PHARMACOTHERAPY FOR
CHRONIC PAIN SYNDROMES
(SPEED DATING WITH THE PHARMACIST)

Lee Kral, PharmD, BCPS, CPE
April 2016
Participating with Poll Everywhere
How to vote via the web or text messaging

From any browser

From a text message

These materials provided for reference use at the 43rd Annual Family Medicine Refresher Course for the Family Physician.
Permission from the author must be sought before reuse or redistribution.
How's my presentation so far?

- Respond at PollEv.com/presenterpete
- Text PRESENTERPETE to 22333 once to join, then A, B, or C

A. It's amazing.

B. It's incredibly amazing!

C. It's aw'right
Just another day at the synapse

(SP, EAAs)

NK-1,
AMPA,
NMDA

These materials provided for reference use at the 43rd Annual Family Medicine Refresher Course for the Family Physician. Permission from the author must be sought before reuse or redistribution.
Peripheral Sensitization

Adaptive mechanism until the tissue heals
Peripheral sensitization reduces the pain threshold
Neuroplasticity and Central Sensitization

Glial Cell (NK-1, AMPA, NMDA)

Neurotransmitters
Axon of nerve cell
Synapse
Dendrite of nerve cell
Receptors

(SP, EAAs)
Getting to know microglia

• Microglial activation
  • Trauma (psychological, physical)
  • Hypoxia/ischemia
• Neurodegenerative disorders (Alzheimer’s, Parkinson’s, MS, AIDS-related dementia)
• Infection (bacterial, viral)
• Toxins (lead, diesel exhaust particles)
• Medications (opioids)

www.aapainmanage.org.resources/pain-practitioner/articles
Trigger, Stimulus

Pain transmitting neurons: NO, PGs

Primary Afferents: SP, ATP, EAAs

IL-1β, IL-6, TNF, ROS, NO, EAA, PG, ATP

Enhance Pain Transmitting Neuron Excitability

Enhance primary afferent release of SP, EAA
Consequences

• NO BRAKES!!

• May be related to reduced levels of 5-HT, NE, endorphin, and other neuropeptides that mediate descending pain transmission in the CNS

• Reversible regional decreases in gray matter volume reported in patients with chronic pain!

• May be related to continuous or repetitive acute pain that sensitizes the CNS

Case

• 82 yr old male with h/o shingles on the left side of his forehead and scalp. His lesions have healed but he complains of constant intractable burning pain and allodynia of his scalp. He also reports occasional shooting pain in his right left face down into his orbital area and cheek.

• Amitriptyline caused urinary retention
Treating Neuropathic Pain

- Reduce ascending pathway transduction and transmission
  - Reduce excitatory amino acids
  - Prevent pre-synaptic neurotransmitter release
  - Block receptors (Glutamate, NMDA, etc.)

- Enhance descending pathway inhibition
  - Increase levels of NE and 5HT, endogenous endorphins

- Prevent glial cell activation
C Fiber-Mediated Pain

“Burning”
“Tingling”
“Bugs crawling on skin”
Modulating the Ascending Pathway
Calcium Channel Blockers

- Gabapentin
- Pregabalin

Minimal lab monitoring
Very few drug-drug interactions
A-delta Fiber Mediated Pain

“Sharp”

“Shooting”

“Lancinating”

“Stabbing”
Modulating the Ascending Pathway
Sodium Channel Blockers

- Carbamazepine
- Oxcarbazepine
- Lamotrigine
- Topiramate
- Lacosamide
- Local anesthetics

Several require some lab monitoring
Modulating the Descending Pathway

- “On” and “Off” cells in the CNS either amplify or dampen pain impulses from periphery
- If 5HT and/or NE are depleted, minor “incoming” signals are amplified

Chronic Pain
Depression
Anxiety
PTSD

Tricyclic antidepressants
Venlafaxine
Duloxetine
Milnacipran
Opioids for neuropathic pain?

• Compared with the pts taking any dose of opioid, pts not taking opioids had statistically lower disability and higher physical functioning scores, after adjusting for disease severity.

• Compared with pts prescribed opioid therapy on an ongoing basis, pts who were not prescribed had statistically lower disability and higher physical functioning scores, after adjusting for disease severity.

Case

- 65 yr old female with chronic low back pain s/p L5-S1 PLIF 10 years ago ("it never worked, my pain is just as bad or worse than it was before the surgery")
- She rates her pain severity as 50/10
- NSAIDs upset her stomach and acetaminophen doesn’t work.
Low Back Pain

• Back pain is commonly multi-factorial
  • Musculoskeletal
    • Facet joint arthritis
    • Muscle strain/spasm
    • Myofascial pain
  • Neuropathic/radicular
  • Central sensitization LBP
Treating Musculoskeletal Pain

• Acetaminophen
  • Usually first-line due to safety
  • Acetaminophen vs. placebo for spinal pain and osteoarthritis found acetaminophen to be ineffective for long-term use in chronic pain.¹

• NSAIDs
  • All equally effective
  • Better than placebo for back pain without sciatica, but not for back pain with sciatica²,³
  • Increased risk for patients with heart disease
  • More effective for osteoarthritis pain than acetaminophen

Treating Myofascial Pain

• Correct structural and mechanical balance
  • Stretching, establish new movement patterns
  • Massage/Myofascial release, TENS, Ultrasound

• Education/Stress reduction
  • Identify triggers, promote sleep, increase physical activity
  • DBT, Biofeedback, meditation

• Pharmacologic
  • NSAIDs, tizanidine (antispasticity, not antispasmodic)
  • Dry needling/Trigger point injections/Botulinum toxin

Treating Neuropathic Pain

Ascending pathway

• Topiramate, gabapentin, pregabalin offer only small improvements for back pain with radiculopathy.
• Combination therapies targeting both nociceptive and neuropathic components have shown greater benefit.

Treating Neuropathic Pain

Descending pathway

• Tricyclic antidepressants
  • Modest analgesia compared to placebo
  • No improvement in function
• Duloxetine
  • Reduces low back pain compared to placebo
  • Reduces use of opioids

Opioids for Low Back Pain

- Tramadol better than placebo for pain and function (low-moderate quality) but not better than NSAIDs
- Transdermal buprenorphine not better than placebo for pain or function
- Opioids better than placebo but not better than antidepressants for pain or function

Case

- 42 year old female with fibromyalgia, migraines, chronic abdominal pain
- Cyclobenzaprine caused more fatigue, she got inadequate relief with NSAIDs, pregabalin and duloxetine.
Central/Functional Pain Syndromes

- Visceral
  - Irritable bowel syndrome
  - Functional abdominal pain syndrome (FAPS)
  - Pelvic pain (interstitial cystitis, etc)

- Somatic
  - Fibromyalgia
  - Low back pain
  - Temporomandibular disorder
  - Osteoarthritis
  - Peripheral nerve injury

Chronic NonCancer Pain Syndromes

• Central hypersensitivity
  • Elevated levels of glutamate, EAAs

• Dysfunctional endogenous opioid system
  • Causing down-regulation of receptors and desensitization

• Overactive inflammatory response
  • Glial activation
  • Elevated ESR and inflammatory mediators
Fibromyalgia Pathophysiology

- Imbalance in neurotransmitters
  - Increase in excitatory neurotransmitters in CNS
    - Glutamate (2-fold increase)
    - Substance P (3-fold increase)
  - Decrease in inhibitory neurotransmitters
    - Norepinephrine
    - Serotonin
- Exaggerated response to
  - Personal stressors
  - Noxious stimuli (*hyperalgesia*)
  - Non-noxious sensory stimuli (*allodynia*)

Modulating the Ascending Pathway

• Decrease levels of glutamate in the CNS by binding to the alpha-2-delta subunit of voltage-gated calcium channels, preventing release of glutamate from pre-synaptic terminals

• Improve average pain scores and patient perception of improvement, but failed to show improvement in FIQ scores
  • Pregabalin
  • Gabapentin
Modulating the Descending Pathway

• Increase norepinephrine and serotonin in CNS

• Improve pain, sleep, sense of well-being
  • Tricyclics (TCA’s) – amitriptyline, nortriptyline
  • Cyclobenzaprine

• Improve average pain, FIQ scores, physical function, sense of well-being
  • Duloxetine
  • Milnacipran

• SSRI’s, venlafaxine not very effective, independent of their effects on depression
“The Talk - Realistic Expectations”

- “I can’t think of any other medications that might help your pain. And medications AT BEST, only improve pain by 30%”

- “YOU must take control of managing your pain so that it doesn’t control your life. I can’t do that for you. I CAN make a referral to a specialist who can help you get a handle on this. Anyone who is dealing with this much suffering and misery deserves a chance to talk with an expert”

- “Physical activity will not harm you. You may be sore, but that is because you are going to use muscles that you haven’t been using. It’s OK and if you stick with it, the muscles will heal themselves faster every time you exercise”
"NURSE, THIS BOY NEEDS SOME COOKIES AN’ ICE CREAM."