PainWeek®

Non-opioid Analgesics

Thomas B. Gregory, PharmD, BCPS, FASPE, CPE

Title & Affiliation

Thomas B. Gregory, PharmD, BCPS, CPE, FASPE
Pain / Palliative care and Emergency Medicine Specialist
Cox Health Systems
Springfield, MO

Disclosures

- Nothing to disclose

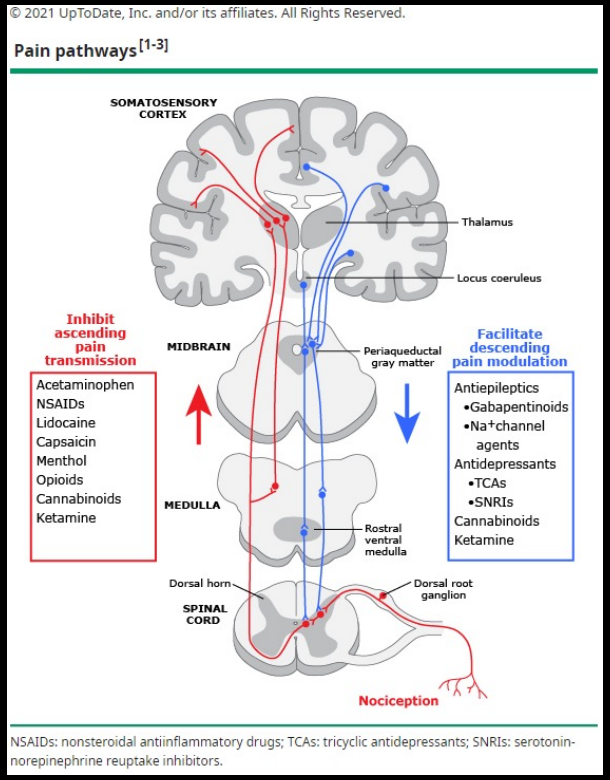
PAINWEEK®

Objectives

- Describe where adjuvant analgesics act in the pain pathway and their differences in mechanism of action
- Compare risks and benefits for different adjuvant analgesics
- Choose an adjuvant analgesic based on current guidelines and/or evidence-based medicine as well as individual patient factors
- Compare risks and benefits of different adjuvant analgesics for a given patient

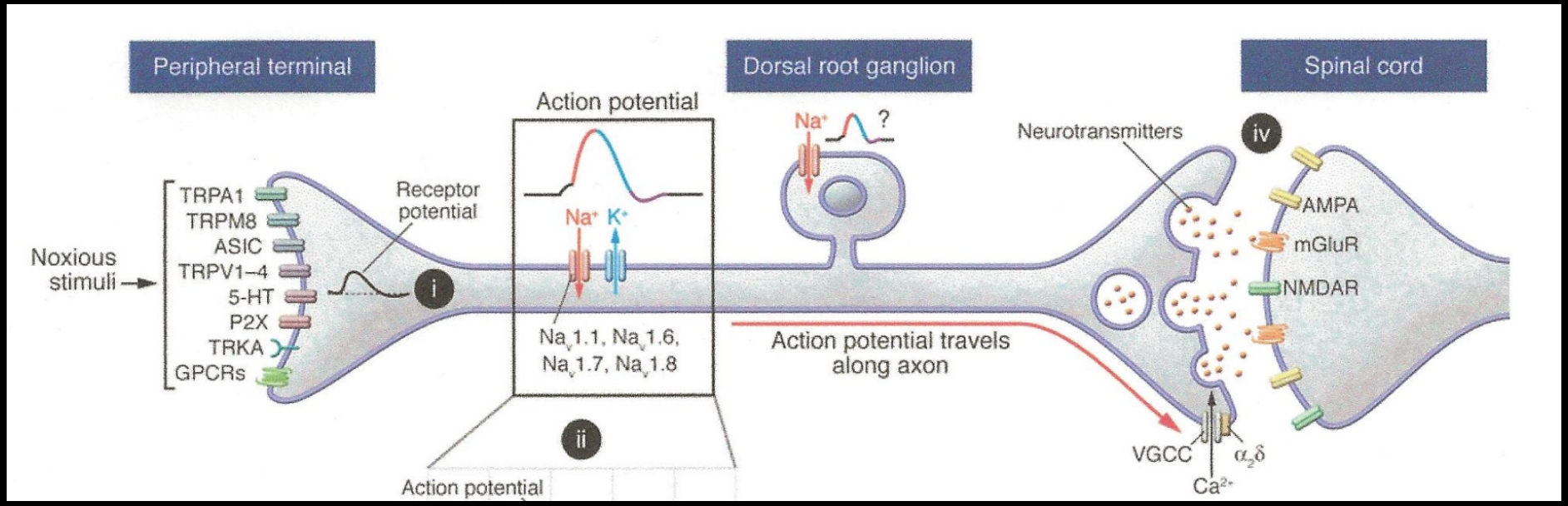
Hitting the Targets

- Stimulation of nociceptors causes signal transduction to the dorsal horn
  - –Transduction
- The spinothalamic tract transmits the signals to the brain where pain is first experienced
  - –Transmission
  - –Perception
- Descending pathways from the brain attempt to block the signal from the periphery
  - –Modulation



https://www.uptodate.com/contents/image?imageKey=ANEST%2F127212 accessed 4.20.2021

Where do these agents work?



Non-opioid classes and specific pain conditions

- Acetaminophen
- NSAIDs
- Corticosteroids
- Anticonvulsants
- Local anesthetics
- Antidepressants
- Counter irritants
- Skeletal muscle relaxants

- Inflammatory pain
- Neuropathic pain
- Musculoskeletal pain

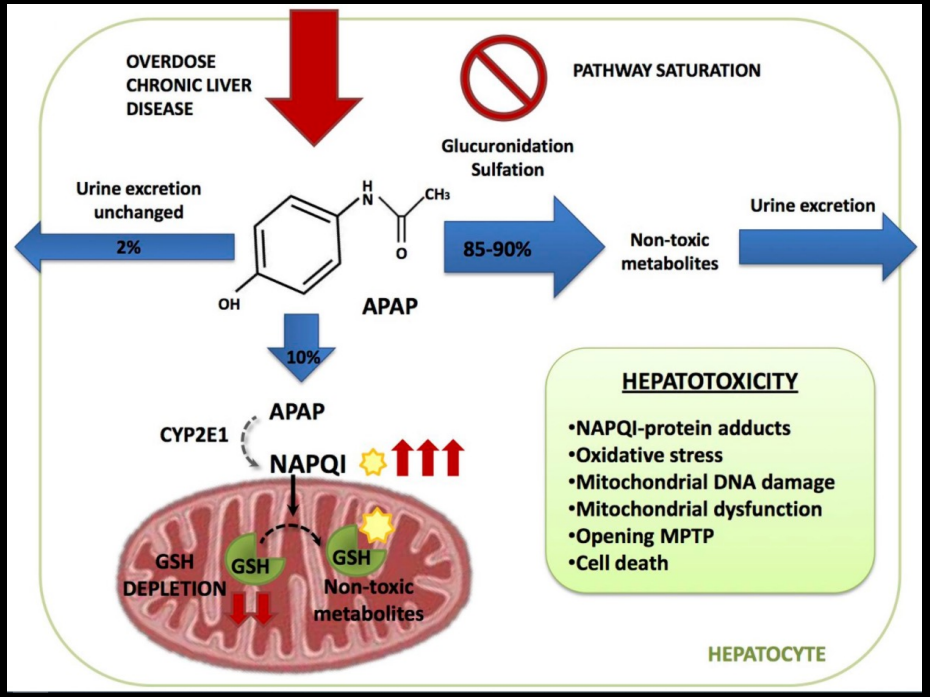
Acetaminophen

- Mechanism of action is still not entirely known
  - Thought to be a partial COX inhibitor
- March 2014 FDA mandates all prescription drug combination products containing acetaminophen cap the dose at 325 mg
- Maximum daily dose limits vary based on comorbidities and who you ask
  - FDA
    - 3250 mg[1] daily
  - Johnson and Johnson
    - 3000 mg[2] daily

1. http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm165107.htm accessed 4.20.2021
2. https://www.tylenol.com/safety-dosing/usage/dosage-for-adults accessed 4.20.2021

Acetaminophen (cont'd)

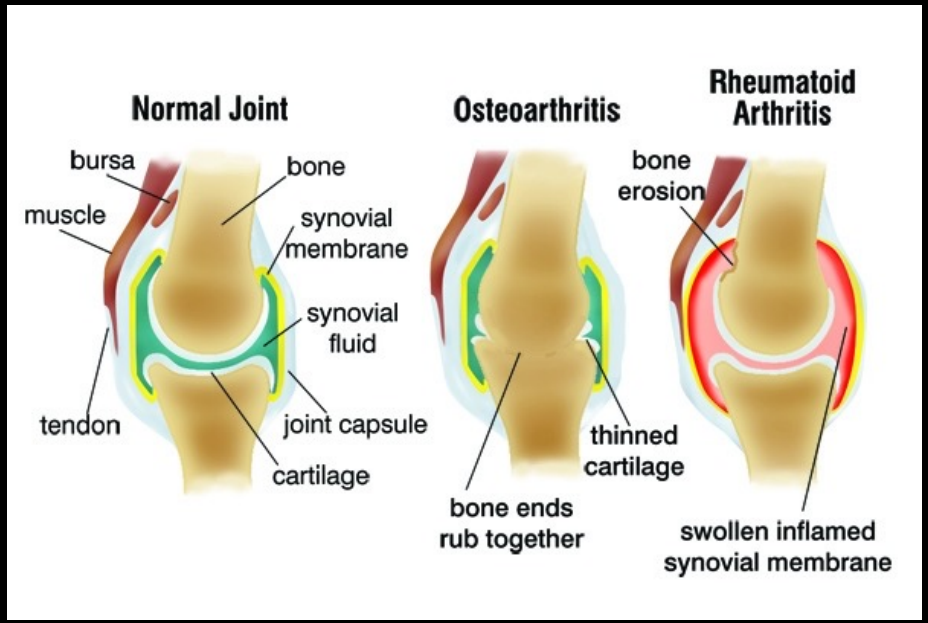
- Largest concern is unintentional overdoses
- Metabolism of acetaminophen by the liver is a saturable process
- Over the counter products and cumulative acetaminophen dosing



https://www.frontiersin.org/files/Articles/369124/fphar-09-00453-HTML/image_m/fphar-09-00453-g001.jpg accessed 4.20.2021

Inflammatory Pain

- NSAIDs
  - –Ibuprofen
  - –Naproxen
  - –Ketorolac
  - –Meloxicam
  - –Celecoxib
- Corticosteroids

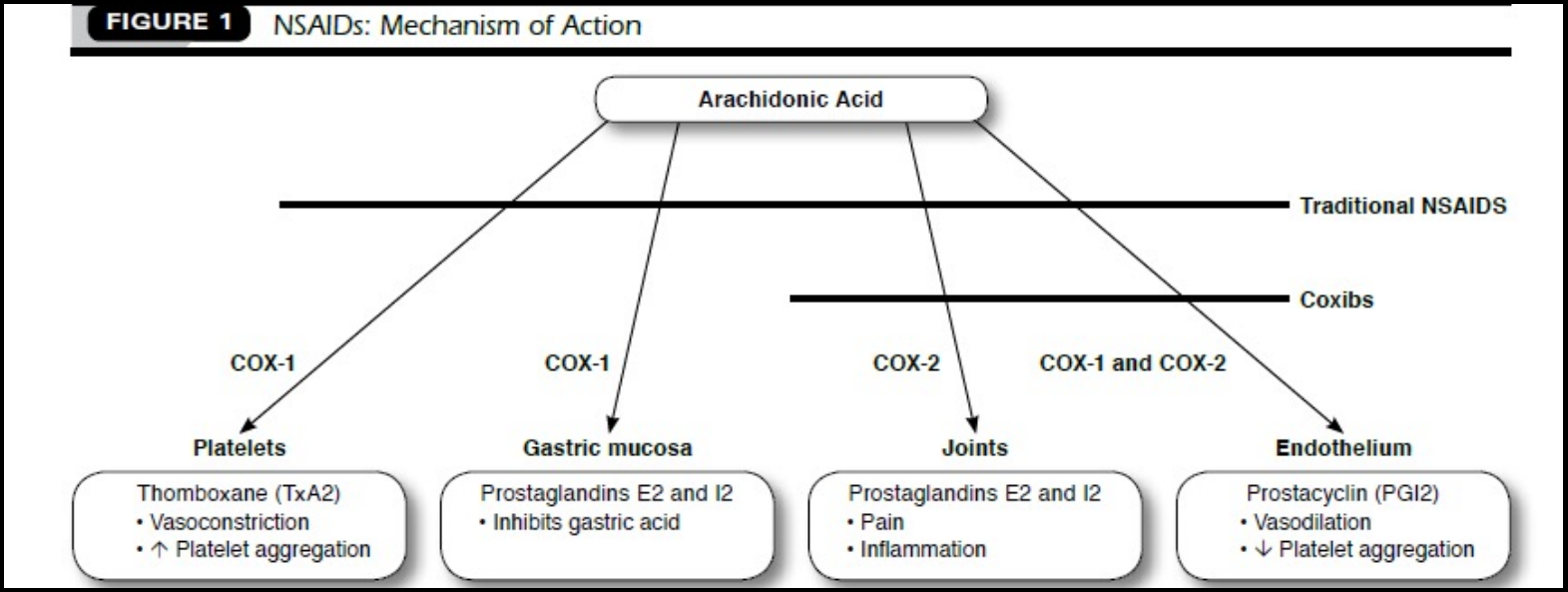


https://www.practicalpainmanagement.com/pain/myofascial/inflammatory-arthritis/pain-management-inflammatory-arthritis accessed 8.20.2021

Nonsteroidal Anti-Inflammatory Agents

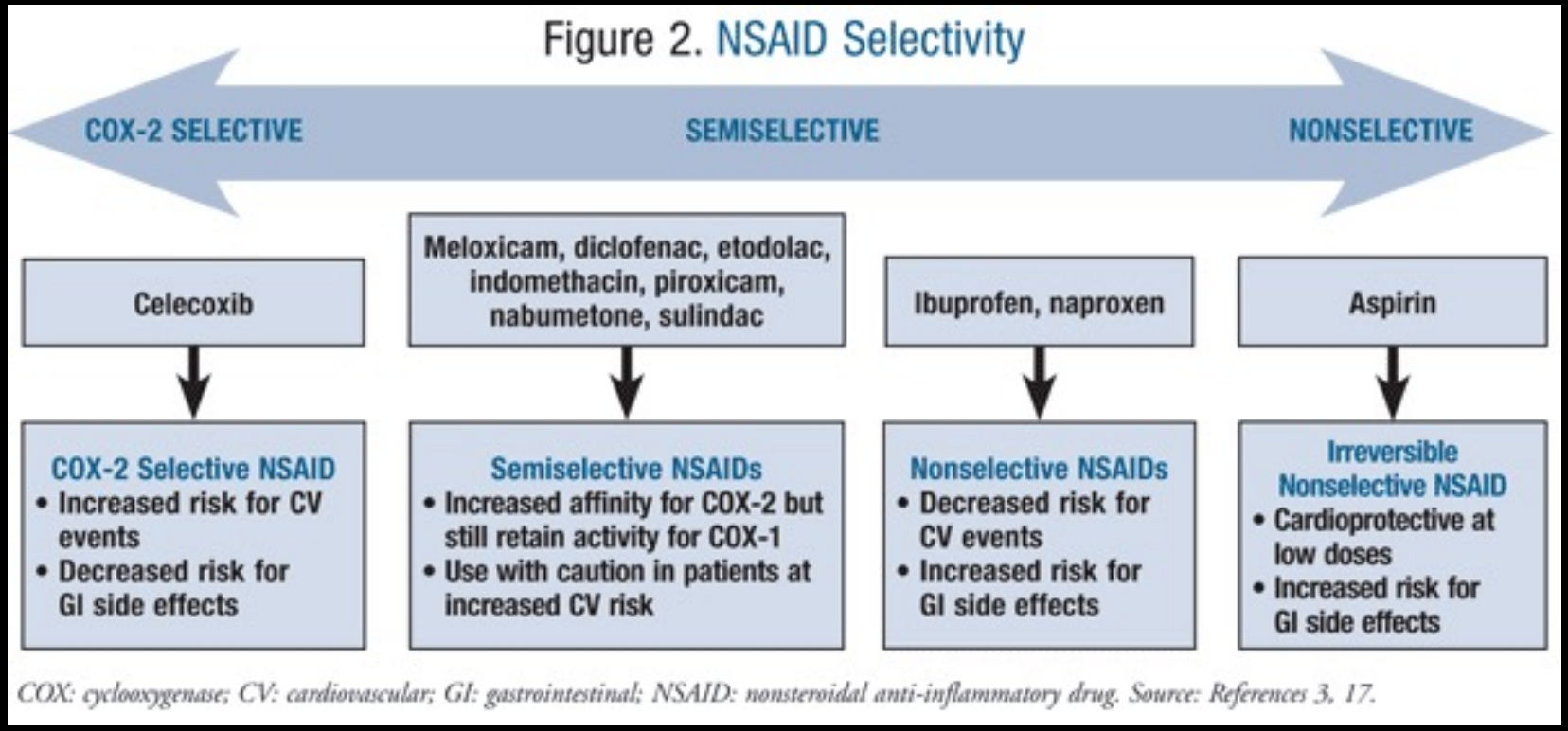
- COX 1 more specific to the GI tract and renal homeostasis
- COX 2 more specific to inflammation and platelet aggregation
- Certain co-morbidities limit the dosing on most NSAIDs
  - –Patients on anticoagulants
  - –Patients with renal dysfunction
  - –Pregnancy

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)



JMCP. 2013;19(9):S3-S19

NSAIDs and COX Selectivity



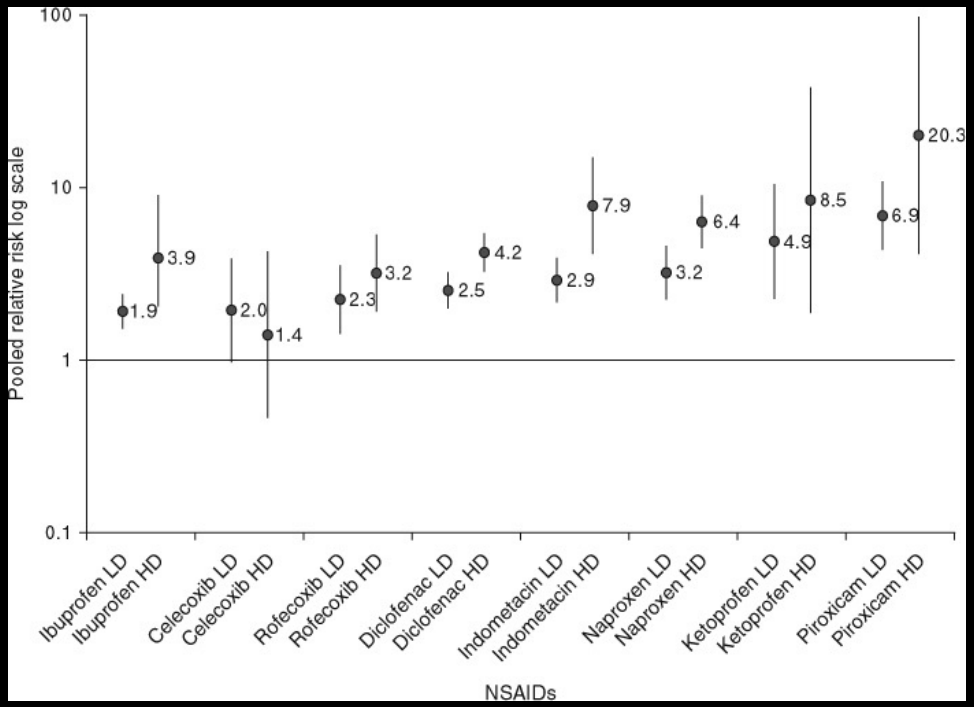
https://www.uspharmacist.com/article/cardiovascular-risk-associated-with-nsaids-and-cox2-inhibitors accessed 8.20.2021

NSAIDs and GI Adverse Effects

- Strategies to prevent gastric mucosal damage in chronic NSAID users
  - –Proton pump inhibitor
  - –Histamine-2 receptor antagonist
  - –Use of COX-2 selective NSAID
- Risk factors for NSAID-related GI toxicity
  - –History of peptic ulcer disease or upper GI bleed
  - –Age ≥65 years
  - –Presence of comorbidities such as rheumatoid arthritis
  - –Concomitant use of anticoagulants, aspirin or corticosteroids

Am J Gastroenterol. 2009;104:728-738
JMCP. 2013;19(9):S3-S19
Circulation. 2007;115:1634-1642

NSAIDs and GI Complications (GIC)



- Meta-analysis of GIC from individual NSAIDs
- GIC included ulceration, perforation, obstruction, and bleeding
- All COX nonspecific NSAIDs increase in risk of GIC when taken daily

Individual NSAIDs and Upper Gastrointestinal Complications. Drug Safety 2012; 35(12): 1127-1146

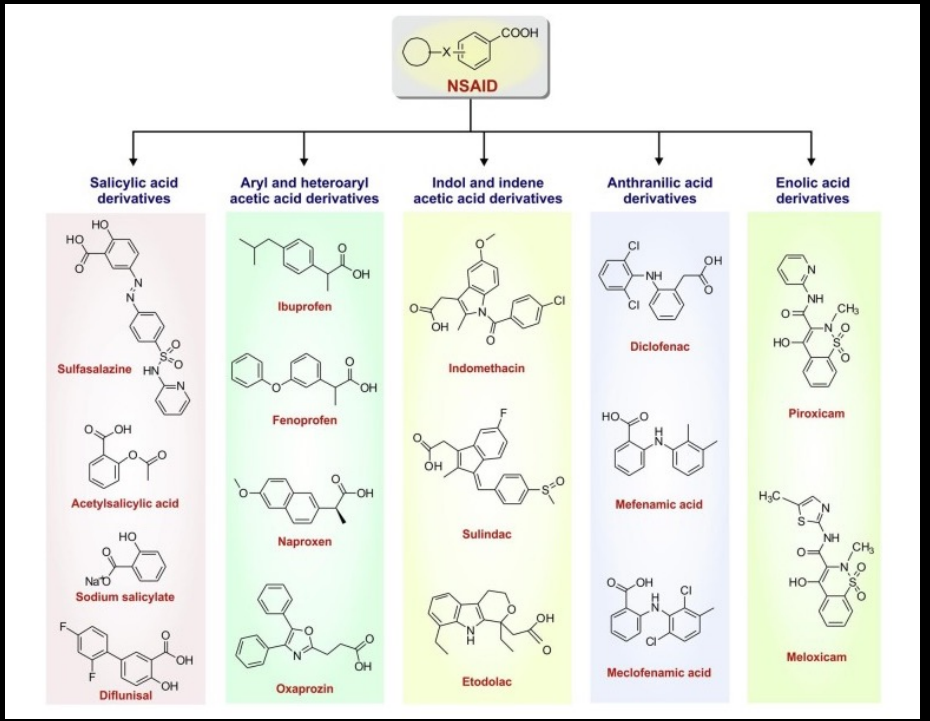
Use of NSAIDs and Fracture Healing

- Concern related to NSAIDs reducing mechanical strength and increasing the risk of non-union
  - Decreased risk with the COX-2 specifics agents compared to non-COX specific NSAIDs
- Four studies have fueled this paradigm
  - Each had major flaws in study design
    - Three were retrospective in nature, did not account for confounders [smoking]
    - The prospective trial had a total of 13 patients, raising a concern for power

J Orthop Trauma 33; e158–e182: 2019

Use of NSAIDs and Fracture Healing, cont.

- Two meta-analyses concluded there are no high-quality literature to support the thesis of NSAIDs leading to fracture non-union
- Opioids also impair immune function independently of NSAID use as well as other risks from the use of opioids
- NSAIDs should be considered for inflammatory pain conditions, even in those with fractures



https://europepmc.org/article/MED/32653589 accessed 5.7.2021

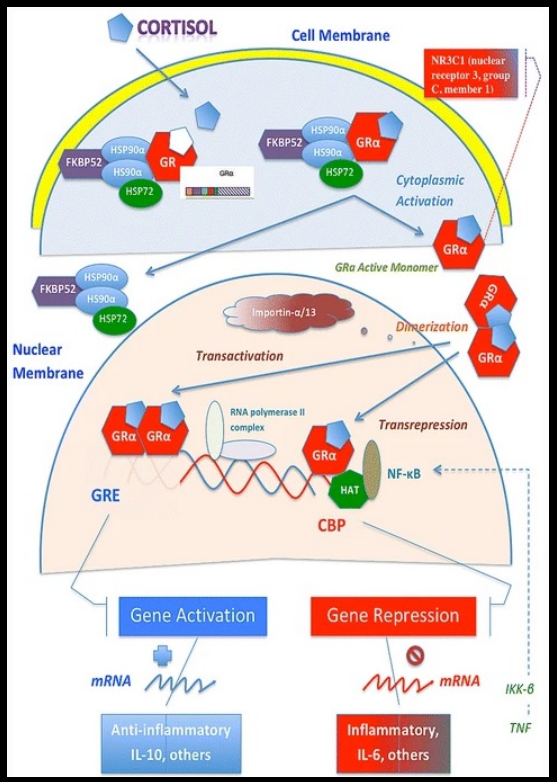
J Orthop Trauma 33; e158–e182: 2019

Topical NSAIDs

- Diclofenac sodium 1% gel
  - Upper extremity (hands, elbows, wrists) 2 g applied QID up to 8 g on any one joint
  - Lower extremity (knees, ankles, and feet) 4 g applied QID up to 16 g on any one joint
- Diclofenac epolamine 1.3% patch
  - 1 patch applied BID to the most painful area
- Both products carry the same boxed warnings but are proposed to have a more favorable safety profile than oral NSAIDs
- Application site reactions have been reported

1.Pain Medicine 2013; 14: S35–S39
2.Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD007400

Glucocorticoids



Increased transcription

- Lipocortin-1
- β2-adrenoreceptor
- Secretory leucocyte inhibitory protein
- Clara cell protein (CC10)
- IL-1 receptor antagonist
- IL-IR2 (decoy receptor)
- IκB-α

Decreased transcription

- Cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL- 6, IL-11, IL-12, IL-13, TNF-α, GM-CSF, and stem cell factor)
- Chemokines (IL-8, RANTES, MIP-1α, MCP-1, MCP-3, MCP-4, and eotaxin)
- iNOS
- COX-2
- Cytoplasmic PLA_2
- Endothelin-I
- NK_1-receptors, NK_2-receptors

https://icm-experimental.springeropen.com/articles/10.1186/s40635-017-0123-8 accessed 4.5.2021
International Journal of Endocrinology Volume 2012, ID 561018 doi:10.1155/2012/561018

Glucocorticoids, cont.

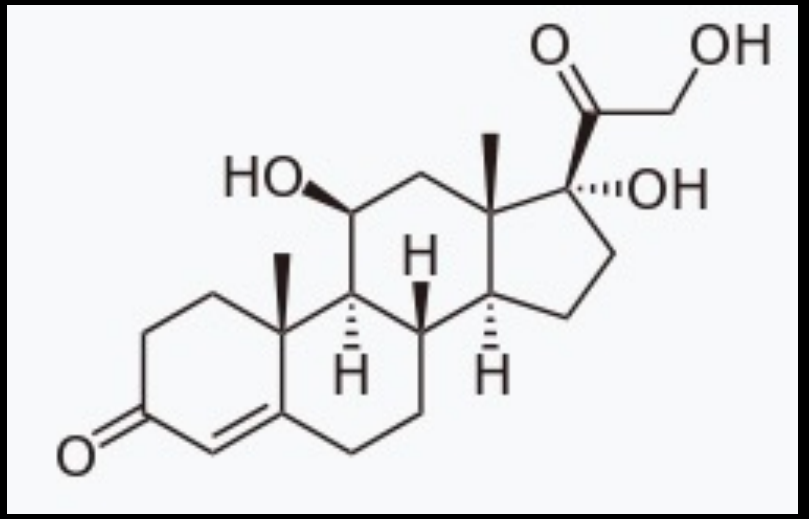
- Mechanism of action leads to an increase in anti-inflammatory mediators and a decrease in inflammatory molecules
- Multiple routes of administration
  - –Oral
  - –Parenteral
    - IV
    - IM depot
    - Intra-articular
    - Peri-neural

Agent	Relative Glucocorticoid Potency	Relative Mineralocorticoid Potency	Duration of Action
Hydrocortisone (Cortisol)	1	1	Short
Prednisolone	4-5	0.25	Short
Methylprednisolone	5-6	0.25	Short
Dexamethasone	18	<0.01	Long

adapted from http://tmedweb.tulane.edu/pharmwiki/doku.php/glucocorticoid_pharmacology 8.19.2021

Glucocorticoids, cont'd

- Caution should be exercised in patients with the following conditions
  - –Diabetes
  - –Psychiatric history
  - –Heart failure
  - –Adrenal suppression
    - •Taper needed when therapy exceeds 10 to 14 days
  - –Immunocompromised



https://en.wikipedia.org/wiki/Glucocorticoid accessed 8.19.2021

Topical glucocorticoids for pain?

- Skin serves as a physical and a chemical barrier to medication absorption
  - Stratum corneum contains alternating lipid and hydrophilic regions

Glucocorticoid	Prednisone	Methylprednisolone	Dexamethasone	Hydrocortisone
Molecular weight (Daltons)	360	370	390	362

  - Keratinocytes possess cytochrome P450 enzymes which metabolize substances that make it into the dermis
- Generally newer delivery techniques (iontophoresis, etc.) for glucocorticoid delivery into the skin are needed to penetrate deep tissue, joint or bone
- Over the counter creams and ointments will not penetrate sufficiently to reach deep tissue, joint or bone

Blood Purif 38; 154-7: 2014

Neuropathic Pain

- Anticonvulsants
  - –Gabapentin
  - –Pregabalin
  - –Carbamazepine
- Local anesthetics
- Antidepressants
  - –SNRIs
- Muscle relaxants
- Counter Irritants

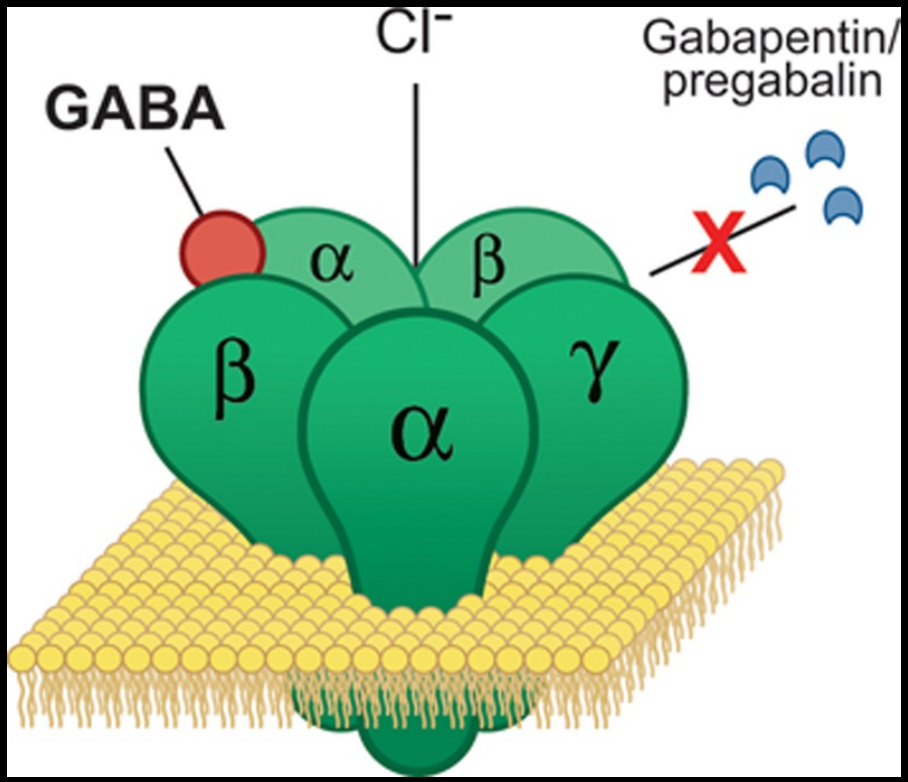
https://www.everydayhealth.com/neuropathy/guide/symptoms/ accessed 8.19.2021

Anticonvulsants Gabapentin & Pregabalin

- Structurally related to GABA but it does not bind to $GABA_A$ or $GABA_B$ receptors or influence the degradation or uptake of GABA
- Binds to the α_2-δ subunit of voltage-gated Ca^{2+} channels in CNS and peripheral nerves
- Reduces the Ca^{2+} -dependent release of pro-nociceptive neurotransmitters, possibly by modulation of Ca^{2+} channel function
- Pregabalin may also interact with descending noradrenergic and serotonergic pathways in the brainstem

J Clin Psychiatry. 2007 Mar;68(3):483-4

Mechanism of action α_2-δ ligands



Gabapentin

- Initial dose
  - 100 mg to 300 mg by mouth up to three times daily
  - Then increase dose based on response and tolerability to a maximum total daily dose of 3600 mg
- Renal dose adjustment required
- NO hepatic adjustment needed
- Most common adverse effects
  - Dizziness and drowsiness
  - Ataxia
  - Fatigue

https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6961 accessed 8.19.2021

Gabapentin ER

- Do not use interchangeably with other gabapentin products
- Max dose 1200 mg/day in single dose with evening meal or twice daily
- Renal dose adjustment required
- Same common side effects as gabapentin immediate release

- Titration recommendations
  - –Day 1-3: 600 mg daily
  - –Day 4-6: 600 mg twice daily
  - –No additional benefit shown for doses over 1200 mg total daily dose

https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/3414739 accessed 8.19.2021

Pregabalin

- Initial dose
  - 25 mg to 150 mg by mouth once or twice a day
  - Then increase the dose in one week based on tolerability to a maximum daily dose of 450 mg
  - Doses up to 600 mg have been evaluated with no significant additional benefit
- Renal dose adjustment required
- NO hepatic adjustment needed
- Most common adverse effects
  - Dizziness and somnolence
  - Peripheral edema

https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/152621 accessed 8.19.2021

Anticonvulsants: Alternative Options

- **Carbamazepine**
  - Drug of choice for trigeminal neuralgia
  - May require titration of dose to maximum of 1200 mg per day
  - Consider obtaining baseline CBC and LFTs
    - Consider periodic monitoring of CBC and LFTs thereafter

- **Oxcarbazepine**
  - Better tolerability compared to carbamazepine
  - Titration begins at 150 mg twice daily to a maximum dose of 1800 mg per day
  - Patients allergic to carbamazepine should also avoid oxcarbazepine
    - 25% allergic cross-reactivity

* Not FDA approved for the management of pain

Hooten M, et al. Institute for Clinical Systems Improvement. Pain: Assessment, Non-Opioid Treatment Approaches and Opioid Management. Updated September 2016
Update on neuropathic pain treatment for trigeminal neuralgia. Neuroscience, 20.2.107-14 2015

Anticonvulsants: Alternative Options (cont'd)

❖**Lamotrigine**

- Data supports use in refractory trigeminal neuralgia, central poststroke pain, SCI pain with incomplete cord lesion and brush-induced allodynia, HIV-associated neuropathy in patients on antiretroviral therapy, and diabetic neuropathy
- Most effective at doses between 200-400 mg per day
  - Follow strict titration schedule to reduce the risk of serious skin reactions
- Immune response

❖**Topiramate**

- Data supports use in diabetic neuropathy, refractory trigeminal neuralgia, and for migraine prophylaxis
- Dosing generally ranges from 50-100 mg per day
- Dosing over 200 mg is generally side-effect limiting

* Not FDA approved for the management of pain

Neurol Sci (2006) 27:S183–S189
R.H. Dworkin et al. / Pain 132 (2007) 237–251

Anticonvulsants—Neurocognitive

- Psychomotor reaction time
- Learning, memory, and executive function
- Word finding
- Considerable variance based on
  - –Age
  - –Multiple anticonvulsants
  - –Serum drug concentrations
- All anticonvulsants appear to have some effect on neuropsych batteries

Meador KJ. *Epilepsy Res.* 2006;68(1):63-67
Pandina GJ, et al. *Pediatr Neurol.* 2010;42(3):187-195
Koch MW, Polman SKL. Oxcarbazepine versus carbamazepine monotherapy for partial onset seizures. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD006453
Jassen P, et al. *Acta Neurol Scand.* 2009;119(3):194-198

Local Anesthetics

- Mechanism of action is through membrane stabilization of sodium channels preventing depolarization and signal transduction
- Acute uses for local anesthesia (procedures, etc.)
  - –Topical application
    - •Cream, ointment, patch, etc
  - –Intradermal injections
  - –Nerve blocks
- Patches are indicated for the management of postherpetic neuralgia

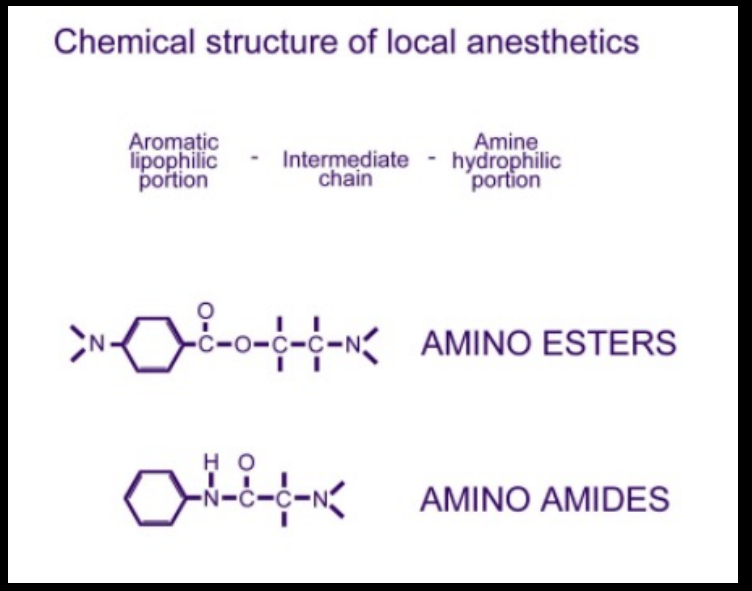
Local anesthetics

Amino-Amide agents

- Lidocaine
- Mepivacaine
- Bupivacaine/ Levobupivacaine
- Prilocaine
- Ropivacaine

Amino-Ester agents

- Tetracaine
- Chloroprocaine
- Procaine
- Benzocaine
- Cocaine



Adapted from https://emedicine.medscape.com/article/873879-overview#:~:text=Commonly%20used%20amino%20amides%20include,etidocaine%2C%20and%20ropivacaine%20and%20levobupivacaine.&text=Commonly%20used%20amino%20esters%20include,tetracaine%2C%20chloroprocaine%2C%20and%20benzocaine. accessed 4.6.2021

Lidocaine

- May be used topically or by injection
- Topical patch available in 0.5% to 5%
- 5% patch applied directly to area of post-herpetic neuralgia
  - No more than 3 patches concurrently
  - 12 hours on, 12 hours off
- Trigger point injections
  - Caution in patients on anticoagulants
  - Local anesthetic allergy history

Khalil V, et al. Topical lidocaine for the treatment of postherpetic neuralgia. Cochrane Database Syst Rev 2007;18:CD004846
Alvarez DJ, et al. Trigger Points: Diagnosis and management. American Family Physician 2002 65 (4): 653-61

Tricyclic Antidepressants

- Mechanism of action is through inhibition of norepinephrine and serotonin reuptake and inhibition of sodium channel action potentials
- The antidepressant effects and the neuropathic pain analgesia are independent
  - –Higher dosing and longer treatment time needed for antidepressant effects
- Caution should be exercised in patients
  - –With cardiac arrhythmias
  - –Over the age of 65

Tricyclic Antidepressants, cont.

Initial doses for neuropathic pain

- Nortriptyline 10 mg PO at bedtime
- Desipramine 25 mg PO at bedtime
- Amitriptyline 10-25 mg PO at bedtime
  - Increase by 10-25mg PO every 7 days
  - Use doses UNDER 100 mg per day when possible
  - Use with caution in BPH, glaucoma, cardiac disease, and those at risk for suicide

- Not FDA approved for this indication

Lancet Neurol 2015; 162–73

BPH = benign prostatic hyperplasia

Tricyclic Antidepressants, cont.

Tertiary amines	Secondary amines (NE>5HT)
Amitriptyline Imipramine Clomipramine Doxepin Trimipramine	Nortriptyline Desipramine Protriptyline

- Secondary amines tolerated better than tertiary amines
- Secondary amines equally effective in pain as tertiary amines
- Therapeutic drug monitoring of questionable utility
- Alzheimer's risk and anticholinergic activity

Watson. *Neurology.* 1998;51:1166-1171
McQuay. *Pain.* 1996;68:217-227
Table adapted from Lexi-Drugs Online. www.uptodate.com. Accessed 8.20.2021
Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review

Tricyclic Antidepressants—Cardiovascular Risk

- Orthostatic/postural hypotension
- Slowed cardiac conduction, tachycardia, ventricular fibrillation, heart block, and ventricular premature complexes (think Class 1a anti-arrhythmic agents)
- Sudden cardiac death (unclear association with QTc prolongation)
  - Avoid doses greater than 100 mg per day of amitriptyline equivalents
- Avoid in those with cardiovascular disease or established conduction abnormalities
- Baseline ECG recommended by some in those > 40 years of age (> 50 years of age based on APA Depression Guidelines)
- Routine ECG monitoring not recommended unless CV symptoms arise

Ray WA, et al. *Clin Pharmacol Ther*. 2004;75:234-241
Gelenberg AJ, et al. Practice guideline for the treatment of patients with Major Depressive Disorder, 3rd Edition. www.psychiatryonline.org. Accessed 8.20.2021

Serotonin Norepinephrine Reuptake Inhibitors (SNRI)

- Mechanism of action is through inhibition of norepinephrine and serotonin reuptake
- Dosing is generally higher for treating neuropathic pain compared to treating depression
  - –Duloxetine 60 mg twice daily versus duloxetine 60 mg daily
- Withdrawal syndromes can occur if patients are taken off SNRI therapy abruptly
  - –Anxiety, irritability, headache, paresthesia, nervousness
- Caution should be exercised in patients with liver dysfunction, uncontrolled hypertension, or moderate cardiovascular disease

SNRI

Venlafaxine*

- Target dose (either IR or SA) is 225 mg/day
- Renal dose adjustment necessary
- Hepatic dose adjustment necessary
- Use with caution in cardiovascular disease (can increase blood pressure and cause EKG changes)

Duloxetine

- Target dose 60 mg to 120 mg daily
  - Low back and osteoarthritis of the knee
  - Fibromyalgia
  - Diabetic neuropathy
- Not recommended for use in patients with ESRD or severe renal impairment
- Not recommended for use in hepatic insufficiency or impairment

*Not FDA approved for any pain indications

https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7862 accessed 8.19.2021

https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6798 accessed 8.19.2021

SNRI, cont'd

Milnacipran

- Initial dose and titration schedule
  - 12.5 mg PO once daily on day 1
  - 12.5 mg PO BID on days 2-3
  - 25 mg PO BID on days 4-7
  - 50 mg PO BID thereafter
- Target dose
  - 50 mg PO BID
- Maximum dose
  - 100 mg PO BID
- Dose adjustment required in renal impairment

https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/518 accessed 8.19.2021

Serotonin Syndrome

- Mental status changes
  - Anxiety, agitated delirium, restlessness, disorientation
- Autonomic hyperactivity
  - Diaphoresis, tachycardia, hyperthermia, HTN, vomiting, and diarrhea
- Neuromuscular changes
  - Tremor, muscle rigidity, myoclonus, hyperreflexia, and clonus
- Severity may range from benign to lethal
- Solely a clinical diagnosis
- Patient and caregiver education paramount

Boyer EW, et al. *N Engl J Med.* 2005;352(11):1112-1120
Mackay FJ, et al. *Br J Gen Pract.* 1999;49(448):871-874

Diagnosis of SS: Hunter Criteria

- Serotonergic agent PLUS one of the following
  - Spontaneous clonus
  - Inducible clonus and agitation or diaphoresis
  - Ocular clonus and agitation or diaphoresis
  - Tremor and hyperreflexia
  - Hypertonia
  - Temp above 38°C (100.4° F)
- Although clinical dx, consider CBC, BMP, INR, CPK, LFTs, UA, chest X-ray, head CT, to rule out differentials

Dunkley EJ, et al. *QJM*. 2003;96(9):635-642

Capsaicin 8 % Patch

Dose is a single 60-minute application of up to 4 patches

May be repeated every 3 months or as warranted by the return of pain	Only physicians or healthcare professionals under supervision of a physician are to administer capsaicin 8% patch	Consider monitoring BP during or shortly after patch application Patients may require short-term pain medication postapplication

https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6521 accessed 8.19.2021

Neuropathic Pain guidelines

- Amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia)
  - –Carbamazepine as initial treatment for trigeminal neuralgia
- Tramadol only if acute rescue therapy is needed
- Capsaicin cream for people with localized neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments

https://www.nice.org.uk/guidance/cg173/resources/neuropathic-pain-in-adults-pharmacological-management-in-nonspecialist-settings-pdf-35109750554053 accessed 4.29.2021

Muscle relaxants

- Spasticity
  - Upper motor neuron disorder characterized by muscle hypertonicity and involuntary jerks
- Indications
  - Multiple sclerosis
  - Cerebral palsy
  - Spinal cord injury
  - Acute muscle spasms

Chou R, et al. J Pain Symptom Manage. 2004;28:140-75
Van Tulder MW, et al. Cochrane Database Syst Rev. 2003;(2):CD004252
Pharmacotherapy 2008;28(2):207–213
Ann Intern Med. 2007 Oct 2;147(7):478-91
Skeletal Muscle Relaxants: Quick Reference. Compiled by Nolan MJ and Fudin J
Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc.,; Hudson, OH; 1 May 2015

Anti-spasticity agents

Baclofen

- GABA analogue
- Selective GABA-B receptor agonist (↑ K+ conductance, ↓ Ca++ conductance)
- Muscle relaxant and analgesic (reduced substance P)
- 5 mg PO TID, may titrate every 3 days to effect
- Max dose: 80 mg/day
- Adverse effects: somnolence, increased seizure activity

Tizanidine

- Agonist of α2 receptors (presynaptic)
- Reduces adrenergic input to alpha motor neurons
- No effect on spinal cord reflex
- Less antihypertensive effect than clonidine
- 2 to 8 mg PO TID
- Max dose: 36 mg /day
- Side effects: hypotension, asthenia, elevated LFTs, hepatotoxicity

Pharmacotherapy 2008;28(2):207–213
Skeletal Muscle Relaxants Quick Reference. Compiled by Nolan MJ and Fudin J

Antispasmodics

- Antispasmodics
  - Primarily used for treatment of musculoskeletal conditions, such as back pain, sciatica, herniated discs, spinal stenosis, myofascial pain

  - Cyclobenzaprine
  - Metaxalone
  - Methocarbamol
  - Orphenadrine citrate
  - Carisoprodol

Indicated for **acute** use in low back pain!

- Less than 4 weeks use to treat an episode
- May be effective for an acute-on-chronic pain episode

Antispasmodics, cont.

- Cyclobenzaprine—sedation, structurally a TCA
- Tizanidine—sedating, hypotension, best data
- Methocarbamol—less sedating, limiting evidence
- Orphenadrine—sedating, sodium channel blockade
- Carisoprodol—sedating, high abuse potential
- Diazepam—sedating, high abuse potential
- Metaxalone—less sedating, expensive
- Baclofen—data primarily intrathecal
- Dantrolene—hepatotoxicity

Musculoskeletal Pain Management

- Acute pain from non–low back, musculoskeletal injuries with topical nonsteroidal anti-inflammatory drugs (NSAIDs) with or without menthol gel as first-line therapy Strong recommendation

- Acute pain from non–low back, musculoskeletal injuries with oral NSAIDs
- Acute pain from non–low back, musculoskeletal injuries with specific acupressure, with transcutaneous electrical nerve stimulation, or oral acetaminophen to reduce pain
- Acute pain from non–low back, musculoskeletal injuries with opioids, including tramadol

Annals of Internal Medicine 173; 9: 739-48 2020

Conclusions

- Adjuvant and coanalgesics require judicious monitoring for safe use
- Extensive patient education regarding potential adverse effects is paramount
- Comorbid disease processes and concurrent medications may obscure adverse effects