Non-Opioid Pain Medications For Chronic Non Cancer Pain

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Originally presented by George Comerci, MD and Eugene Koshkin, MD
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Objectives

- At the end of this presentation the participant will:
  - Describe the role of non-opiate pain medications in the care of the patient with chronic pain
  - Name the various categories of non-opiate pain medications
  - Identify the indications, safe usage and contraindications of a prototypical medication from each category of non-opiate pain medications
Road Map

- Pain Basics & Nociceptors
- Categories of non-opioid pain medications
  - ASA, APAP, NSAIDs
  - Neuropathic Agents (Anticonvulsants)
  - Antidepressants
  - Tramadol
  - Muscle Relaxants
  - Topical Analgesics
Three types of pain
- Somatic pain
- Visceral pain
- Neuropathic

Three types of pain receptors
- Chemical
- Mechanical
- Thermal
The Nociceptor

- A transducer...converts one form of energy to another
- Specialized neuron that responds to mechanical, thermal and/or chemical stimuli
The Nociceptor (Nature.2001)
The Nociceptor (J Clin. Invest. 2010)
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Categories of non-opioid pain medications

- *Primary analgesics*: NSAIDs, acetaminophen and ASA
- *Neuropathic Agents*
- *Anesthetics*
- *Antidepressants*: TCAs and SNRIs
- *Muscle Relaxants*: Anti-spasticity and anti-spasmotic drugs
- *Topicals*: lidocaine, NSAIDs, NTG and capsaicin
Non–Opioid Pain Medications

- Non–opioid pain medications include those medications that are considered by their pharmacologic action to be “analgesics”
  - Aspirin/ Non–Steroidal Anti–inflammatory drugs
  - APAP (acetaminophen)
- Adjuvant medications include any category of medication whose primary pharmacologic effect is not analgesia, but with secondary effects that ameliorate pain.
WHO Analgesic Ladder

Pain persisting or increasing →

Freedom from cancer pain

Step 3
Opioid for moderate-to-severe pain
± Nonopioid
± Adjuvant

Step 2
Opioid for mild-to-moderate pain
± Nonopioid
± Adjuvant

Step 1
Nonopioid
± Adjuvant

Pain

ASA, APAP and “NSAIDs”

- Prototypical Drugs: *Ibuprofen, Celecoxib, ASA and APAP*
- Act by the inhibition of COX-1/2/3 enzymes which convert arachidonic acid to prostaglandins
- **Indications and efficacy:**
  - nociceptive pain
  - NNT 2–4 patients for a 50% reduction in moderately severe pain
  - All NSAIDs are probably equal in analgesic efficacy
NSAIDs (cont.)

- **Adverse effects:**
  - GI: ulcerations of gut, hepatitis (fulminant: APAP)
  - Renal: renal insufficiency and interstitial nephritis
  - Cardiac: increased risk of MI
    - (COX-2 > Non-selective)

- **Contraindications**
  - Gut ulceration
  - Bleeding tendency
  - Renal disease
  - Caution with pregnancy
  - Sulfa-allergic patients (celecoxib)
NSAIDs (cont.)

“Pearls”

- Check CBC, LFTs, chem 7 periodically
- Consider concomitant PPI/ H2 Blocker
- Beware of the elderly patient and consider occult GIB with fatigue, weakness or stool changes
- Limit APAP to <3 gm/d and remember that acetaminophen is “everywhere”
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Neuropathic Agents

- Prototypical Agents:
  - Gabapentin (Neurontin)
  - Pregabalin (Lyrica)
  - Carbamazepine (Tegretol, Carbatrol)
  - Valproic acid (Depakene, Depakote, Stavzor)
  - Topiramate (Topamax)

- Act by a reduction of neuronal irritability due to ion flux (Ca^{++} and Na^{+}) resulting in “membrane stabilizing effect”
Neuropathic Agents: Indications

- Neuropathic pain
  - Gabapentin/ Pregabalin:
    - PHN, DPN, fibromyalgia
  - Valproic Acid, Topiramate:
    - migraine
  - Carbamazepine:
    - Trigeminal neuralgia
Neuropathic Agents

Gabapentin

- Binds to the α2-δ subunit of presynaptic voltage dependent Ca^{++} channels
- Reduces the release of glutamate, NE, substance P dopamine and serotonin
- Has nothing to do with GABA !!
- Uses include:
  - Fibromyalgia (off-label)
  - DPN (off-label)
  - Post Herpetic Neuralgia (approved)
Neuropathic Agents

Gabapentin

- **Dosing:** *start low, go slow*
  - Strive for a dose of 1800–3600 mg/day
  - Stack doses at nighttime
  - Adjust for renal creatinine clearance
  - Never stop abruptly

- **Adverse Effects**
  - Somnolence!!
  - Can cause leucopenia, thrombocytopenia
  - **Black Box:** increased suicidal thinking

- **Contraindications**
  - Renal failure
Neuropathic Agents

Pregabalin (a.k.a. Lyrica)

- Approved indications:
  - PHN, DPN, Fibromyalgia, spinal neuropathic pain
  - better absorption, decreased somnolence
  - Improvement in Stage 4 sleep
  - 150mg/d in divided doses...up to 600mg/d (maximum dosage dependent upon treated condition)
  - Reduce dose by 50% if Clcr 30–60 mL/min

- Adverse Effects
  - Somnolence, dysphoria, euphoria
  - Increased risk of angioedema—caution with ACE-I
  - Black Box: Increased risk of suicidal thinking
  - Never stop abruptly
Neuropathic Agents

Topiramate

- **Uses:**
  - Migraine prophylaxis (approved)
  - Cluster HA, Diabetic Peripheral Neuropathy (DPN), neuropathic pain (not approved)

- **Dose** 25–100mg daily

- **Adverse affects:**
  - Acidosis, nephrolithiasis
  - Diminished cognition
  - Reduce dose with renal insufficiency
  - **Black Box**: increased suicidal thinking
Neuropathic Agents

Carbamazepine/Oxcarbamazepine*
- Trigeminal neuralgia (approved)
- Neuropathic pain (non–approved)
- Patients of Asian descent should be screened for the variant HLA–B 1502 allele prior to initiating therapy

Valproic Acid*
- Migraine prophylaxis (approved)
- DPH /neuropathic pain syndromes (unapproved)

*both drugs are associated with risk of fluid/electrolyte abnormalities and increased suicidal thinking
Antidepressants

- Prototypical Agents: *Amitriptyline (TCA), Venlafaxine and Duloxetine (SNRI)*

- Thought to cause enhancement of endogenous descending antinociceptive systems via inhibition of reuptake of norepinephrine and serotonin
**Antidepressants: TCAs**

- **Indications and Efficacy**
  - Neuropathic pain *
    - (peripheral > central)
    - DPN, PHN
  - Other chronic pain: *
    - Fibromyalgia, LBP
    - HA syndromes
  - NNT (TCA) = 2–4 for 50% reduction in pain.

*non-FDA approved
Choosing a TCA is very much like choosing an antihypertensive…consider comorbid conditions

- Doxepin, and amitriptyline: most sedating and anticholinergic
- Imipramine, nortriptyline and desipramine: less sedation and anticholinergic side effects
Antidepressants: TCAs

- Dose low and go slow: (10 mg–25mg)
- For pain lower doses of 75mg–100mg = OK!
- **Side effects:** Many!!
  - sedation
  - orthostatic hypotension
  - anti-cholinergic effects
  - cardio–toxicity
- Black box warning for increased suicidal thinking
TCAs: pearls of caution/cardiac effects

- Type I Anti-arrhythmics
- Prolong PR, QRS and QTc intervals
- Increase risk of cardiac complications with doses >100mg/d but...
- Doses but below 100mg/d probably safe
- Safe in patients with chronic pain
- EKG for patients >40 years
Venlafaxine (Effexor) – non-FDA approved for pain

-Probably need to dose at least 100mg for pain effect
-Effective in: DPN, other neuropathic pain states, fibromyalgia, headaches, especially migraine
-NNT: 3.1
-Cautions:
  -Can worsen hypertension!
  -Serotonin syndrome: especially with other “serotonin” drugs
  -Black box: increased suicidal thinking

Antidepressants: SNRI
Antidepressants: SNRI

Duloxetine (Cymbalta)

- *Diabetic peripheral neuropathy*
  - 60mg/d resulted in 50% pain reduction: NNT: 6
- *Fibromyalgia*
  - 60mg day: NNT: 8
- *Chronic Musculoskeletal Pain*
  - 60mg day: NNT: 8
- Use in doses up to 60mg–90mg/d
Antidepressants: SNRI

- Duloxetine
  - Side Effects
    - **Black Box**: increased suicidal thinking
    - N/V most common reason for discontinuation
    - Transaminitis is not uncommon
    - Do not use in patients with liver disease
    - Adjust dosage for severe renal insufficiency
    - **Serotonin syndrome**: especially with other “serotonin” drugs
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Tramadol (C-IV)

- Centrally acting analgesic
  - Acts as opioid (<<affinity for mu receptor)
  - Primary effect is thought to be via activation of descending inhibitory pain systems like NSRIs
- Approved for moderate to severe pain
  - Generally used with an NSAID in OA
- Dosage: 50–400mg
- NNT = 6
- Adverse effects:
  - Somnolence and serotonin syndrome
  - Can be habituating
Tramadol (C-IV)

- **Side effects:** N/V, dizziness, constipation, somnolence, seizures!
- **Dosage:** 50–100 q 4–6 hours (max = 400mg/d)
- **Special Considerations:**
  - Neuroexcitatory properties of Tramadol are increased by SSRIs and to an extent TCAs
  - Beware of MAO-Inhibitors!!! (linezolid, selegiline)
  - Metabolism by CYP-2D6, CYP-3A4
- **Adjustments:**
  - *Cirrhosis:* 50 mg/q 12 hr (max = 100mg/d)
  - *Renal Insufficiency:* 50–100 q12 hr (max = 200mg/d)
Spasticity ≠ Muscle Spasms

- Spasticity: loss of descending inhibition to spinal motor neuron due to upper motor neuron disease/Exaggeration of the tone/stretch reflexes.
- Muscle Spasm: simply sudden movement of the muscles.
- Stiffness may be present in BOTH.

Antispasticity Drugs

- Baclofen,
- Tizanidine,
- Diazepam,
- Dantrolene,
- Botulinum Toxin
Baclofen: (GABA–mimetic agent)
- Inhibits spinal interneuron that stimulates muscle contraction in the reflex arc.
- Multiple sclerosis, other central spastic conditions
- Dose low, go slow:
  - maximum dose = 120mg/d (but most clinicians rarely use > 80 mg/d)
  - + withdrawal syndrome with intrathecal administration.
- Discontinuation of the oral regimen usually results in delayed return of spasticity/spasms weeks later!
Benzodiazepines (GABA–mimetic)
- Diazepam is the prototypical benzo for this
- Dosages needed to produce spasmolysis are in excess of 4mg/d
- Increased risk of hip fracture in elderly
- Caution with opiates!!

Tizanidine (central alpha mimetic)
- 4mg tid up to 36mg daily
- Think clonidine (hypotension is very common)
- Dose titration over 2–4 weeks.
- Watch LFTs and EKG
Muscle Relaxants:

- **Antispasmodics:**
  - Act by relieving muscle spasm caused by local tissue trauma from acute muscle damage or strain
  - Generally, should be used short-term

**Cyclobenzaprine**
- Think “TCA”: anticholinergic, prolongs QT
- Seems most efficacious for short term usage

**Others:**
- methocarbamol (Robaxin),
- orphenadrine (Norflex),
- metaxalone (Skelaxin) – mode of action not well understood
Carisoprodol (SOMA)

DON’T USE THIS DRUG!!
(Metabolizes to meprobamate, which has been removed by the FDA due to AE, including seizures and addiction potential).
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Topical Analgesics

Why topical medications
- No systemic effects (*transdermal* products are intended to have a systemic effect)
- To maximize concentration of drug at target tissue
- Less systemic drug concentration
- Patients like the concept of applying medicines to where they are sore!
Topical analgesics

- **NSAIDs**
  - diclofenac, ketoprofen, naproxen

- **Lidocaine**
  - 5% patch approved for PHN
  - Also as ointment, cream and gel
Capsaicin Cream: (0.025%, 0.075%)

- Effective for:
  - PHN,
  - DPN,
  - surgical neuropathic pain,
  - osteoarthritis,
  - neck pain
- Works at the vanilloid (temperature) receptor
- Chronic distal painful neuropathy:
  - HIV – DSP
Summary

We have talked about....

- Basic pain physiology
- NSAIDS, ASA and APAP
- Neuropathic Agents
- Antidepressants
- Muscle relaxers
- Topical agents
References


