



**Nonopioid Analgesics:
The Selection and Use of Adjuvant Therapies**

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Disclosures

- Nothing to disclose



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



Are opioids still a concern?

- Drug overdose fatalities involving opioids in the US from 1999 to 2017¹ ▪ 399,230 (56.8% of all cases)
- Drug overdose fatalities involving opioids in the US in 2017¹ ▪ 47,600 (67.8% of all cases)
- Rate of overdose fatalities involving opioids in women age 30-64 from 1999 to 2017 increased by² ▪ 492%

1. Schott L, Seth P, Kertisa M, Wilson N, Baldwin G. Drug and Opioid-Involved Overdose Deaths — United States, 2013–2017. *MMWR Morb Mortal Wkly Rep* 2019;67:1419–1427.
 2. VanHooken JP, Rudd RA, Ballesteros MF, Meek KA. Drug Overdose Deaths Among Women Aged 30–64 Years — United States, 1999–2017. *MMWR Morb Mortal Wkly Rep* 2019;68:1–5.



Risk Factors for Opioid Overdose or Addiction

Risk factors for overdose

- Daily dose > 100 MEDD
- Long-acting (LA) or extended-release (ER) formulation
- Combination with benzodiazepines
- Long-term use (> 3 months)
- Period shortly after initiation of LA/ER formulation

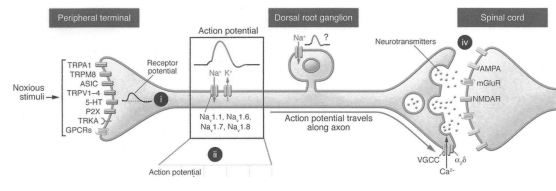
Risk factors for addiction

- Age > 65 years
- Sleep disordered breathing
- Renal/hepatic impairment
- Depression
- Substance use disorder
- History of overdose

Volkow NJ et al. *NEJM*.2016;374:1253-1263.
 MEDD = morphine equivalent daily dose

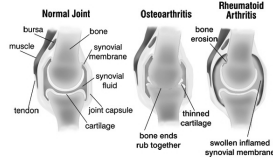


Where Do Adjuvants Work?



Inflammatory Pain

- NSAID
 - Ibuprofen
 - Naproxen
 - Ketorolac (IV form)
 - Meloxicam
 - Celecoxib
- Corticosteroids



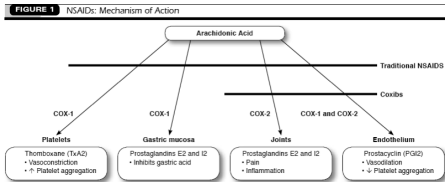
<http://www.painweek.com/ibuprofen/celecoxib/meloxicam/ketorolac/naproxen/ibuprofen/celecoxib> accessed 3/11/2019



Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

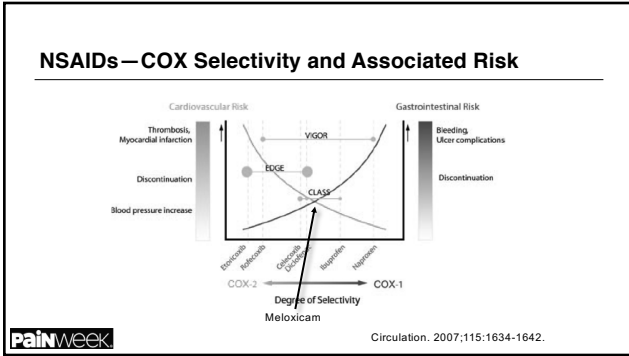


Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)



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





Celecoxib & Cardiovascular (CV) Safety

- **Clinical question:** How does the CV safety of celecoxib, a COX-2 selective NSAID, compare to that of a nonselective NSAID, such as ibuprofen or naproxen?
- Primary composite outcome of CV death (including hemorrhagic death), nonfatal MI, or nonfatal stroke
- Mean treatment duration of 20.3±16.0 months and a mean follow-up period of 34.1±13.4 months
- In regards to the primary outcome, celecoxib was found to be **noninferior** to both ibuprofen and naproxen
- Risk of GI events was **significantly lower** with celecoxib compared to both ibuprofen and naproxen
- Study funded by Pfizer

N Engl J Med 2016; :2519-2529.

NSAIDs and GI Adverse Effects

- Strategies to prevent gastric mucosal damage in chronic NSAID users:
 - Proton pump inhibitor (PPI)
 - Histamine-2 receptor antagonist (H2RA)
 - Use of COX-2 selective NSAID
- Risk factors for NSAID-related GI toxicity:
 - History of peptic ulcer disease or upper GI bleed
 - ≥65 years old
 - Presence of comorbidities such as rheumatoid arthritis
 - Concomitant use of anticoagulants, aspirin or corticosteroids

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

Topical NSAIDs

- Diclofenac sodium 1% gel
 - Dosing:
 - Upper extremity (hands, elbows, wrists): 2g applied QID up to 8g on any one joint
 - Lower extremity (knees, ankles, and feet): 4g applied QID up to 16g 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
- Most common adverse effect: application site reactions

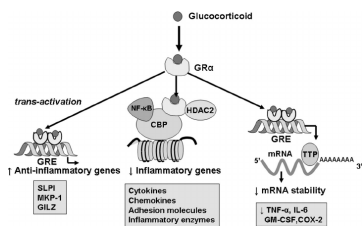


1. Pain Medicine 2013; 14: S35-S39.
2. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD007400.

Corticosteroids



Corticosteroids



<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3410000/>

Glucocorticoids

- Mechanism of action leads to a decrease in production of heat shock proteins intracellularly leading to a decrease inflammation
- Multiple routes of administration
 - Oral
 - Parenteral
 - IV
 - IM depot
 - Intraarticular



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



Neuropathic Pain

- Anticonvulsants
 - Gabapentin
 - Pregabalin
 - Carbamazepine/oxcarbazepine
 - Lamotrigine (off-label indication)
 - Topiramate (off-label indication)
- Antidepressants
 - TCAs (off-label indication)
 - SNRIs
- Local anesthetics



<http://www.royalcollegeofphysicians.com/healthcare/2014/03/12/2019>



Anticonvulsants

Painweek

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 $\alpha_2\text{-}\delta$ 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

Painweek

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

Mechanism of action $\alpha_2\text{-}\delta$ ligands

Painweek

By EthicalMind1 - Own work. CC BY-SA 4.0. https://commons.wikimedia.org/wiki/File:GABA_A_receptor_mechanism_of_action.png (revised 3/12/2019)

Anticonvulsants

Gabapentin

- Initial dose: 100 mg to 300 mg by mouth up to 3 times daily
- Increase dose based on response and tolerability to a maximum total daily dose of 3600 mg
- Renal dose adjustment required
- NO hepatic adjustment needed
 - Gabapentin is not metabolized by hepatic enzymes
- Most common adverse effects:
 - Dizziness and drowsiness (approx. 20%)
 - Ataxia
 - Fatigue

https://online.lexi.com/docui/section/cp/bet/betlevel/docid/docatch_69981 accessed 3.12.2019



Anticonvulsants (cont'd)

Pregabalin

- Initial dose: 25 mg to 150 mg by mouth once or twice a day
- Increase dose in 1 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
 - Pregabalin is minimally metabolized by hepatic enzymes
- Most common adverse effects:
 - Dizziness and somnolence
 - Peripheral edema

https://online.lexi.com/docui/section/cp/bet/betlevel/docid/docatch_69982 accessed 3.12.2019



Anticonvulsants: Alternative Options

▪ Carbamazepine

- Drug of choice for trigeminal neuralgia
- May require titration of dose to maximum of 1200 mg/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/day
- Patients allergic to carbamazepine should also avoid oxcarbazepine, 25% allergic cross-reactivity

1. Hooten M, et al. Institute for Clinical Systems Improvement. Pain: Assessment, Non-Opioid Treatment Approaches and Opioid Management. Updated September 2016.
 2. Update on neuropathic pain treatment for trigeminal neuralgia. Neuroscience, 20:2:107-14 2015.



Anticonvulsants: Alternative Options (cont'd)

- **Lamotrigine** (off-label indication)
 - 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/day
 - Note: follow strict titration schedule to reduce the risk of serious skin reactions
 - Immune response?

- **Topiramate** (off-label indication)
 - Data supports use in diabetic neuropathy, refractory trigeminal neuralgia, and for migraine prophylaxis
 - Dosing generally ranges from 50-100 mg/day
 - Dosing over 200 mg is generally side-effect limiting

1. *Neurol Sci* (2006) 27:S183-S189.
2. 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

1. Meador KJ. *Epilepsy Res.* 2006;68(1):63-67.
2. Pandina GJ, et al. *Psychiatr Neurol.* 2010;42(3):187-195.
3. Koch MW, Prilman SKL. Oxcarbazepine versus carbamazepine monotherapy for partial onset seizures. *Cochrane Database of Systematic Reviews* 2009, Issue 4, Art. No.: CD009453. DOI: 10.1002/14651858.CD009453.pub2.
4. Hassen E, et al. *Acta Neurol Scand.* 2009;119(3):194-198.



Antidepressants



Tricyclic Antidepressants (TCAs)

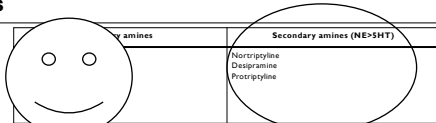
Initial dosing of TCAs

- **Nortriptyline** 10 mg at bedtime (off-label indication)
- **Desipramine** 25 mg at bedtime (off-label indication)
- **Amitriptyline** 10-25 mg at bedtime (off-label indication)
 - Use with caution in BPH, glaucoma, cardiac disease, and those at risk for suicide



Lancet Neurol 2015; 162–73.

TCAs



- 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

1. Watson, Neurology, 1998;51:1156-1171.
 2. McCarty Pain 1996;6(2):17-22.
 3. Table adapted from Lexi-Drugs Online. www.lexi-drugs.com. Accessed 2/9/2018.
 4. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review



TCAs—Anticholinergic & Sedation

- **Muscarinic receptor antagonists**
 - Blurred vision, constipation, dry mouth, urine retention, constipation, tachycardia, confusion, delirium, increased ocular pressure
 - Secondary amines < tertiary amines
- **Antihistaminergic effects (sedation, delirium)**
 - Maprotiline, amitriptyline, doxepin, and trimipramine



TCAs—Cardiovascular Risk

- Orthostatic/postural hypotension
 - Alpha adrenergic blockade (even at low doses)
- Slowed cardiac conduction, tachycardia, ventricular fibrillation, heart block, and ventricular premature complexes (similar to Class Ia AA)
- Sudden cardiac death (unclear association with QTc prolongation)
 - Avoid doses > 100 mg/day amitriptyline equivalents
- Avoid in those with cardiovascular disease or established conduction abnormalities
- Screen for known heart disease, syncope, palpitations, dyspnea, or chest pain
- 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

1. Ray WA, et al. Clin Pharmacol Ther. 2004;75:224-241.
 2. Gelenberg AL, et al. Practice guideline for the treatment of patients with Major Depressive Disorder, 3rd Edition.
www.psychiatryonline.org. Accessed 3/9/2018



TCAs—Behavioral Health Risks

- Abrupt discontinuation
 - Withdrawal symptoms (GI, malaise, chills, rhinitis, and myalgias)
 - Rebound depression
- Increased suicidality vs overdose toxicity
 - Boxed warning for children, adolescents, young adults (18-24 years of age)
 - Cardiac (QTc) and anticholinergic toxicity at doses as little as 10 x prescribed

1. Libbati LA, Fava M, Rosenbaum JF, et al. Drugs for the treatment of depression. In: Handbook of Psychiatric Drug Therapy, 6th ed. Lippincott Williams & Wilkins, Philadelphia 2010.
 2. Dattai A, et al. J Clin Psychopharmacology. 1998;18:343-344.
 3. Fava MA, et al. Am J Psychiatry. 2009;166:156-172.
 4. Van Scheyen JD, et al. Arch Gen Psychiatry. 1979;36:560-565.



SNRI

Venlafaxine (off label)

- Initial dose: 37.5 mg to 75 mg ER by mouth once a day
- Increase dose by 37.5 mg to 75 mg ER daily every week
 - Target dose of 225 mg ER once daily
- Renal and hepatic dosing adjustments necessary
- Discontinuing therapy should be done over 2 to 4 weeks
- Most common adverse effects
 - Suicidal ideations [Black box warning]
 - Children and up to 24 years of age
 - Anxiety, insomnia

Duloxetine

- Initial dose: 30 mg by mouth once a day
- Increase dose to 60 mg ER every week
 - Maximum daily dose 120 mg
- Avoid use with severe renal or hepatic impairment
- Discontinuing therapy should be done over 2 to 4 weeks
- Most common adverse effects
 - Suicidal ideations [Black box warning]
 - Children and up to 24 years of age
 - Cognitive impairment

<https://online.lexi.com/docaction/home> accessed 3.13.2019



SNRI (cont'd)

- Milnacipran for fibromyalgia
 - Initial dose: 12.5 mg PO once daily on Day 1
 - Titration schedule:
 - 12.5 mg PO BID on Days 2-3
 - 25 mg PO BID daily on Days 4-7
 - 50 mg PO BID thereafter
 - Target dose: 50 mg PO BID (100 mg/day)
 - Maximum: 100 mg PO BID (200 mg/day)
 - Dose adjustment required in renal impairment

Painweek https://online.lexi.com/doc/lectio/doc/2627e5e0d6c0d7a84c_18516 accessed 3.13.2019

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

Painweek 1. Boyer EW, et al. *N Engl J Med* 2005;352(11):1112-1120.
2. Mackay FJ, et al. *Br J Gen Pract* 1999;49(446):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

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

SNRI Bleeding Risk

- Blocked serotonin uptake into platelet
- De-amplification of platelet aggregation
- Controversial data suggests:
 - Minimal risk of upper GI bleed as monotherapy
 - Increased risk of upper GI bleed in combination with NSAIDs
 - Acid suppression therapy decreases risk

1. Dalton SO, et al. Arch Intern Med. 2003;163(1):59-64.
2. Laha TK, et al. Aliment Pharmacol Ther. 2008;27(1):31-40.
3. McCloskey DG, et al. Transl Res. 2008;151(3):168-172.
4. de Abajo FJ, et al. Arch Gen Psychiatry. 2008;65(7):795-803.



Local Anesthetics




Lidocaine

- May be used topically or by injection
- Topical patch available in 0.5% to 5%
- 5% patch applied directly to area of postherpetic neuralgia¹
 - No more than 3 patches concurrently
 - 12 hours on, 12 hours off
- Trigger point injections²
 - Lidocaine or procaine
 - Caution in patients on anticoagulants and local anesthetic allergy history

1. Kalso W, et al. Topical lidocaine for the treatment of postherpetic neuralgia. Cochrane Database Syst Rev 2007;1:CD004646.
2. Alvarez DJ, et al. Trigger Points: Diagnosis and management. American Family Physician 2002 65 (4): 653-61.





Antispasticity and Antispasmodic Agents



Muscle Spasms


- Baclofen
- Tizanidine
- Other agents
 - Cyclobenzaprine, the TCA ?

Muscle Relaxants

- Antispasticity agents
 - Spasticity: upper motor neuron disorder characterized by muscle hypertonicity and involuntary jerks
 - Multiple sclerosis, cerebral palsy, spinal cord injury
 - Tizanidine
 - Baclofen
 - Diazepam

1. Chou R, et al. Pain Symptom Manage. 2004;28:140-75.
 2. Van Tulder HP, et al. Cochrane Database Syst Rev. 2005;(3):CD004312.
 3. Pharmacotherapy. 2008;38(2):207-210.
 4. Ann Intern Med. 2007;147(2):478-81.
 5. StatPearls Publishing. Quick Reference. Compiled by Robin M and Fadi J.
 6. Lexi-Comp, Inc. Lexi-Comp®. Lexi-Comp, Inc., Hudson, OH. 1 May 2015.




III. Centrally-acting agents (spasmodic drugs)

Muscle Relaxants (cont'd)

<p>Baclofen</p> <ul style="list-style-type: none"> 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 	<p>Tizanidine</p> <ul style="list-style-type: none"> 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
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1. Pharmacotherapy 2008;28(2):207-213.
 2. Skeletal Muscle Relaxants Quick Reference. Compiled by Nolan M. Hays, FRCPC, J.




Muscle Relaxants (cont'd)

- 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



Cyclobenzaprine, or Something Else?

Cyclobenzaprine Hydrochloride
Tablets, USP

10 mg

1000 TABLETS


NDC 16276-176-17

Amitriptyline Hydrochloride
Tablets USP

150 mg

Rx Only

1,000 Tablets



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