PainWeek®

Pain Therapeutics: Adjuvants and Nonopioid Analgesics

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Disclosure

- Abigail Brooks
  - Nothing to disclose
- Courtney Kominek
  - Honoraria: Quest Diagnostics

- The views and opinions expressed in this presentation are those of the authors and do not necessarily reflect the official policy or position of any agency of the United States government, including the Department of Veterans Affairs, as well as employers, employee affiliates and/or pharmaceutical companies mentioned or specific drugs discussed.

Learning Objectives

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

Case #1

- MT is a 39-year-old male Iraqi War veteran presenting to clinic with complaints of low back pain that's limiting his ability to do his normal daily activities. He's tried acetaminophen, ibuprofen, and naproxen without benefit. He asks for a muscle relaxant today.
- He also reports flashbacks and nightmares of war. For the past few months he's been avoiding his military friends and isolating himself at home.
- Additionally, he reports hypertension controlled with hydrochlorothiazide/lisinopril 25mg/20 mg by mouth daily with a blood pressure today of 128/79 mmHg.
- Further work-up is completed and the patient is diagnosed with lumbar spondylosis and post-traumatic stress disorder (PTSD).
- The patient is open to physical therapy and working with a psychologist but is also requesting medication options because the symptoms are so distressing. What might you consider prescribing?

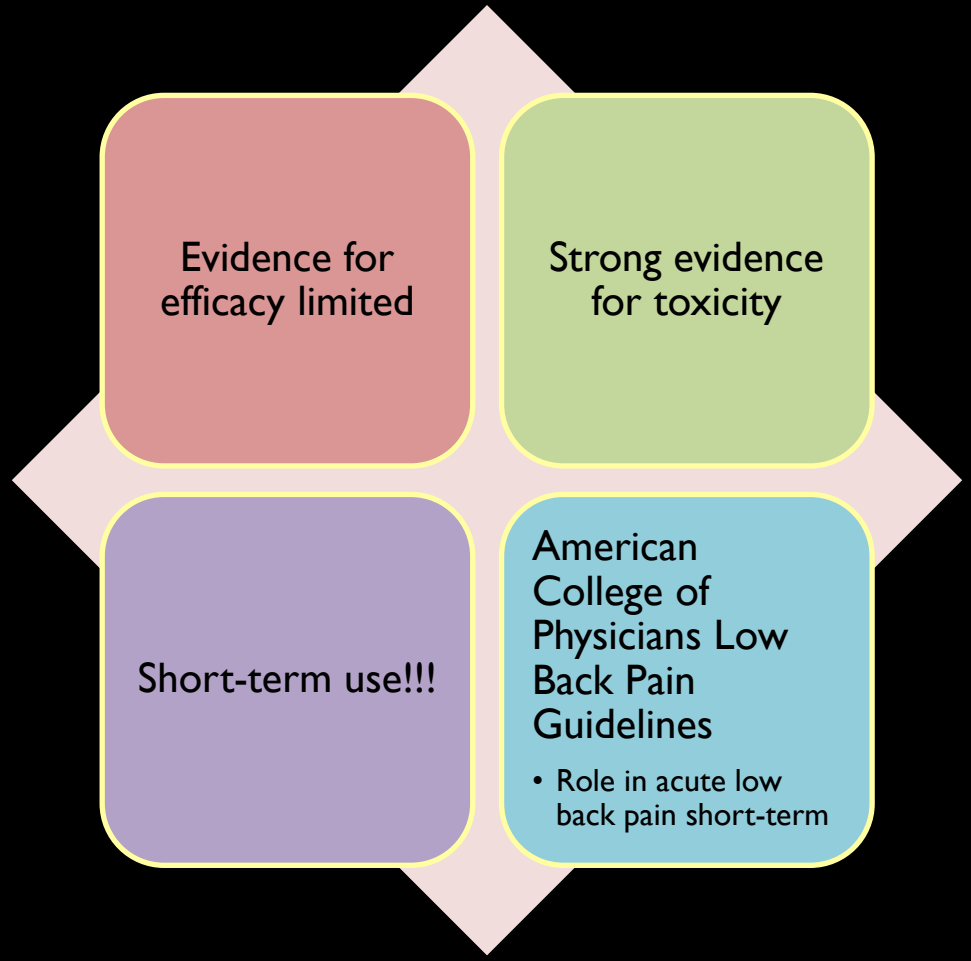
Skeletal Muscle Relaxants

Skeletal Muscle Relaxants

- Heterogeneous group
- Structurally not related
- 2 million people per year report use of SMR
- 300,000 elderly patients use SMR
- Associated with sedation and weakness as well as other adverse effects
- Spasticity vs spasms vs myofascial pain

Fudin J, Raouf M. A review of skeletal muscle relaxants for pain management. Practical Pain Management. 2016; 16(5):1-18.
Chang WJ. Muscle relaxants for acute and chronic pain. Phys Med Rehabil Clin N Am. 2020;31:245-254.

Antispamodics Place in Therapy



Qaseem A, Wilt TJ, McLean RM et al. Noninvasive treatmenst for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2017;166(7):514-530.
Chang WJ. Muscle relaxants for acute and chronic pain. Phys Med Rehabil Clin N Am. 2020;31:245-254.

Centrally Acting - Sedative

Carisoprodol

- Changes interneuronal activity
- Schedule IV – abuse potential
- CNS and respiratory depressant – additive effects
- Avoid in children < 12 (or EVERYONE)
- Seizures
- Metabolism via CYP2C19 – pharmacogenomics

Chlorzoxazone

- Inhibits polysynaptic reflex
- Rare hepatoxicity
- Urine discoloration
- GI irritation ulcer

Methocarbamol

- Discoloration of urine
- Altered mental status

Metaxalone

- Bioavailabiltiy increased with high fat meal
- Metabolized by CYP1A2, CYP2D6, CYP2E1, CYP3A4
- Rare leukopenia and hemolytic anemia
- Avoid with renal or hepatic failure
- Avoid < 12 years of age

Fudin J, Raouf M. A review of skeletal muscle relaxants for pain management. Practical Pain Management. 2016; 16(5):1-18.
Chang WJ. Muscle relaxants for acute and chronic pain. Phys Med Rehabil Clin N Am. 2020;31:245-254.

Centrally Acting - Others

TCA-like - Cyclobenzaprine	GABA agonist – Diazepam	Alpha-adrenergic- Tizanidine	Antihistamine - Orphenadrine
• Anticholinergic effects • Serotonin syndrome	• Long half-life • Dependence and abuse • Avoid renal or hepatic impairment • Withdrawal with abrupt discontinuation	• Liver toxicity • DDI with ciprofloxacin • Short half-life	• Anticholinergic effects • GI effects • Contraindicated with duodenal or pyloric obstruction or stenosing peptic ulcers

Fudin J, Raouf M. A review of skeletal muscle relaxants for pain management. Practical Pain Management. 2016; 16(5):1-18.
Chang WJ. Muscle relaxants for acute and chronic pain. Phys Med Rehabil Clin N Am. 2020;31:245-254.

Tricyclic Antidepressants (TCA)

Role in Pain Management

Effects independent of BH disorder

Lower doses compared to MDD

Neuropathic pain

Migraine prophylaxis

Fibromyalgia

Low back pain?

Dharmshaktu P, Tayal V, Kalra BS. Efficacy of antidepressants as analgesics: a review. *J Clin Pharmacol.* 2012;52(1):6-17.
NICE guideline. Neuropathic pain in adults: pharmacological management in non-specialist settings. Available at: https://www.nice.org.uk/guidance/cg173/resources/neuropathic-pain-in-adults-pharmacological-management-in-nonspecialist-settings-pdf-35109750554053 2013. Accessed June 30,2021.
Mu A, Weinberg E, Moulin DE, Clarke H. Pharmacologic management of chronic neuropathic pain. Can Fam Physician. 2017;63(11):844-852.

Pharmacodynamics

Ach M=acetylcholine muscarinic receptor, α_1 =alpha-1 adrenergic receptor, H_1=histamine-1 receptor,

Medication	Ach M	α_1	H_1	5-HT_3	NE
Secondary amines					
Desipramine	+	+	+	+	++++
Nortriptyline	+	+	+	++	+++
Tertiary amines					
Amitriptyline	+++	+++	++	++++	++
Clomipramine	+	++	+	+++	++
Doxepin	++	+++	+++	++	++
Imipramine	++	+	+	+++	+++

Adapted from: DeBattista C. Chapter 30. Antidepressant Agents. In: Katzung BG, Vanderah TW eds. Basic & Clinical Pharmacology. 15th ed. New York: McGraw-Hill; 2012. https://accessmedicine.mhmedical.com/content.aspx?bookid=2988&sectionid=250593594. Accessed June 20,2021.
VandenBerg AM. Major Depressive Disorder. In: DiPiro JT, Yee GC, Posey L, Haines ST, Nolin TD, Ellingrod V. eds. *Pharmacotherapy: A Pathophysiologic Approach, 11e*. McGraw Hill. Available at: https://accesspharmacy.mhmedical.com/content.aspx?bookid=2577&sectionid=234138584.Accessed June 30, 2021.

Tricyclic Antidepressants (TCAs)

- **May initiate as follows:**
  - **Nortriptyline** 10mg PO at bedtime
  - **Desipramine** 25mg PO at bedtime
  - **Amitriptyline** 10-25mg PO at bedtime
- Increase by 10-25mg PO every 3-5 days
- Use doses <100mg/day when possible
- Do not exceed 50mg/day in patients on SSRI or SNRI

Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol.* 2015; 162–73.

Adverse Drug Effects (ADE)

Cardiac → Avoid in CV disease

Sudden cardiac death with doses > 100 mg/day	QTc prolongation • Baseline ECG recommended by some in those >40-50 years of age • Routine ECG monitoring not recommended	Arrhythmias	Tachycardia	Orthostatic hypotension

Amitriptyline package insert. Cranbury, NJ: Sun Pharmaceuticals: March 2021 VandenBerg AM. Major Depressive Disorder. In: DiPiro JT, Yee GC, Posey L, Haines ST, Nolin TD, Ellingrod V. eds. *Pharmacotherapy: A Pathophysiologic Approach, 11e*. McGraw Hill. Available at: https://accesspharmacy.mhmedical.com/content.aspx?bookid=2577&sectionid=234138584.Accessed June 30, 2021.

ADE

Anticholinergic → Elderly

- Dry mouth
- Constipation
- Urinary retention → BPH
- Tachycardia
- Confusion
- Blurred vision → Glaucoma

Amitriptyline package insert. Cranbury, NJ: Sun Pharmaceuticals: March 2021.

ADE

Withdrawal symptoms

Suicide risk

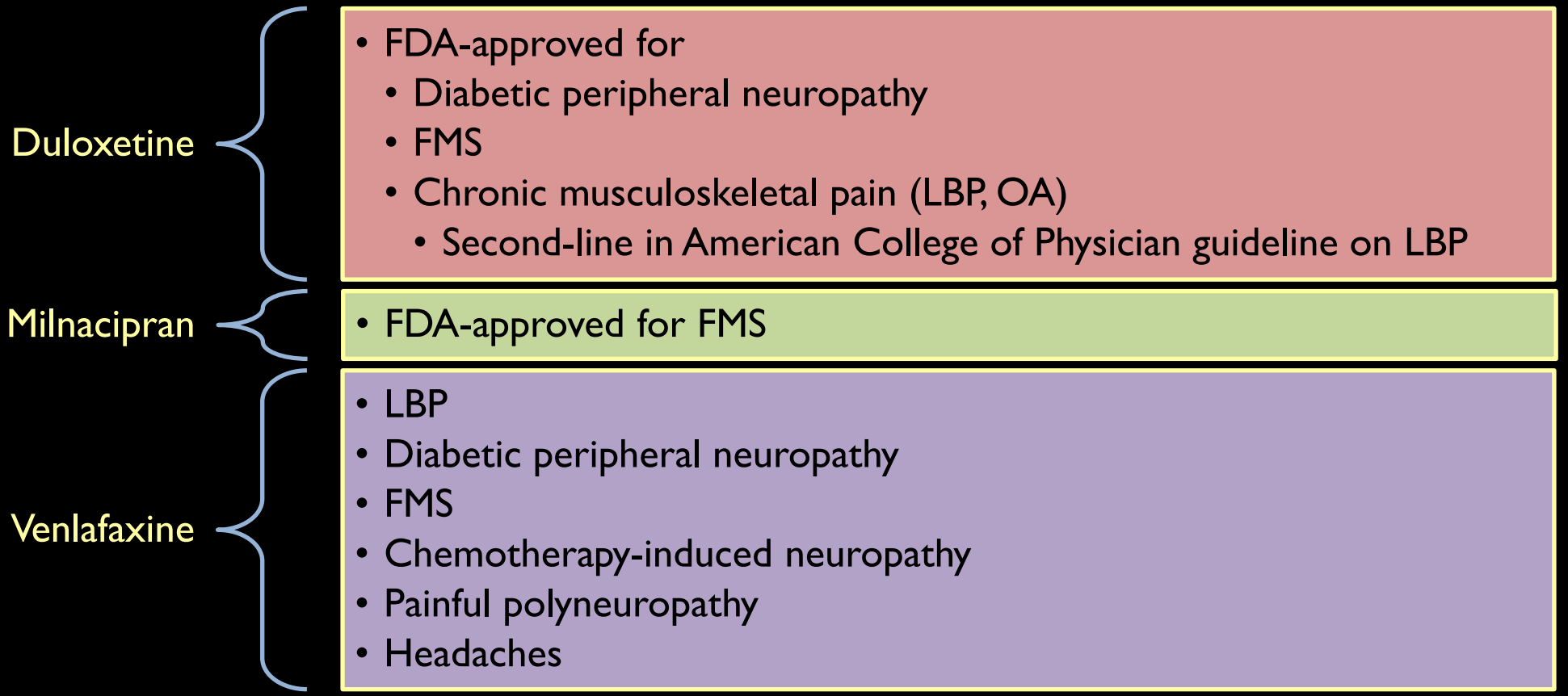
Seizure risk

Histamine receptor antagonism → Sedation

Amitriptyline package insert. Cranbury, NJ: Sun Pharmaceuticals: March 2021.

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

Role in Pain Management



Cymbalta package insert. Indianapolis, IN: Lilly USA, LLC; April 2020.
Savella package insert. Irvine, CA: Allergan; Dec 2017.
Dharmshaktu P, Tayal V, Kalra BS. Efficacy of antidepressants as analgesics: a review. *J Clin Pharmacol.* 2012;52(1):6-17.

ADE

Common

- Nausea
- Somnolence
- Dry mouth
- Hyperhidrosis
- Erectile dysfunction
- Constipation

Others

- Hypertension
- Hyponatremia
- Urinary retention
- Increased bleeding risk
- Withdrawal symptoms with abrupt discontinuation

Cymbalta package insert. Indianapolis, IN: Lilly USA, LLC; April 2020.
Effexor package insert. Philadelphia, PA.:Wyeth; Dec 2018.
Savella package insert. Irvine, CA: Allergan; Dec 2017

SNRI—Suicidality

- Warnings
- Effected populations
- Timing of risk
- Monitoring and follow-up

Cymbalta package insert. Indianapolis, IN: Lilly USA, LLC; April 2020.
Effexor package insert. Philadelphia, PA: Wyeth; Dec 2018.
Savella package insert. Irvine, CA: Allergan; Dec 2017

SNRI Bleeding Risk

- Block serotonin uptake into platelet
- Decreased platelet aggregation
- Risk increases with age, concomitant meds, comorbidities, use of alcohol
- PPIs may lower risk
- Consider addition of PPI if using SNRI + NSAID
- No evidence to suggest holding prior to procedures or surgery

Bixby AL, Vandenberg A, Bostwick JR. Clinical management of bleeding risk with antidepressants. Ann Pharmacother. 2019;53(2):186-194.

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
- Patient and caregiver education paramount

Cymbalta package insert. Indianapolis, IN: Lilly USA, LLC; April 2020.
Effexor package insert. Philadelphia, PA: Wyeth; Dec 2018.
Savella package insert. Irvine, CA: Allergan; Dec 2017
Garel N, Greenway KT, Tabbane, Joober R. Serotonin syndrome: SSRIs are not the only culprit. J Psychiatry Neurosci. 2021;46(3):E369-E370.

Duloxetine Dosing and Considerations

- Dosing
  - Initiate at 30mg PO daily x1 week, then increase to target dose of 60mg PO daily
  - Continue for 2 weeks at 30 mg daily in elderly
  - In fibromyalgia and chronic MSK pain, no evidence that doses >60mg/day provide additional benefit
- ADE
  - Hyperglycemia
  - Avoid in chronic hepatic disease or cirrhosis
  - Avoid < 30 mL/min
  - Contraindicated uncontrolled closed-angle glaucoma

Cymbalta package insert. Indianapolis, IN: Lilly USA, LLC; April 2020.

Venlafaxine Dosing and Considerations

- Dosing
  - Initiate at venlafaxine SA 37.5 mg PO daily
  - Titrate dose q2 weeks to 75 mg daily, 150 mg daily, 225 mg daily
- QTc prolongation
  - Consider baseline ECG in those with cardiac disease history
- Caution with renal disease – reduce doses
  - Mild to moderate: reduce total daily dose by 25-50%
  - Severe: reduce total daily dose by 50% or more
- Caution with hepatic disease – reduce doses
  - Mild to moderate: reduce total daily dose by 50%
  - Severe: reduce total daily dose by at least 50% or more
- Caution uncontrolled closed-angle glaucoma

Effexor package insert. Philadelphia, PA.:Wyeth; Dec 2018.

Milnacipran Dosing

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

Savella package insert. Irvine, CA: Allergan; Dec 2017

Milnacipran Considerations

- Hepatoxicity – no dose adjustment recommendations
- Use with caution in moderate renal impairment
- Severe renal impairment (CrCl 5-29 mL/min), the maintenance dose should be reduced by 50% to 50 mg/day (25 mg twice daily). May increase to 50 mg BID
- Not recommended in ESRD

Savella package insert. Irvine, CA: Allergan; Dec 2017

Post-traumatic Stress Disorder Treatment

- First-line
  - Sertraline
  - Paroxetine
  - Fluoxetine
  - Venlafaxine
- Second-line
  - Imipramine
- Suggest against
  - Amitriptyline
- Inadequate evidence for or against
  - Duloxetine
  - Other TCAs

VA/DoD clinical practice guideline for the management of posttraumatic stress disorder and acute stress disorder. 2017. Available at: https://www.healthquality.va.gov/guidelines/MH/ptsd/. Accessed June 30, 2021.

Return to Patient Case #1

- Only use muscle relaxers for acute exacerbations short-term
- Initiate venlafaxine SA 37.5 mg PO daily
- Titrate dose q2 weeks as tolerated to at least 150 mg PO daily
- Monitor BP
- Psychotherapy for PTSD

Patient Case #2

- MP is a 68-year-old male with diabetic peripheral neuropathy and knee osteoarthritis. His past medication history is significant for type 2 diabetes, uncontrolled hypertension, chronic kidney disease with CrCl = 43 mL/min, and benign prostatic hypertrophy (BPH).
- The patient has a history of alcohol use disorder that was in remission until recently. He reports that he has been drinking 10 beers a day lately for his pain but wants to return to sobriety.
- The patient was started on amitriptyline 25 mg daily a week prior for pain control, and his wife is reporting that he has been confused and is having problems urinating. He presents to you for help with his pain.
- During medication reconciliation, you learn he is taking ibuprofen 400 mg q6h that he takes for knee arthritis.

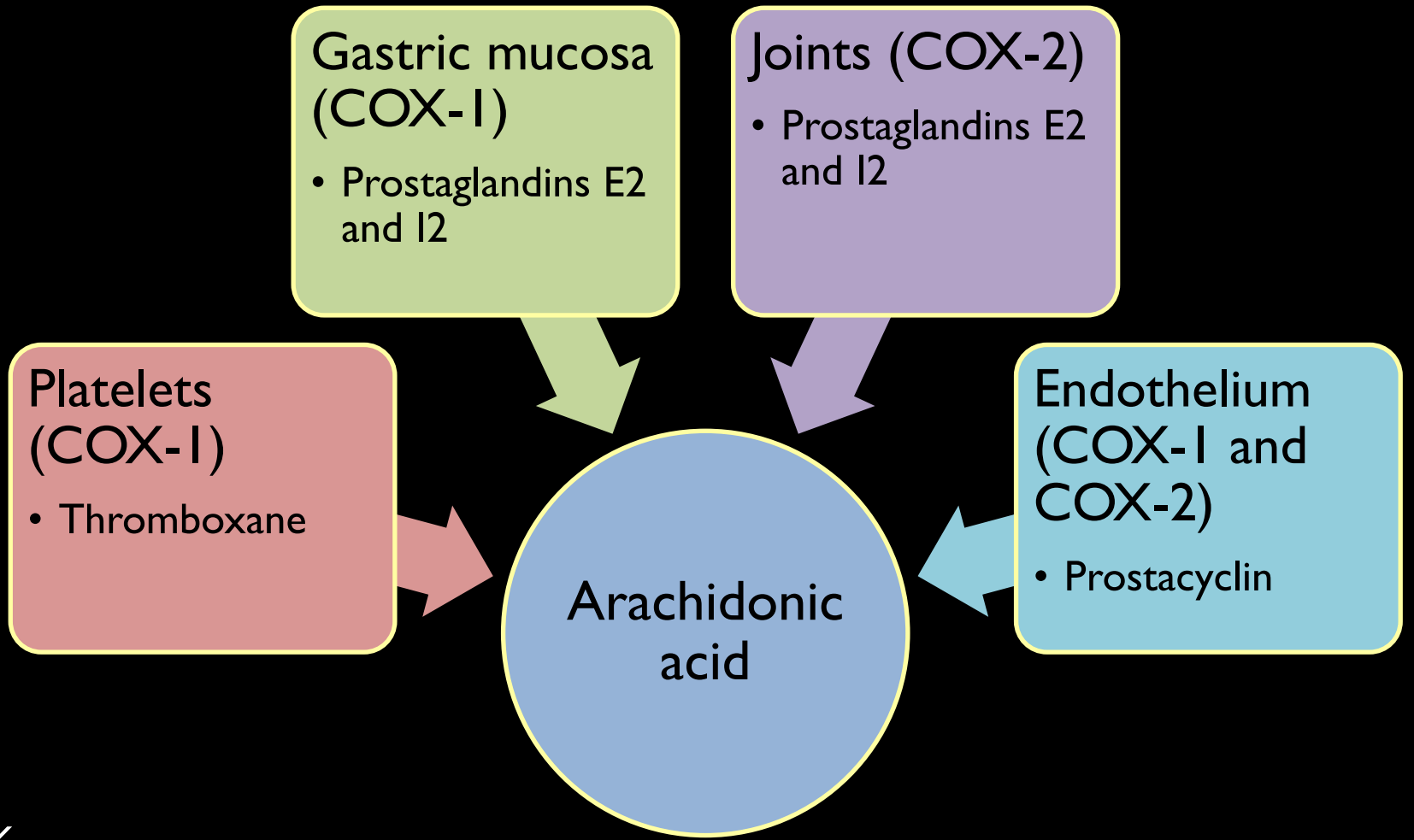
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAID Role in Pain

- American College of Physicians Low Back Pain Guidelines
  - First-line – acute and subacute low back pain
  - First-line – chronic low back pain
- American College of Rheumatology/Arthritis Foundation OA Hand, Hip, Knee
  - First-line pharmacologic approach

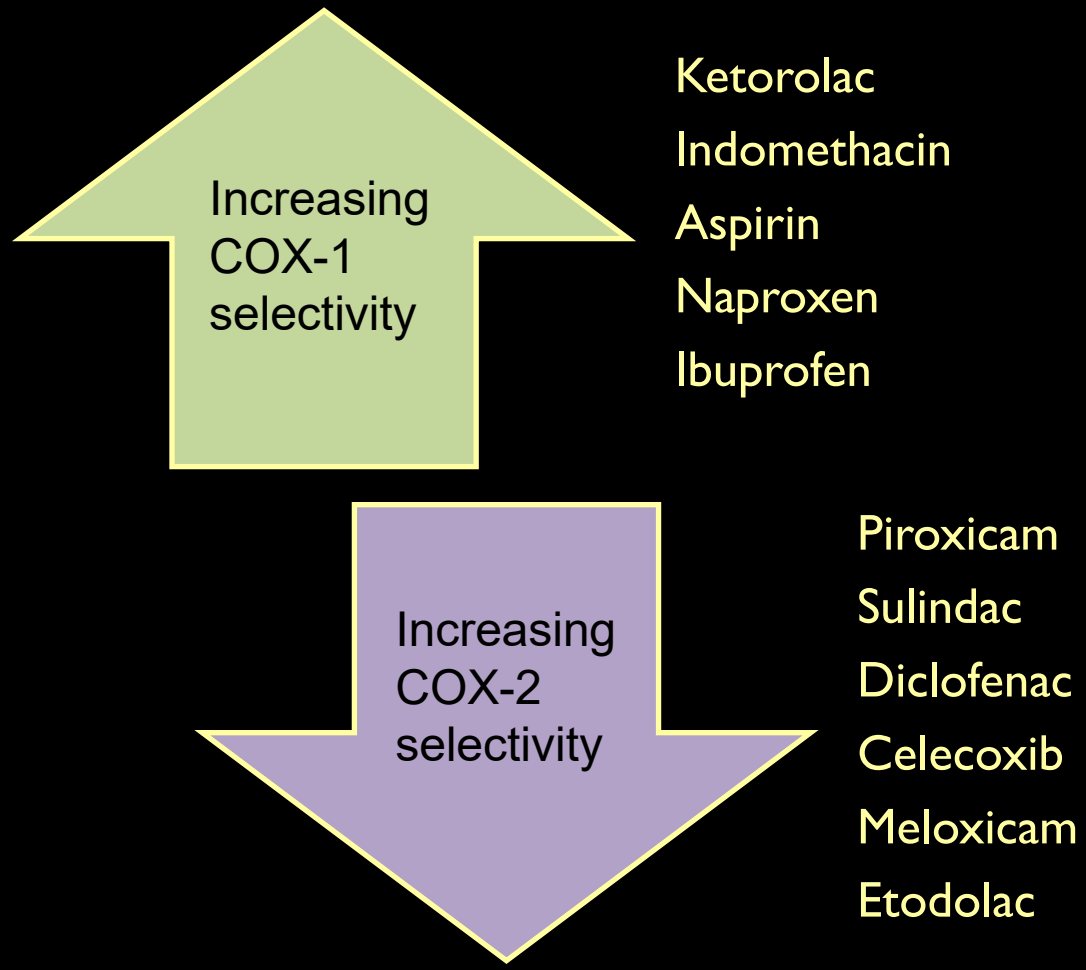
Qaseem A, Wilt TJ, McClean RM et al. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2017;166(7):514-530.
Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the management of osteoarthritis of the hand, hip, knee. Arthritis Rheumatol. 2020;72(2):220-233.

Mechanism of Action



Atchison JW, Herndon CM, Rusie E. NSAIDs for musculoskeletal pain management: current perspectives and novel strategies to improve safety. J Manage Care Pharm. 2013;19(9):S3-S19.

COX-2 and COX-2 Selectivity



Schmidt M, Lamberts M, Schjerning Olsen AM, et al. Cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs: review and position paper by the working group for Cardiovascular Pharmacotherapy of the European Society of Cardiology. Eur Heart J Cardiovasc Pharmacother. 2016;2(2):108-118,

NSAID Boxed Warnings

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, MI, and stroke which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at a greater risk.
- NSAIDs are contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.

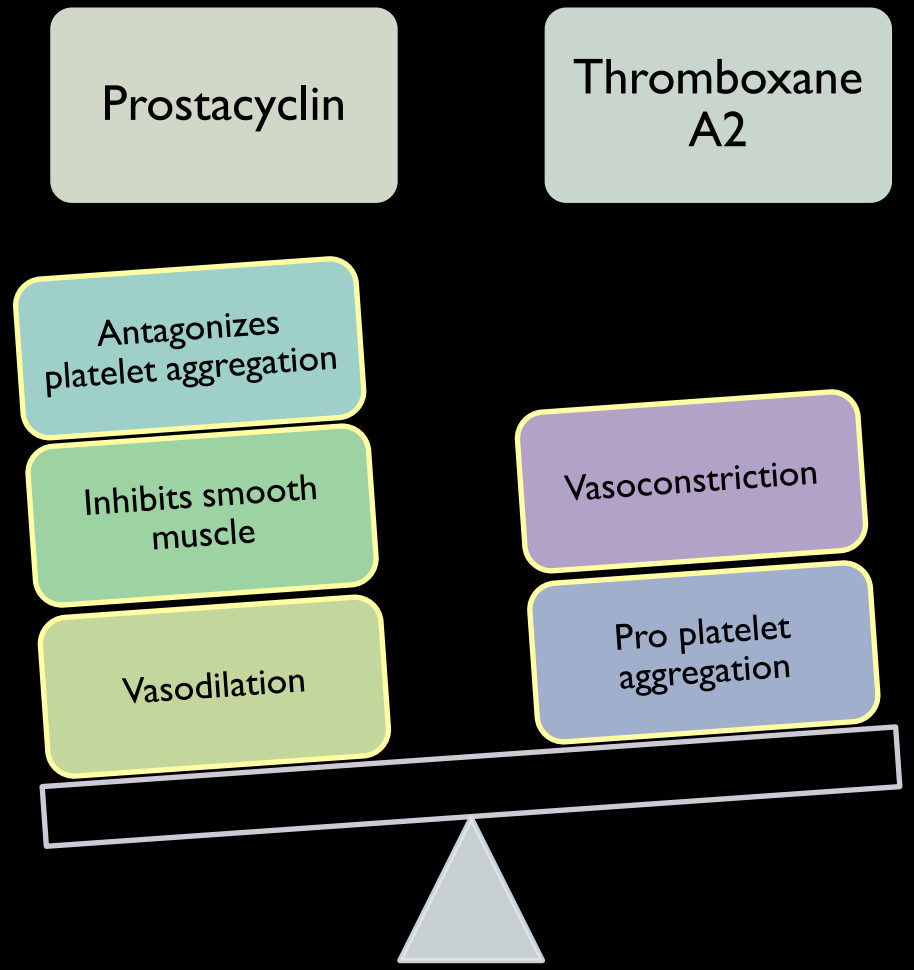
Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

Circulation. 2007;115:1634-1642.
Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc,; Hudson, OH; 20 April 2015.

Cardiovascular Risk

Inhibition of COX-2 suppresses prostacylin



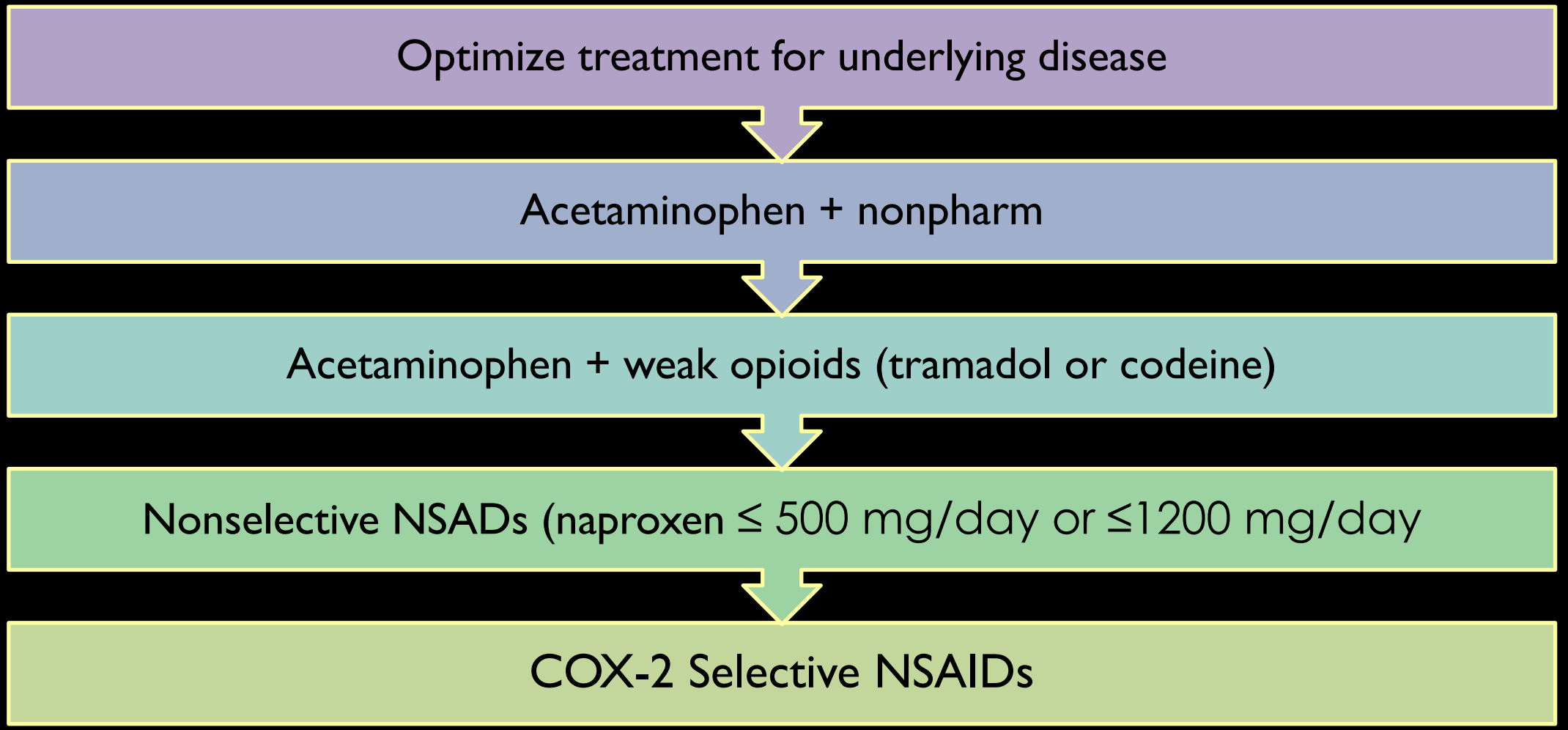
Schmidt M, Lamberts M, Schjerning Olsen AM, et al. Cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs: review and position paper by the working group for Cardiovascular Pharmacotherapy of the European Society of Cardiology. Eur Heart J Cardiovasc Pharmacother. 2016;2(2):108-118.

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
- 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

Niseen SE, Yeomans ND, Soloman DH et al. Cardiovascular safety of celecoxib, naproxen or ibuprofen for arthritis. N Engl J Med 2016;375(26):2519-2529.

Patients With or High Risk of Cardiovascular Disease



Schmidt M, Lamberts M, Schjerning Olsen AM, et al. Cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs: review and position paper by the working group for Cardiovascular Pharmacotherapy of the European Society of Cardiology. Eur Heart J Cardiovasc Pharmacother. 2016;2(2):108-118,

NSAIDs and Renal Dysfunction

Avoid in people with GFR < 30 ml/min

Long-term therapy is not recommended in people with GFR < 60 ml/min

Avoid with lithium

Avoid in people taking RAAS blocking agents

Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis. 2014;64(5):713-735.

NSAIDs and Renal Dysfunction

Sulindac and salsalate may have less renal hemodynamic changes

Limit dose and frequency

Topicals

Short-acting NSAIDs preferred

Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis. 2014;64(5):713-735.
Pham PC, Khaing K, Sievers TM, et al. 2017 update on pain management in patients with CKD. Clin Kidney J. 2017;10(5):688-697.

NSAIDs and Liver Dysfunction

Mild to moderate dysfunction

- Normal doses: ibuprofen, etodolac, diclofenac
- Dose reduction: naproxen, celecoxib, sulindac

Avoid in patients with cirrhosis

Menashehoff S, Goldstein L, Brown S, Stickevers S. Safe usage of analgesics in patients with chronic liver disease: a review of the literature. Practical Pain Management. 2013;13(9).
Dwyer JP, Jayasekera C, Nicoll A. Analgesia for the cirrhotic patient: a literature review and recommendations. J Gastroenterol Hepatol. 2014;29:1356-1360.

Drug-Drug Interactions

Anticoagulants, anti-platelets,

Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs)

Cyclosporine, tacrolimus

Methotrexate

Angiotensin converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs)

Lithium

Diuretics

Ibuprofen + aspirin

Patrono C, Baigent. Nonsteroidal anti-inflammatory drugs and the heart. Circulation. 2014;129:907-916.
Crofford LJ. Use of NSAIDs in treating patients with arthritis. Arthritis Res Ther. 2013;15(Suppl 3):1-10.

Topical Products

Topical NSAIDs: Agents

Medication	Indication	Dosing
Diclofenac gel 1%	Joint amenable to topical application (knee and hands)	2 g for each elbow, wrist or hand 4 g for each knee, ankle, or foot Max 32 mg/day
Diclofenac sodium topical solution	OA of knee	10 drops at a time on each of 4 sides of knee 40 drops QID
Diclofenac epolamine patch 1.3%	Topical treatment of acute pain due to minor strains, sprains, and contusion	1 patch to painful area BID

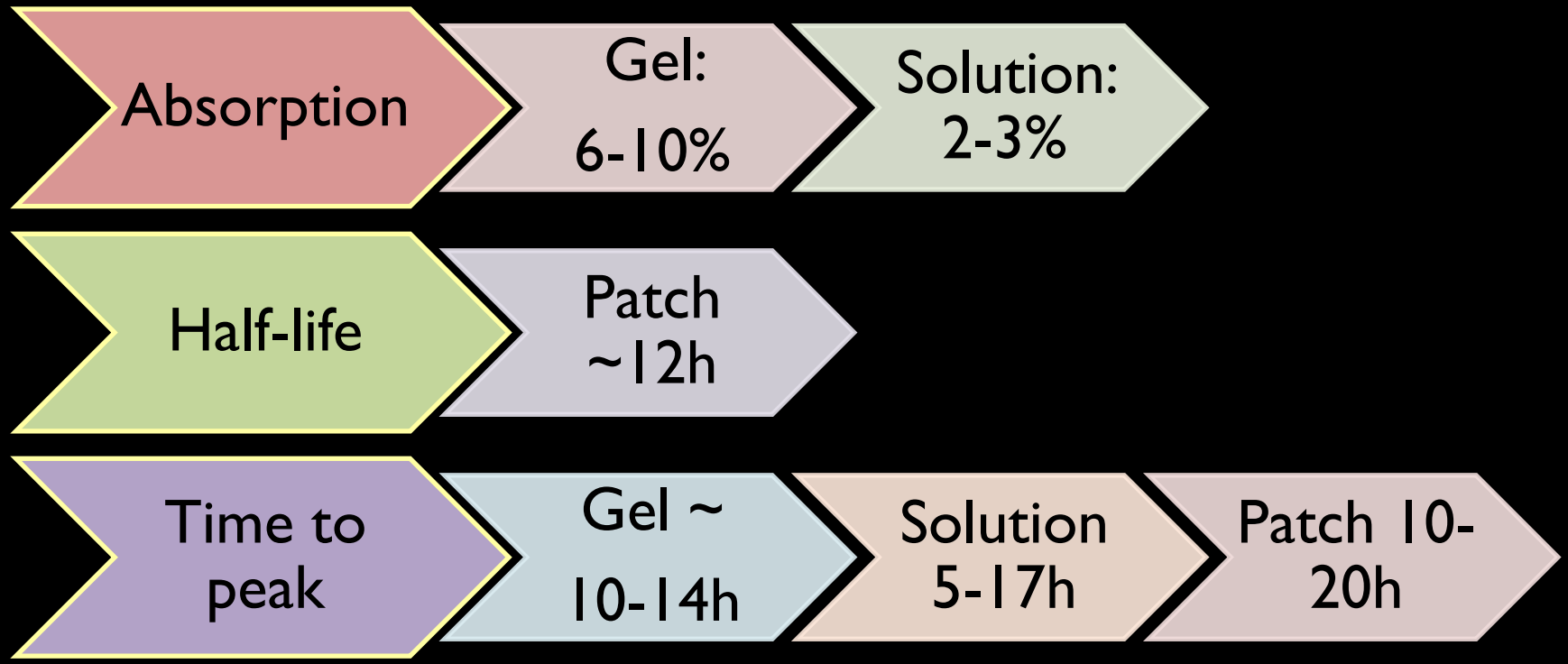
McPherson ML, Cimino NM. Topical NSAID formulations. Pain Med. 2013 Dec;14 Suppl 1:S35-9.

Topical NSAIDs: Place in Therapy

- American College of Rheumatology
  - Initial management of hand or knee OA may include topical NSAID
- American Geriatric Society
  - May consider topical NSAID for localized, non-neuropathic persistent pain
- European League Against Rheumatism (EULAR)
  - Hand OA: topical NSAIDs over systemic
  - Hand or Knee OA: topical NSAIDs with clinical efficacy and safety
- National Institute for Health and Clinical Excellence (NICE)
  - Topical NSAIDS considered in addition to nonpharmacological
  - Consider topical NSAIDs or acetaminophen prior to PO NSAIDs

Kolasinki SL, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res (Hoboken). 2020 Feb;72(2):149-162.
Altman RD, et al. Topical therapies for osteoarthritis. Drugs. 2011 Jul 9;71(10):1259-79.
Kloppenburg M, et al. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. Ann Rheum Dis. 2019 Jan;78(1):16-24.
NICE Guidelines, Osteoarthritis: care and management. Published 12 Feb 2014, last updated 11 Dec 2020. Available at: https://www.nice.org.uk/guidance/cg177, Last accessed July 6, 2021.

Topical NSAIDs: Pharmacokinetics



Voltaren gel package insert. Malvern, PA: Endo Pharmaceuticals; September 2018.
Flector patch package insert. New York, NY: Pfizer; August 2018.
Diclofenac sodium 1.5% topical solution package insert. Baton Rouge, LA: Sola Pharmaceuticals: Jan 2021

Lidocaine

- Topical anesthetic and Class 1b anti-arrhythmic
- Sodium channel blockade Na(v) 1.7
- Inhibition of acid sensing ion channels (ASIC)
- Available via OTC (0.5%-4%) and prescription (1.8% or 5%)
- Lidocaine 5% patch applied directly to area of PHN
  - No more than 3 patches concurrently
  - 12 hours on, 12 hours off
- Lidocaine 1.8% patch also for PHN
  - Delivers same amount as the prescription patch but superior in staying attached for 12 hrs
- OTC lidocaine 4% patch
- IV infusion is a potential treatment option

Lin J, et al. Inhibition of acid sensing ion channel currents by lidocaine in cultured mouse corticol neurons. *Anesth Analg* 2011:112:977-81.
Gudin J, Webster LR, Vought K, Patel K, Kuritzky. Open-label adhesion performance studies of a new lidocaine topical system 1.8% verus lidocaine patches 5% and lidocaine medication plaster 5% in health subjects. J Pain Res. 2021;14:513-526.
Lidocaine 1.8% patch [package insert]. Palo Alto, CA: Scilex Pharmaceuticals Inc; 2021.

Capsaicin 8% Patch

Dose is a single, 30-60-minute application of up to 4 patches

FDA-approved for painful diabetic peripheral neuropathy (PDPN) and PHN	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

Capsaicin 8% patch [package insert]. Ardsley, NY: Averitas Pharma, Inc.; 2020.

Gabapentinoids

Mechanism of Action

Structurally related to GABA and has GABA-mimetic properties

Do not

- Alter uptake or breakdown
- Convert into GABA
- Bind to $GABA_a$ or $GABA_B$

Binds to the α2-δ subunit of the voltage-gated calcium channel

Reduces the Ca^{2+} -dependent release of pro-nociceptive neurotransmitters

Decreases release of glutamate, NE, and substance P

Dworkin RH et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain. 2007 Dec 5;132(3):237-251.
Schifano F. Misuse and abuse of pregabalin and gabapentin: cause for concern?. CNS Drugs. 2014 Jun;28(6):491-6.
Pfizer. Neurontin: highlights of prescribing information. 2020. http://labeling.pfizer.com/ShowLabeling.aspx?format=PDF&id=630. Accessed 5 July 2021

Role in Pain

- NICE
  - Gabapentin - 1st line treatment for neuropathic pain
- ADA Diabetic Peripheral Neuropathy
  - Consider pregabalin or duloxetine as initial approach
- AAN Diabetic Peripheral Neuropathy
  - Offer pregabalin
  - Consider gabapentin
- Neuropathic Pain Special Interest Group of International Association for the Study of Pain
  - Gabapentin, pregabalin first line

Smith RV, et al. Gabapentin misuse, abuse and diversion: a systematic review. Addiction. 2016 Jul;111(7):1160-74.
Bril V, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology. 2011 May 17;76(20):1758-65.
Pop-Busui R, et al. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. Diabetes Care. Diabetes Care 2017 Jan; 40(1): 136-154.
Dworkin RH, et al. Recommendations for the Pharmacological Management of Neuropathic Pain: An Overview and Literature Update. Mayo Clin Proc. 2010 Mar; 85(3 Suppl): S3-S14.

Role in Pain

Acute or chronic sciatica

No benefit for pregabalin

Nonspecific low back pain

Ineffective

Contribute to ADE

Mathieson S, et al. Trial of Pregabalin for Acute and Chronic Sciatica. N Engl J Med 2017; 376:1111-1120.
Shanthanna H, et al. Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials. PLoS Med. 2017 Aug 15;14(8):e1002369.
Qaseem A, Wilt TJ, McClean RM et al. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2017;166(7):514-530.

Role in Pain – Controversy with Perioperative Use

- Associated with reduced opioid requirements after surgery when gabapentin 600-1200 mg or pregabalin 150 or 300 mg is given 1-2 hours prior to surgery

- Recent meta-analysis concluded that perioperative gabapentinoids did not result in a clinically significant analgesic effect nor did it have an effect on development of postoperative chronic pain

Chou R, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain. 2016 Feb;17(2):131-57.

Verret M, Lauzier F, Zarychanski R, et al. Perioperative use of gabapentinoids for the management of postoperative acute pain: A systematic review and meta-analysis. *Anesthesiology*. 2020;133:265-79.

Gabapentin

Gabapentinoid Medication	FDA-Approved Indications	Dosing	Renal Dose Adjustments
Gabapentin (Neurontin®) - ***available as capsule, tablet, and oral solution***	• PHN • Adjunctive treatment of partial onset seizures	• Initiate at 100-300 mg PO QHS or TID. • Doses can be increased by 100-300 mg/day every 1-7 days / • Maximum dose 3600 mg/day • Exceeding 1800 mg/day may not provide further benefit owing to saturable nonlinear kinetics	• ≥60 mL/min – no change • 30-59 mL/min – 400-1400 mg/day in 2 divided doses • 15-29 mL/min 200-700 mg in 1 daily dose • 15 100-300 mg in 1 daily dose • Hemodialysis – provide supplemental dose based on estimated CrCl

Pfizer. Neurontin: highlights of prescribing information. 2020. http://labeling.pfizer.com/ShowLabeling.aspx?format=PDF&id=630. Accessed 5 July 2021.

Gabapentin ER

Gabapentinoid Medication	FDA-Approved Indications	Dosing	Renal Dose Adjustments
Gabapentin (Gralise®) – *not interchangeable with other gabapentin products*	• PHN	Take once daily with evening meal. Day 1: 300 mg Day 2: 600 mg Day 3-6: 900 mg Days 7-10: 1200 mg Days 11-14; 1500 mg Day 15; 1800 mg Maximum dose 1800 mg/day	• > 60 mL/min – none • 30-60 mL/min – 600-1800 mg • < 30 mL/min do not use • Hemodialysis: do not use

Depomed. Gralise Full Prescribing Information. 2020. https://www.gralise.com/pdfs/gralise-prescribing-information.pdf. Accessed 5 July 2021.

Gabapentin enacarbil

Gabapentinoid Medication	FDA-Approved Indications	Dosing	Renal Dose Adjustments
Gabapentin enacarbil (Horizant®) – ***swallow whole, take w/ food***	• Moderate to severe RLS • PHN	• 600 mg in AM x 3 days • Then increase to 600 mg PO BID. • Maximum dose 1200 mg/day	• > 60 mL/min no change • 30-59 mL/min – initiate at 300 mg QAM x 3 days, may increase up to 600 mg BID • 15-29 mL/min – 300 mg in QAM x 3 days then increase to 300 mg BID • < 15 mL/min – 300 mg every other day, may increase to 300 mg QAM • Hemodialysis – 300 mg after dialysis may increase to 600 mg after dialysis

Arbor Pharmaceuticals L. Horizant: Highlights of prescribing information. 2016. https://www.horizant.com/pdf/Horizant-Prescribing-Information.pdf. Accessed 5 July 2021.

Pregabalin

Gabapentinoid Medication	FDA-Approved Indications	Dosing	Renal Dose Adjustments
Pregabalin (Lyrica) – *available as capsule and oral solution*	• DPN • PHN • Adjunctive therapy for partial onset seizures • Fibromyalgia • Neuropathic pain associated with SCI	• Initiate at 150 mg/day in 2 or 3 divided doses. • Increase dose to 300 mg/day within 1 week. • Maximum doses vary depending on indication	• > 60 mL/min – no change needed • 30-60 mL/min – 75-300 mg divided BID or TID • 15-30 mL/min – 25 – 150 mg divided daily or BID • < 15 mL/min – 25-75 mg daily • Hemodialysis – provide supplemental doses after dialysis based on daily dose

Pfizer. Lyrica: Highlights of prescribing information. 2020. http://labeling.pfizer.com/showlabeling.aspx?id=561. Accessed 5 July 2021.

Pregabalin CR

Gabapentinoid Medication	FDA-Approved Indications	Dosing	Renal Dose Adjustments
Pregabalin CR – ***must be swallowed whole and administered once daily after evening meal***	• PHN • DPN	• DPN: Starting dose:165 mg/day, Maximum dose: 330 mg/day • PHN: Initial dose: 165 mg/day. Maximum dose: 330-660 mg/day	Renal dosage adjustments needed

Lyrica® CR (pregabalin) extended-release tablets [package insert]. 2020. http://labeling.pfizer.com/ShowLabeling.aspx?id=9678. Accessed 5 July 2021.

Gabapentinoid Abuse

- Some users of gabapentinoids experience euphoric effects, particularly at high doses
  - Users describe as the “ideal psychotropic drug”, “great euphoria”, “opiate buzz”
- Systematic review of 59 studies showed increasing numbers of patients self-administering higher than prescribed doses to achieve euphoric highs
  - Risk factors identified: history of SUD, particularly OUD, and psychiatric co-morbidities
- Recent article evaluating trends in adult exposures to gabapentin reported to poison centers
  - Gabapentin exposures increased by over 70% from 2013 to 2017
  - Significant increase in both suicide attempts and non-suicidal intentional exposures

Schifano F, D’Offizi S, Piccione M, et al. Is there a recreational misuse potential for pregabalin? Analysis of anecdotal online reports in comparison with related gabapentin and clonazepam data. *Psychother Psychosom*. 2011;80:118-22.
Evoy KE, Morrison MD, Saklad SR. Abuse and misuse of pregabalin and gabapentin. *Drugs*. 2017;77:403-26.
Reynolds K, Kaufman R, Korenoski A, Fennimore L, Shulman J, Lynch M. Trends in gabapentin and baclofen exposures reported to U.S. poison center. *Clin Toxicol*. 2019, DOI: 10.1080/15563650.2019.1687902.

Gabapentin legislation

Schedule V Controlled Substance

- Alabama
- Kentucky
- Minnesota
- North Dakota
- Tennessee
- Virginia
- West Virginia

Reported to PDMP

- States on left as well as:
- Connecticut
- District of Columbia
- Indiana
- Kansas
- Louisiana
- Massachusetts
- New Jersey
- Ohio
- Oregon
- Wyoming

National Council for Prescription Drug Programs. (2019 Oct 18). *Implementation information for state prescription monitoring programs.* https://www.ncpdp.org>media>pdf>State_PMP_Tracking_Document. Accessed June 4, 2021.

Gabapentinoids and Respiratory Depression

- FDA Drug Safety Communication released in 2019
- All gabapentinoid package inserts now include warning related to respiratory depression
- Serious, life-threatening, or fatal respiratory depression when co-administered with central nervous system (CNS) depressants, including opioids, or in the setting of underlying respiratory impairment
- If co-prescribing with CNS depressant or prescribing in individual with underlying respiratory condition(s), monitor for symptoms of respiratory depression and sedation

FDA Drug Safety Communication. FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR). Released 12/19/19. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin?utm_campaign=FDA%20MedWatch%20-%20gabapentin%20and%20pregabalin%29%3A%20Drug%20Safety%20Communication&utm_medium=email&utm_source=Eloqua. Accessed June 4, 2021.

Return to Patient Case #2

- Discontinue amitriptyline
- After resolution of side effects
  - Initiate gabapentin 300 mg PO QHS
  - Titrate by 300 mg/day q3-5 days as tolerated
  - Max dose 1400 mg/day in 2 divided doses
- Discontinue ibuprofen
- Consider topical diclofenac 1% TID

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

Learning Assessment Question #1

- The patient is a 75 year-old male with benign prostatic hypertrophy, diabetes, hypertension BP=150/95, and chronic kidney disease with CrCl 45 mL/min. He complains to his PCP that he has pins and needles in his feet. What medication is best to treat this patient's diabetic peripheral neuropathy?

A. Gabapentin 300 mg PO TID
B. Amitriptyline 25 mg QHS
C. Duloxetine 30 mg PO daily x 2 weeks, then 60 mg PO daily
D. Pregabalin 75 mg PO BID

Learning Assessment Question #2

- The same patient 75 year old male with benign prostatic hypertrophy, diabetes, hypertension BP=150/95, and chronic kidney disease with CrCl 45 mL/min is complaining of chronic knee pain from osteoarthritis. What medication is best for this patient?

A. Ibuprofen 400 mg PO TID
B. Diclofenac topical 1% TID
C. Celecoxib 100 mg PO daily
D. Duloxetine 30 mg PO daily x 2 weeks, then 60 mg PO daily

Learning Assessment Question #3

- True or False: There is robust data to support perioperative use of gabapentinoids for opioid-sparing and improved analgesia effects.