise, the provider’s impression of this patient was depressed mood and they were considering adding an SSRI to her regimen. The provider asks you which medication would be best.
- Upon reviewing her medication history, you discover that the patient has been coming in for early refills on her APAP/hydrocodone for the last six months.
- What treatment options would you, the pharmacist, recommend to the provider for this patient?

**Pain Categories**

- Five basic types of pain
  - Nociceptive Pain
    - Normal - Serves to warn the body about actual or potential damage to tissues
    - Types of nociceptive pain
      - Somatic Pain - related to skin and deeper tissues
      - Visceral Pain - related to internal organs
  - Inflammatory Pain
    - Cell mediated, can be a normal part of healing but can also be chronic and debilitating
  - Neuropathic Pain
    - Abnormal Pain - Linked to neurologic damage causing persistent nociception in the absence of injury
  - Functional Somatic Syndromes
    - Chronic pain conditions of unknown etiology
  - Sympathetic Pain
    - Complex regional pain syndrome (CPRS) - possibly over-activity of sympathetic nervous system

**Five basic types of pain**

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Nociceptive Pain

1) Transduction
   Chemical, Mechanical or Thermal energy directly or indirectly affecting nociceptors.
   • Mediators include:
     - Prostaglandins
     - Substance P
     - Histamine
     - Serotonin
     - Inflammatory Cytokines
     - Direct ion channel stimulation (TRPV1)

2) Conduction
   • Action potential in nerve fibers transmitted to CNS
   • C-fibers - unmyelinated, slowest conduction
   • Likely responsible for dull, aching pain
   • A (α,β,δ) - fibers - myelinated, faster conduction
   • Likely responsible for sharp, pricking pain
   • More related to thermal and mechanical stimulus

3) Transmission
   • Process of first order neurons communicating with second order neurons in dorsal horn and from dorsal horn to the brain

Transmission Neurochemistry

Key Players
   Excitatory
   Glutamate
   NMDA
   Substance P
   Na⁺, Ca⁺⁺ channels

Inhibitory
   GABA
   Opioid
   5-HT
   NE
4) Modulation

- Attenuation or amplification of pain transmission

- (-) Pain Gate Theory
  - Neuronal inhibition of pain pathway

- (+) Dorsal Horn “wind up”
  - Increase frequency of action potential with repeated stimulation

- (+/-) Neuronal Plasticity
  - Change in neurotransmitter activity and receptors in response to pain stimulation
  - Acute to chronic pain (more in a later section)

5) Perception

- Largely subjective

- International Association for the Study of Pain (IASP) defines pain as:
  - An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage
Sensitization

- Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs.
- Central Nervous System
- Peripheral Nervous System
- Clinically, sensitization can be inferred through the identification of hyperalgesia and allodynia

Definitions from IASP: [www.iasp-pain.org](http://www.iasp-pain.org)

Hyperalgesia - Increased pain from a stimulus that normally provokes pain e.g. Blowing nose repeatedly, increased pain sensation around nares

Allodynia - Pain due to a stimulus that does not normally provoke pain e.g. Gouty arthritis in great toe causing excruciating pain as wind blows over the toe hair

Sensitization = remodeling

- The peripheral and CNS response to pain is a balance of excitation and inhibition
- Site of action for many current and possible future drugs
- Neuroplasticity
  - The physical remodeling of neuronal architecture in response to persistent acute pain
  - Over time, inhibitory neurons die
  - Glial cells remodel dorsal horn neurons making them more sensitive to pain signals

Glial Cells

Astrocyte potentiation of pain signals primarily through release of glutamate and activation of microglia.

- Increases frequency of signals
- Kills inhibitory neurons in the periphery
- Activates glial astrocytes
  - Upregulates excitatory neurotransmitter release
  - E.g. NMDA, Glutamate
  - Upregulates mu-opioid receptor during inflammation
  - Potentiated by opioids themselves
  - Leads to opioid tolerance

Inflammatory Pain

- Acute becomes chronic
- Not always reversible
Types of Inflammatory Pain

- Specifically peripheral
- Myofascial Pain Syndrome
- Arthritis
  - Osteoarthritis
  - Rheumatoid Arthritis
    - Little evidence of opioid efficacy
- Pelvic Inflammatory Disease

Medications

- Transduction
  - NSAIDs - Inhibition of cyclooxygenase
  - Steroids - Suppress inflammatory cytokines
  - Local anesthetics (e.g. lidocaine) - Inhibition of voltage-gated Na channels
  - Capsaicin - Counter irritant and depletion of substance P
    - Substance P depletion dependent on QID dosing for 2-4 weeks
- Transduction and Transmission
  - Opioids
    - Reduces pain in periphery during states of inflammation
    - Inhibits pain signals in ascending and descending pathway

Neuropathic Pain

- Arises from multiple mechanisms
  - Direct damage to nerves leading to inappropriate and persistent activation of voltage-gated Na channels
  - CNS inflammation (along with some peripheral inflammation) leading to remodeling of neuron perpetuating pain signaling

Medications

- Conduction and Transmission
  - APAP - CNS inhibition of prostaglandin
  - Synergistic effect with opioids
  - Local anesthetics - includes nerve blocks & epidural
  - Tricyclic antidepressants
  - Inhibit reuptake of 5-HT, NE, block ion channels, decrease PGE
  - SNRIs
    - Inhibit reuptake of 5-HT, NE, blocks ion channels
    - Why not SSRIs?
  - Gabapentin & Pregabalin
    - Increase GABA release from astrocytes, inhibit action of excitatory C+ channel
  - Opioids
    - Inhibits pain signals in ascending and descending pathway
Medications

- Why do SNRIs work for neuropathic pain and SSRIs don’t?
  - This is mechanistically unclear
  - There is some evidence suggesting the certain SSRIs may help certain kinds of pain but SNRIs have performed much better, including trials of pain with and without depression.4
  - By itself 5-HT can be excitatory and inhibitor in the descending pain pathway
  - With NE, the balance tilts to the inhibitory
  - SNRI special consideration?
    - Seems to inhibit spinal glial cell mediated up-regulation of mu opioid receptor**

- NMDA Receptor Antagonism?
  - NMDA receptor antagonists
    - Ketamine
    - Memantine
    - Amantadine
    - Dextromethorphan
  - Not used because of poor side effect profile, lack of specificity to dorsal horn, abuse potential (ketamine is a hallucinogen, i.e. street name “Special K”)

Functional Somatic Syndromes

- Fibromyalgia
  - “Pain syndrome” including
    - Multiple tender points
    - Joint stiffness
    - Mood disorder
    - Fatigue
    - Cognitive Dysfunction
    - Insomnia
  - Fibromyalgia is a diagnosis of exclusion
  - Three commonalities: pain, fatigue, sleep disturbance

- Medications
  - SNRIs special consideration?
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- Fibromyalgia
  - Theoretic etiology
    - Reduced 5-HT
    - Leading to less pain inhibition, changes in mood and sleep
    - Enhanced central sensitization
    - Reduced descending pathway inhibition
    - NE, dopamine, substance P
  - Lions, tigers, bears… oh my
  - Fact is, there is a lot of unknowns with this syndrome
Treatment Options

- The American Pain Society (APS) and the Association of the Scientific Medical Societies in Germany (AWMF) gave the highest level of recommendation to:
  1. Aerobic exercise
  2. Cognitive behavioral therapy
  3. Amitriptyline*
  4. “Multi-component therapy”

*These guidelines predate duloxetine and pregabalin approval for fibromyalgia

- The European League Against Rheumatism (EULAR) gave the highest level of recommendation to (level of evidence):
  1. Pharmacological tx (A)
  2. Aerobic exercise (B)
  3. CBT (D)

Non-pharmacologic

- Aerobic activity
  - Tai Chi daily was statistically better than TIW aerobic workouts for quality of life and physical symptoms of fibromyalgia

- Cognitive Behavioral Therapy
  - Cannot perform meta-analysis due to differences in study design, but some evidence that CBT may improve QoL, pain, and pain coping skills for as long as 36 months

Pharmacologic

- Serotonergic +
  - tramadol (weak opioid and 5-HT)
  - amitriptyline
  - fluoxetine
  - duloxetine (rationally preferred?)

- GABAergics
  - pregabalin

- Other
  - Pramipexole (dopamine agonist)

- Universal consensus
  - Opioids are not indicated for fibromyalgia

Complex Regional Pain Syndrome

- Complex Regional Pain Syndrome
  - AKA
    - 1851 Civil War - “causalgia” (Greek: kausos=heat, algos=pain)
    - Reflex Sympathetic Dystrophy (RSD)

- Subgroups arising from research
  1) a relatively limited syndrome with vasomotor signs predominating
  2) a relatively limited syndrome with neuropathic pain/sensory abnormalities predominating
  3) a florid CRPS syndrome similar to “classic RSD” descriptions

Sympathetic Pain

CPRS Diagnosis

Diagnostic criteria from National Health Service
1) Blood test to rule out Rheumatoid
2) MRI to rule out tissue injury
3) Biopsy to rule out malignancy
4) X-ray to rule out bone damage
   Then...
5) Physical Examination
6) Sweat Testing
7) Thermography (pictured on left)
8) Electrodiagnostics
Treatment

- Non-pharmacologic
  - Conduction
  - Nerve blocks
  - Psychology
  - CBT
- Pharmacologic
  - Transduction
  - NSAIDs
  - Transmission
  - Opioids, NMDA antagonists, SNRI
  - Other
    - Calcium channel blockers - vasomotor disturbances
    - Bisphosphonates - severe osteopenia

Wrapping it up...

Post-test

1) List as many types of chronic pain as you can.
   i. Inflammatory: muscle, joint, myofascial, visceral, arthritis, osteo- and rheumatoid, SLE
   ii. Neuropathic: diabetic, sciatica, neuritis, postherpetic neuralgia, trigeminal neuralgia, carpel tunnel
   iii. Other: fibromyalgia, CPRS

2) List as many descriptive words about pain that you can.
   i. Inflammatory: dull, ache, red, swollen, hot, pressure, throbbing
   ii. Neuropathic: tingling, burning, lancing, prickly, sharp, stabbing, numb

Post-test

3) Which of the medication is inappropriate for chronic musculoskeletal pain?
   a. Short-acting opioids
   b. Long-acting opioids
   c. SNRI (e.g. duloxetine)
   d. NSAIDs
   e. None of the above

Post-test

4) Inflammatory pain happens in which stage of pain transmission?
   a. Transduction
   b. Conduction
   c. Transmission
   d. Perception

Patient Case - revisited

- The facts:
  - 55 y/o female
  - Chronic low-back pain
  - described as lancing, dull, with some numbness
  - Reduction in function
  - 3-year stable meds
    - IBU 800 mg 1 TID with food
    - APAP/hydrocodone 325/5 mg 1-2 up to TID PRN pain
  - Coming in early for APAP/hydrocodone in last six months
  - Depression Symptoms

- What are your assessments and recommendations?
QUESTIONS?