Treating Chronic Pain in New Mexico:

Non-Opiate Medications for Pain, Treatment

*First Do No Harm: Best Practices in Psychiatric Prescribing in Arizona: NARBHA*

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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
  - 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)

- Stimulus: NGF, Bradykinin, Serotonin, ATP, H⁺, Lipids
- Representative receptor: TrkA, BK₂, 5-HT₃, P₂X₃, ASIC3/VR1, PGE₂/CB₁/VR1, VR1/VRL-1, DEG/ENaC

Diagram showing the interaction of various substances and their receptors in the nociceptor.
The Nociceceptor (J Clin. Invest. 2010)
Analgesics: Non-opioid pain medications include those medications that have analgesia as their primary indication.

Aspirin/ Non-Steroidal Anti-inflammatory drugs (acetaminophen)

Adjuvant medications include any category of medication whose primary pharmacologic effect in not analgesia, but with secondary effects that ameliorate pain.
Categories of non-opioid pain medications

- **Primary analgesics:** NSAIDs, acetaminophen and ASA
- **Anticonvulsants**
- **Anesthetics**
- **Antidepressants:** TCAs and SNRIs
- **Muscle Relaxers:** Anti-spasticity and anti-spasmodic drugs
- **Topicals:** lidocaine, NSAIDs, NTG and capsaicin
WHO Analgesic Ladder

Pain persisting or increasing

Step 1
Mild pain
Nonopioid
± Adjuvant

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

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

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 “in hundreds of Rx and OTC products”
Anticonvulsants

- **Prototypical Agents:** *Gabapentin/Pregabalin*  
  *Carbamazepine, Valproic acid, Topiramate*

- Act by a reduction of neuronal irritability due to ion flux (Ca++ and Na+) resulting in “membrane stabilizing effect”

- **Indications:** Neuropathic pain
  - Gabapentin/ Pregabalin: Post Herpetic Neuralgia, Diabetic Peripheral Neuropathy, fibromyalgia
  - Valproic Acid, Topiramat: 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)
  - PHN (approved)
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 (C V)

- Approved indications:
  - PHN, DPN, Fibromyalgia, spinal neuropathic pain
  - better absorption, decreased somnolence
  - Improvement in Non-REM 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 ideation
  - Never stop abruptly
Anticonvulsants

Topiramate

- **Uses:**
  - Migraine prophylaxis *(FDA approved!)*
  - Cluster HA, DPN, neuropathic pain (not approved)

- **Dose 25–100mg daily**

- **Adverse affects:**
  - Acidosis, nephrolithiasis, inc. intraocular pressure
  - Diminished cognition
  - Reduce dose with renal insufficiency
  - **Black Box:** increased suicidal thinking
Anticonvulsants

Carbamazepine/Oxcarbazepine*

- Trigeminal neuralgia *(FDA approved!)*
- Neuropathic pain (non-approved)
- *Patients of Asian descent should be screened for the variant HLA-B 1502 allele prior to initiating therapy due to increased risk of SJS and TEN if allele is present*

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: TCA

**Indications and Efficacy**

- **Neuropathic pain** *
  - (peripheral > central)
  - Diabetic Peripheral Neuropathy, Postherpetic Neuralgia
- **Other chronic pain:** *
  - Fibromyalgia, Low Back Pain
  - HA syndromes
- **NNT (TCA) = 2–4 for 50% reduction in pain.**
  - (Cochrane Review.2010)

*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
  - Dose low and go slow: (10 mg–25mg)
  - For pain, I don’t go higher than 75mg–100mg

- **Side effects**: Many!! (sedation, orthostatic hypotension, anti-cholinergic effects and cardiotoxicity)
- **Black box warning** for increased suicidal thinking
TCAs: 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 (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
- Pain usage is off-label
- NNT: 3.1
- Cautions:
  - Can worsen hypertension!
  - Serotonin syndrome: especially with other “serotonin” drugs
  - Black box: increased suicidal thinking
Duloxetine

- *Diabetic peripheral neuropathy*
  - 60mg/d resulted in 50% pain reduction: NNT: 6
- *Fibromyalgia (FDA approved!)*
  - 60mg day: NNT:8
- *Chronic Musculoskeletal Pain (FDA approved!)*
  - 60mg day: NNT:8
- Use in doses up to 60mg–90mg/d
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 >2 other drugs that increase serotonergic activity
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 SNRIs
- FDA 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

- **Antispasticity Drugs**
  - Spasticity: loss of descending inhibition to spinal motor neuron due to upper motor neuron disease
  - Baclofen, tizanidine, diazepam, dantrolene, botox

**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
Muscle Relaxants

Benzodiazepines (GABA–mimetic)
- Diazepam is the prototypical benzodiazepine
- Dosages needed to produce spasmolysis are in excess of 10mg/d
- Increased risk of hip fracture in elderly
- Do not use with opiates long term outpatient!!!

Tizanadine (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 (Flexaril™)**
- 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
DON’T USE THIS DRUG!!
(Think meprobamate)
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%, 8%)

- 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


