Non-Opioid Pain Medications For Chronic Non Cancer Pain

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Objectives

• At the end of this presentation the participant will be able to:
  ➢ 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
  - Anticonvulsants
  - Antidepressants
  - Tramadol
  - Muscle Relaxants
  - Topical Analgesics
Pain Basics

• 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)

FIGURE 3. Themolecular complexity of the primary afferent nociceptor is illustrated by its response to inflammatory mediators released at the site of tissue injury.

http://www.nature.com/nature/journal/v413/n6852/fig_tab/413203a0_F3.html#figure-title
The Nociceptor (J Clin. Invest. 2010)
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Categories of non-opioid pain medications

- **Primary analgesics**: NSAIDs, acetaminophen and ASA
- **Anticonvulsants**
- **Anesthetics**
- **Antidepressants**: TCAs and SNRIs
- **Muscle Relaxers**: 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 \textit{“analgesics”}
  
  \textit{Aspirin/ Non-Steroidal Anti-inflammatory drugs}
  
  \textit{APAP (acetaminophen)}

• \textit{Adjuvant medications} include any category of medication whose primary pharmacologic effect is not analgesia, but with secondary effects that ameliorate pain.
WHO Analgesic Ladder

Freedom from cancer pain

Step 1:
- Mild pain
- Nonopioid ± Adjuvant

Step 2:
- Pain persisting or increasing
- Opioid for mild-to-moderate pain
  ± Nonopioid ± Adjuvant

Step 3:
- Pain persisting or increasing
- Opioid for moderate-to-severe pain
  ± Nonopioid ± Adjuvant

Pain


Source: Journal of Hospice & Palliative Nursing © 2003 Lippincott Williams & Wilkins
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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Anticonvulsants

• **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”
Anticonvulsants Indications

• Neuropathic pain
  ➢ Gabapentin/ Pregabalin :
    ➢ PHN, DPN, fibromyalgia
  ➢ Valproic Acid, Topiramate:
    ➢ migraine
  ➢ Carbamazepine:
    ➢ Trigeminal neuralgia
Anticonvulsants

**Gabapentin**
- Binds to the $\alpha_2$-$\delta$ 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)
Anticonvulsants

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
Anticonvulsants

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
Anticonvulsants

**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
Anticonvulsants

**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
Antidepressants: TCAs

- 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
  • (Clin Pharmacol Ther, 2004;75:234-44)

• Safe in patients with chronic pain
  • (Rev Bras Anestesiol. 2009;1:46-55)

• EKG for patients >40 years
Antidepressants: SNRI

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

**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)
Muscle Relaxants Drugs

• **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,
• botox
Muscle Relaxants Drugs

**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
  - + withdrawal syndrome with intrathecal administration.
  - Discontinuation of the oral regimen usually results in delayed return of spasticity/spasms weeks later!
Muscle Relaxants

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!!
(Think meprobamate)
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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
Topical Analgesics

• **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
• Anticonvulsants
• Antidepressants
• Muscle relaxers
• Topical agents
References