

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

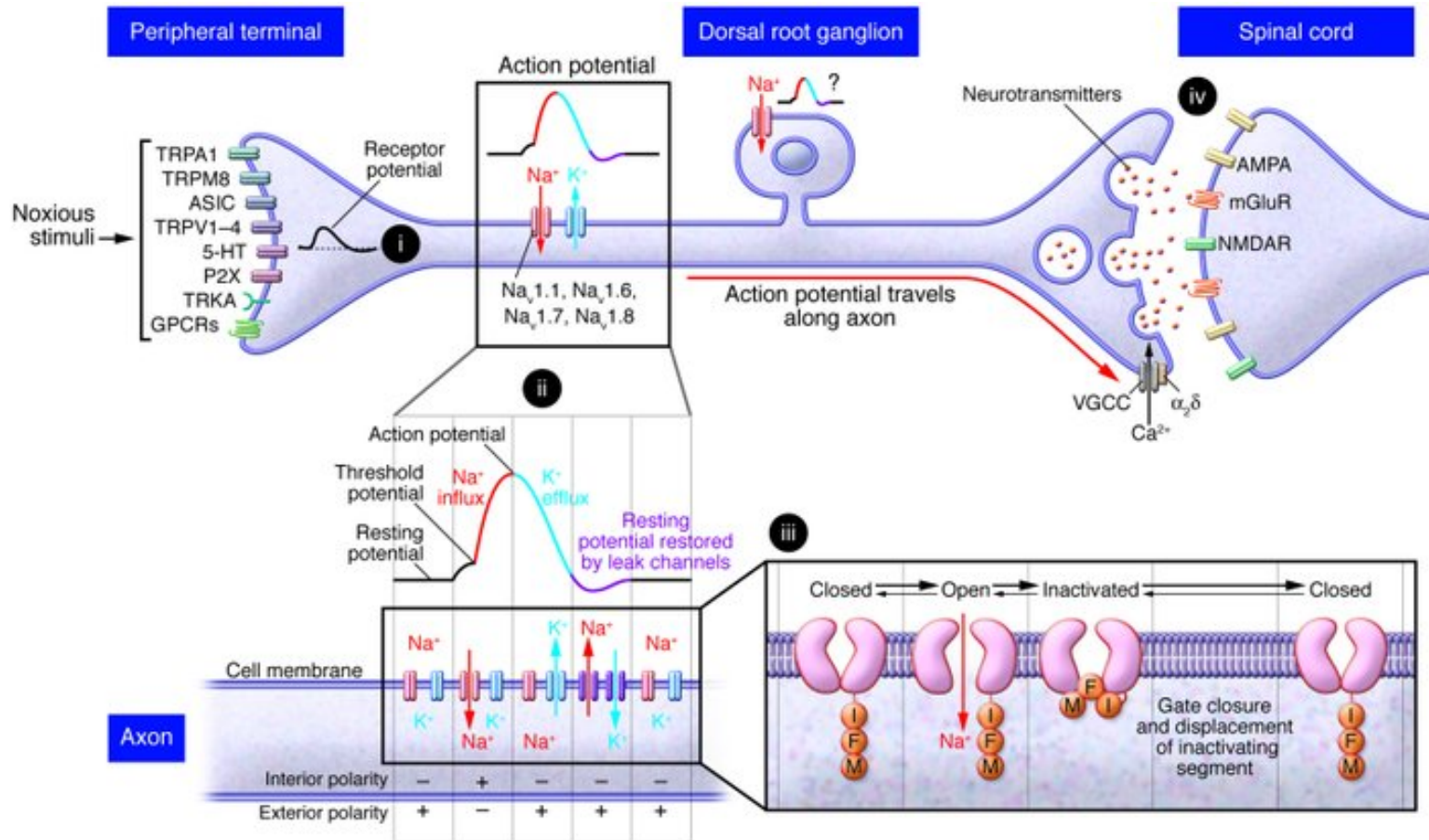
- A transducer...converts one form of energy to another
- Specialized neuron that responds to mechanical, thermal and/or chemical stimuli

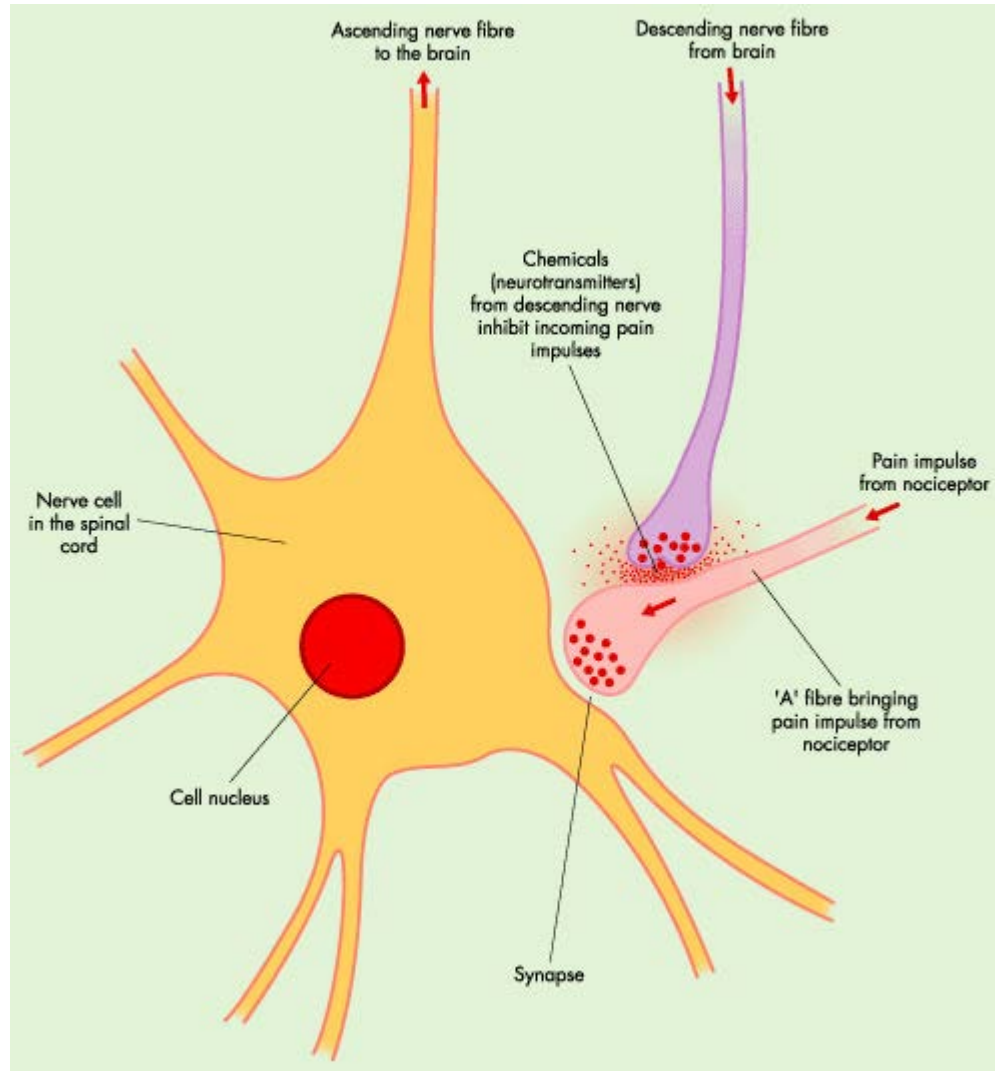
The Nociceptor (Nature.2001)

FIGURE 3. The molecular 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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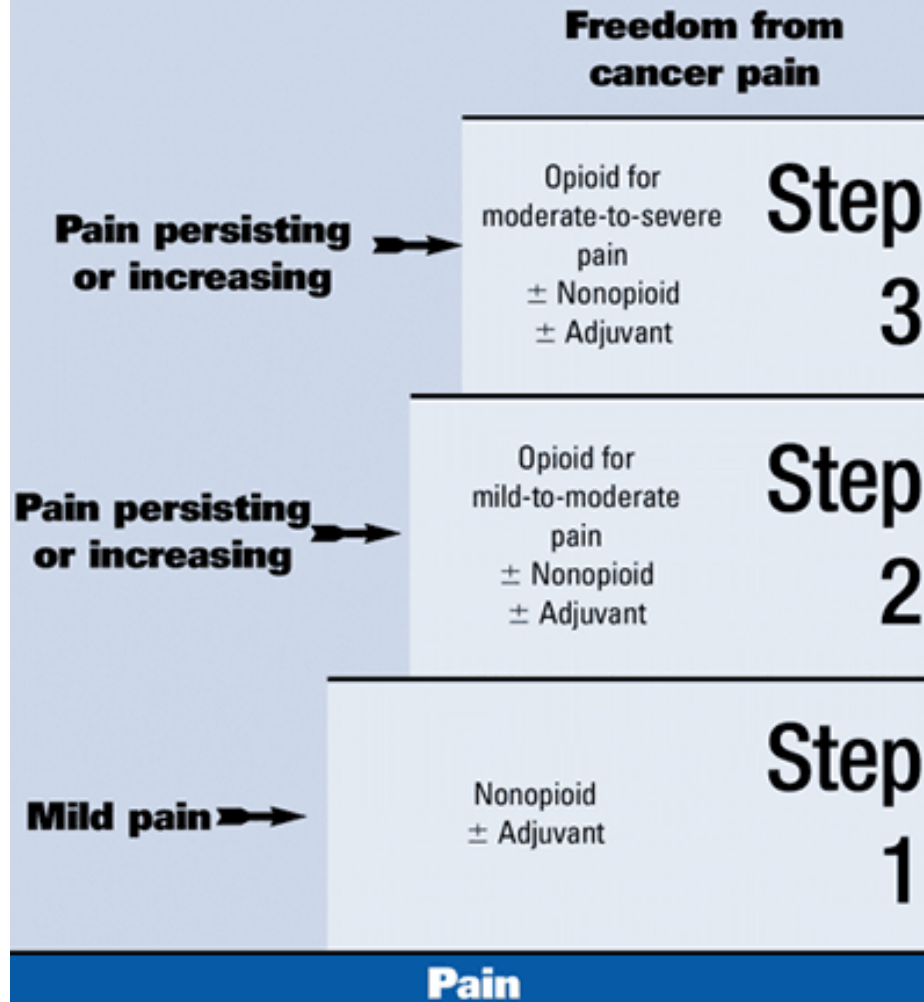
Categories of non-opioid pain medications

- *Primary analgesics*: NSAIDs, acetaminophen and ASA
- *Anticonvulsants*
- *Anesthetics*
- *Antidepressants*: TCAs and SNRIs
- *Muscle Relaxers*: Anti-spasticity and anti-spasmodic 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



Adapted from: World Health Organization. *Cancer pain relief and palliative care*. Geneva: WHO; 1996. Used with permission.

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 $\alpha 2$ - 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)

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 Anesteiol.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

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