Nonopioid Analgesics: The Selection and Use of Adjuvant Therapies

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Disclosures

- Clinical advisory board: Daiichi Sankyo
- The presentation will include “off-label” uses of some medications and indicated on the individual slide

Current Situation

- The opioid epidemic
  - $6 billion over the next 2 years[1]
- Research and development[2]
  - Peptides, kappa agonists, and gene-targeting
- Cannabidiols[3]
  - Current clinical trials for chronic pain

1. http://thehill.com/opinion/healthcare/372875-6-billion-allotted-to-fight-opioid-epidemic-heres-how-we-should-spend-it accessed 2.9.2018
2. https://www.prnewswire.com/news-releases/promising-new-approaches-in-pain-management-672130173.html accessed 2.9.2018
3. https://clinicaltrials.gov/ct2/show/NCT03215940 accessed 2.9.2018

PAINWEEK

Learning 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

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Why Use Adjuvant Analgesics?

- An estimated 1 out of 5 patients with nonmalignant pain or pain-related diagnoses are prescribed opioids
- Almost 2 million Americans abused or were dependent on prescription opioids in 2014
- From 1999 to 2015, >180,000 people died from overdoses related to prescription opioids
- Since 1999, sales of prescription opioids in the United States have quadrupled

https://www.cdc.gov/drugoverdose/prescribing/guideline.html
accessed 2.9.2018

PAINWEEK

Risk Factors for Opioid Overdose or Addiction

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

Addiction

- Daily dose > 100 MEDD
- Long-term opioid use (> 3 months)
- Depression
- Substance use depression
- Adolescence

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

PAINWEEK

Contraindications to Opioids

Respiratory instability
Acute psychiatric instability
Uncontrolled suicide risk
Active, untreated alcohol or substance use disorder
True opioid allergy
Concomitant medications with life-limiting drug interactions
Prolonged QTc (≥500 msec) with methadone
Active diversion
Condition not likely to improve with opioids

PAINWEEK

1. Brooks A, et al. *Med Clin N Amer*. 2016;81-102.
2. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. *Recommendations and Reports*. 2016;65(1);149.
3. Manchikanti L et al. Pain Physician. 2012;15(Suppl 3):S67-116.

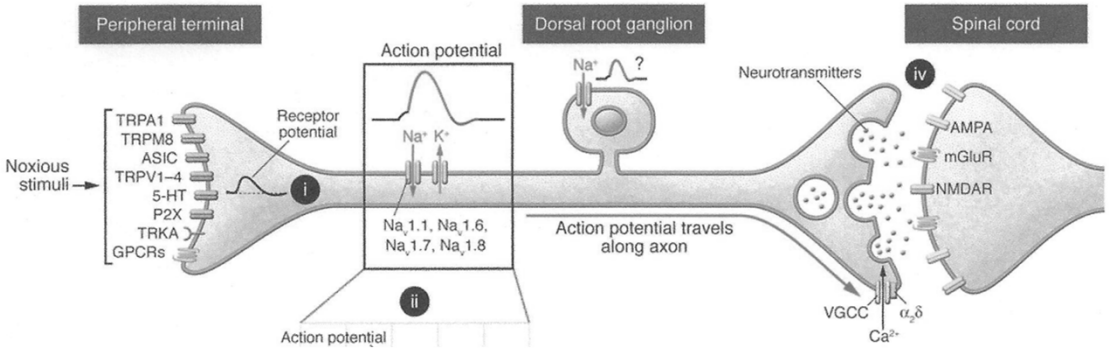
Pharmacotherapy (based on a new taxonomy)

Drug Class / Mechanism of Action	**IASP Pharmacology of Pain**
Opioids	Antinociceptive
Anticonvulsants	Peripheral desensitization
TCAs	Descending modulator
SNRIs	Descending modulator
Local anesthetics	Peripheral desensitization
NSAIDs	Antinociceptive
Acetaminophen	Antinociceptive
NMDA antagonists	Antihyperalgesic
Capsaicin	Peripheral desensitization
Cannabinoids	Antinociceptive
Corticosteroids	Peripheral desensitization
Skeletal muscle relaxants	Descending modulator

PAINWEEK

Beaulieu P, Lussier D, Porreca F, Dickenson AH, eds. Pharmacology of pain. Seattle, WA: International Association for the Study of Pain (IASP) Press; 2010.

Where Do Adjuvants Work?



PainWeek

Pain Terminology

Acute

Acute on Chronic

Chronic

Nociceptive

Neuropathic

PainWeek

Inflammatory Pain

Diagnosis

- Clinical setting
  - Postoperative
  - Trauma
  - Infection
  - Arthritis
- Distribution
  - Joints
  - Area of infection or trauma
  - Surgical incision
- Quality
  - Aching
  - Throbbing
  - Worse with movement
- Physical findings
  - Warm
  - Red
  - Swollen

Drug Management

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

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Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

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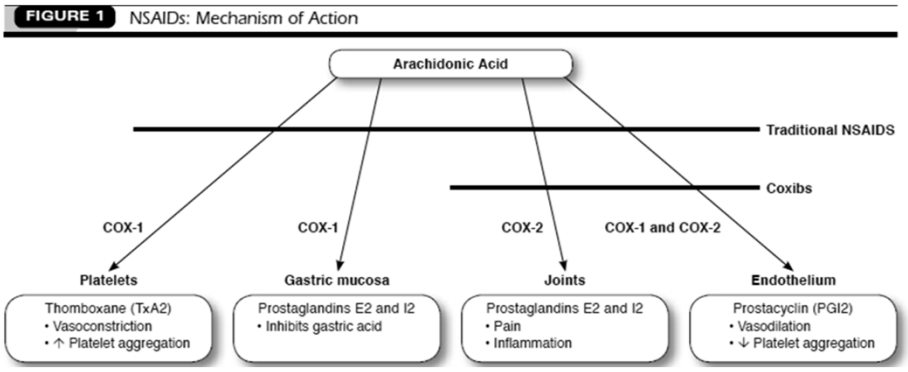
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)



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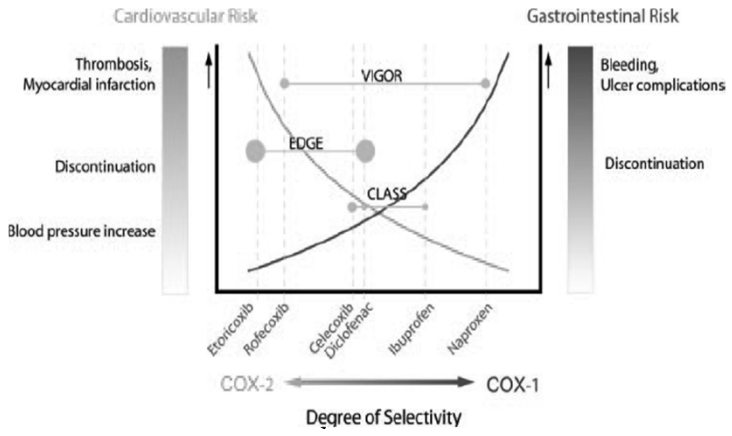
JMCP. 2013;19(9):S3-S19.

NSAIDs—COX Selectivity and Associated Risk



PAINWEEK

Circulation. 2007;115:1634-1642.

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 ***non-inferior*** to both ibuprofen and naproxen
- Risk of GI events was ***significantly lower*** with celecoxib compared to both ibuprofen and naproxen
- Study funded by Pfizer

PaiNweek

N Engl J Med 2016; :2519-2529.

NSAIDs—Dosing

Medication	**Initial Dose**	**Maximum Dose** (depending on indication)
Celecoxib	100 mg daily-BID	200-800 mg/day
Diclofenac	IR tablet: 50 mg TID-QID DR: 150-200 mg/day in 2-4 doses ER: 100 mg/day	IR: 150-200 mg/day DR: 200 mg/day ER: 200 mg/day
Etodolac	IR: 200-400 mg q6-8h	IR: 1000 mg/day
Ibuprofen	400-800 mg q4-6h	2.4-3.2 g
Indomethacin	IR: 25-50 mg BID-TID ER: 75 BID or 150 mg daily	IR: 200 mg/day ER: 150 mg/day

PaiNweek

Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc,; Hudson, OH; accessed 2.9.2018

NSAIDs—Dosing (cont'd)

Medication	Initial Dose	Maximum Dose (depending on indication)
Ketorolac	PO: 20 mg initial then 10 mg q4-6h IV: 30 mg once or 15-30 mg q6h IM: 60 mg once or 30 mg q6h	PO: 40 mg/day IM/IV: 120 mg/day **MAX: x5 DAYS**
Meloxicam	7.5 mg daily	15 mg/day
Naproxen	IR: 250 mg q6-8h, 500 mg q12h ER: 1000 mg daily	IR: 1000-1500 mg/day ER: 1000-1500 mg/day
Piroxicam	20 mg daily	20 mg/day
Sulindac	150-200 mg BID	400 mg/day

PaiNweek

Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc,; Hudson, OH; accessed 2.9.2018

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

PaiNweek

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
  - Dose:
    - 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
  - Avoid showering/bathing for ≥1 hour after application
  - Wearing of clothing or gloves should be avoided for ≥10 minutes after application
- Diclofenac epolamine 1.3% patch
  - Dose: 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

PAINWEEK

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

Corticosteroids

PAINWEEK

Corticosteroids

Prostaglandin inhibition

Cell membrane stabilization

Corticosteroid Mechanism of Action in Analgesia

Sodium channel blocker (neuropathic pain)

Osteoclast inhibition (bone pain)

1. http://www.practicalpainmanagement.com/corticosteroid-use-pain-management accessed 2.9.2018
2. Cont Edu Anaesth Crit Care and Pain. 2010;10(1):1-5.
3. J Endocrinol. 2002 Oct;175(1):155-63.
4. Can Fam Physician. 2010 Dec; 56(12): 1295–1297.

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Corticosteroids (cont'd)

- Intra-articular corticosteroid injection – knee and hip OA
- For RA: *"Low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more conventional synthetic (cs)DMARDs) for up to 6 months, but should be tapered as rapidly as clinically feasible."*
  - "Low dose" defined as ≤ 7.5mg prednisone or equivalent per day
- May consider the addition of an oral corticosteroid as a temporary adjuvant for pain relief
  - In acute disc herniation, acute or persistent migraine, flares of rheumatic pain
  - Use the lowest effective dose for the shortest period of time necessary

1. Arthritis Care & Research. Vol. 64, No. 4, April 2012, pp 465–474.
2. Ann Rheum Dis 2014;73:492–509.
3. Ann Rheum Dis. 2007 Dec;66(12):1560-7.
4. Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc,; Hudson, OH; accessed 2.9.2018

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Corticosteroids (cont'd)

- Dexamethasone:
  - Oral and IV: in divided doses q 6-12h
  - Intra-articular: 0.4 to 6 mg /day
- Prednisone: 5 mg to 60 mg PO daily
  - Discontinuation of long-term therapy requires gradual withdrawal by tapering the dose
- Adverse effects: weight gain, changes in mood and thinking, insomnia, elevated blood glucose, thin/fragile skin, increased bleeding risk, growth suppression, osteoporosis, bone fracture

PaiNweek

1. Arthritis Care & Research. Vol. 64, No. 4, April 2012, pp 465–474.
2. Ann Rheum Dis 2014;73:492–509.
3. Ann Rheum Dis. 2007 Dec;66(12):1560-7.
4. Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc; Hudson, OH; accessed 2.9.2018

Neuropathic Pain

Diagnosis

- Clinical setting
  - Diabetes
  - MS
  - HIV
  - Spine surgery
- Distribution
  - Stocking/glove
  - Peripheral nerve
  - Nerve root/dermatome
- Quality & timing
  - Burning or shooting
  - Worse at night
- Physical findings
  - Allodynia
  - Cooler temps
  - Neurological deficit

Drug Management

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

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* Drug of choice for trigeminal neuralgia

Anticonvulsants

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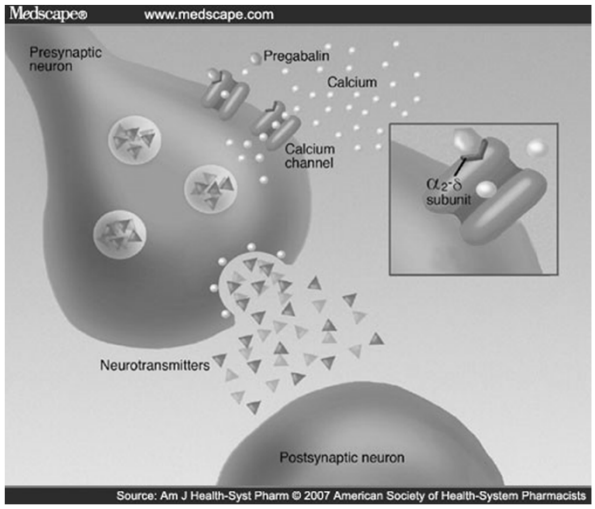
Anticonvulsants Gabapentin & Pregabalin

- 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

PAINWEEK

1. Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc; Hudson, OH; accessed 2.9.2018
2. J Clin Psychiatry. 2007 Mar;68(3):483-4.



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Anticonvulsants

Gabapentin

- Initial dose: 300 mg PO at bedtime
- Increase by 300-400 mg every 3-7 days, as tolerated, to lowest effective dose
- Maximum total daily dose: 3600 mg
- Renal dose adjustment required
- Baseline LFT and SCr and then monitor every 6-12 months thereafter
- Most common adverse effects:
  - Dizziness
  - Weight gain/edema
  - Sedation

Pregabalin

- Initial dose: 75 mg PO BID
- Titrate up to 150 mg PO BID or TID
  - Doses up to 600 mg have been evaluated with no significant additional benefit (increase in ADRs)
- Renal dose adjustment required
- Recommend baseline LFT and SCr and then monitor every 6-12 months thereafter
- Most common adverse effects:
  - Dizziness
  - Weight gain/edema
  - Sedation

PAINWEEK

1. Gabapentin [package insert]. New York, NY: Pfizer, Inc.; 2015.
2. Pregabalin [package insert]. New York, NY: Pfizer, Inc.; 2016.

Anticonvulsants (cont'd)

Gabapentin

- Renal dose adjustment:
  - CrCL >30-59 mL/min: 400-1400 mg/day
  - CrCL >15-29 mL/min: 200-700 mg administered as one daily dose
  - CrCL 15 mL/min: 100-300 mg administered as one daily dose
  - CrCL <15 mL/min: reduce daily dose in proportion to CrCL
- Hemodialysis patients:
  - Patients on hemodialysis should receive maintenance dose based on estimates of CrCL indicated above
  - Posthemodialysis supplemental dose should be administered after each 4 hours of hemodialysis

PAINWEEK

Gabapentin [package insert]. New York, NY: Pfizer, Inc.; 2015.

Anticonvulsants (cont'd)

Pregabalin

- Renal dose adjustment:

CrCL (mL/min)	Total Pregabalin Daily Dose (mg/day)				Dose Regimen
≥60	150	300	450	600	BID or TID
30-60	75	150	225	300	BID or TID
15-30	25-50	75	100-150	150	QD or BID
<15	25	25-50	50-75	75	QD

- Hemodialysis patients:
  - Patients on hemodialysis should receive maintenance dose based on estimates of CrCL indicated above
  - Posthemodialysis supplemental dose should be administered after each 4 hours of hemodialysis

PAINWEEK

Pregabalin [package insert]. New York, NY: Pfizer, Inc.; 2016.

Anticonvulsants (cont'd)

- Gabapentin ER
  - FDA-approved indication: postherpetic neuralgia
  - Do not use interchangeably with other gabapentin products
  - Max dose: Up to 1800 mg/day in single dose with evening meal
  - Titration recommendations:
    - Day 1: 300 mg
    - Day 2: 600 mg
    - Days 3-6: 900 mg
    - Days 7-10: 1200 mg
    - Days 11-14: 1500 mg
    - Day 15: 1800 mg
  - Renal dose adjustment:
    - CrCL 30-60 mL/min: 600-1800 mg
    - CrCL <30 mL/min: not recommended for use
    - Hemodialysis: not recommended for use

PAINWEEK

Gabapentin ER [package insert]. Newark, CA : Depomed, Inc.; 2012.

Anticonvulsants: Alternative Options

- **Carbamazepine**
  - Drug of choice for trigeminal neuralgia
  - May require titration of dose to maximum of 1200mg/day
  - Consider obtaining baseline CBC and LFTs; consider periodic monitoring of CBC and LFTs thereafter
  - Alternative agent: oxcarbazepine (similar efficacy but increased tolerability)
- **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.

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Anticonvulsants: Alternative Options

- **Lamotrigine** (off-label indication)
  - Data supports use in refractory trigeminal neuralgia, central post-stroke pain, SCI pain with incomplete cord lesion and brush-induced allodynia, HIV-associated neuropathy in patients on anti-retroviral 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
  - Hemophagocytic lymphohistocytosis
- **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. https://www.fda.gov/Drugs/DrugSafety/ucm605470.htm accessed 5/10/2018
3. R.H. Dworkin et al. / Pain 132 (2007) 237–251.

PAINWEEK

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. *Pediatr Neurol.* 2010;42(3):187-195.
3. Koch MW, Polman SKL. Oxcarbazepine versus carbamazepine monotherapy for partial onset seizures. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD006453. DOI: 10.1002/14651858.CD006453.pub2.
4. Hessen E, et al. *Acta Neurol Scand.* 2009;119(3):194-198.

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Antidepressants

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Tricyclic Antidepressants (TCAs)

May initiate as follows:

- **Nortriptyline** 10 mg PO at bedtime (off-label indication)
- **Desipramine** 25 mg PO at bedtime (off-label indication)
- **Amitriptyline** 10-25 mg PO at bedtime (off-label indication)
  - Increase by 10-25mg PO every 7 days
  - Use doses <100 mg/day when possible
  - Use with caution in BPH, glaucoma, cardiac disease, and those at risk for suicide

PAINWEEK

Lancet Neurol 2015; 162–73.

TCAs

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

1. Watson. *Neurology*. 1998;51:1166-1171.
2. McQuay. *Pain*. 1996;68:217-227.
3. Table adapted from Lexi-Drugs Online. www.uptodate.com. Accessed 2.9.2018.
4. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review

PainWeek

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

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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
- Unclear increase in risk in those without pre-existing disease
- 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

PAINWEEK

1. Ray WA, et al. *Clin Pharmacol Ther*. 2004;75:234-241.
2. Gelenberg AJ, et al. Practice guideline for the treatment of patients with Major Depressive Disorder, 3rd Edition. www.psychiatryonline.org. Accessed 2.9.2018

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
- Risk of "switching" to mania but small

1. Labbate, 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. Dallal A, et al. *J Clin Psychopharmacology.* 1998;18:343-344.
3. Frye MA, et al. *Am J Psychiatry.* 2009;166:164-172.
4. Van Scheyen JD, et al. *Arch Gen Psychiatry.* 1979;36:560-565.

PAINWEEK

SNRI

Venlafaxine

- Target dose (either IR or SA) is 225 mg/day
- Renal dose adjustment:
  - Mild (CrCL 60-89 mL/min) or moderate (CrCL 30-59 mL/min) impairment: total daily dose reduced by 25%-50%
  - Severe (CrCL <30 mL/min) impairment or hemodialysis: total daily dose reduced by 50% or more
- Hepatic dose adjustment:
  - Mild (Child-Pugh 5-6) to moderate (Child-Pugh 7-9) impairment: total daily dose reduced by 50%
  - Severe impairment (Child-Pugh 10-15) or hepatic cirrhosis: total daily dose reduced by 50% or more
- Use with caution in cardiovascular disease (can increase blood pressure and cause EKG changes)

Duloxetine

- Initiate at 30 mg PO daily x1 week, then increase to target dose of 60 mg PO daily
- In fibromyalgia and chronic MSK pain, no evidence that doses >60 mg/day provide additional benefit
- Not recommended for use in patients with ESRD or severe renal impairment
- Not recommended for use in hepatic insufficiency or impairment

PAINWEEK

1. Venlafaxine XR [package insert]. Philadelphia, PA: Pfizer, Inc.; 2016.
2. Duloxetine [package insert]. Indianapolis, IN: Eli Lilly and Company; 2011.

SNRI (cont'd)

- Milnacipran
  - FDA-approved indication 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

Milnacipran [package insert]. Irvine, CA: Allergan USA, Inc.; 2016.

PAINWEEK

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(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

PAINWEEK

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

SSRI/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. Loke YK, et al. Aliment *Pharmacol Ther.* 2008;27(1):31-40.
3. McCloskey DJ, et al. *Transl Res.* 2008;151(3):168-172.
4. de Abajo FJ, et al. *Arch Gen Psychiatry.* 2008;65(7):795-803.

PAINWEEK

SSRI/SNRI—Cardiac Conduction

- Previously not associated with QTc prolongation or *Torsades de Pointes*
- Venlafaxine
- Citalopram > escitalopram
- Dose limits
  - Citalopram 40 mg adults, 20 mg ≥65 years
  - Escitalopram 20 mg adults, 10 mg ≥65 years
- Consider baseline ECG in those with cardiac disease history

1. Anon. Drug Safety Update. 2011;5(5):A1.
2. http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON137769. Accessed 2.9.2018
3. https://crediblemeds.org/ Accessed 2.9.2018

PAINWEEK

Topical Products

PainWeek

Lidocaine

- Topical anesthetic and Class 1b anti-arrhythmic
- Available via OTC (0.5 % and 4 %) and prescription (5 %)
- Lidocaine 5 % patch applied directly to area of PHN
  - No more than 3 patches concurrently
  - 12 hours on, 12 hours off

PainWeek

1. Lin J, et al. Inhibition of acid sensing ion channel currents by lidocaine in cultured mouse corticol neurons. *Anesth Analg* 2011:112:977-81.
2. Kaliq W, et al. Topical lidocaine for the treatment of postherpetic neuralgia. Cochrane Database Syst Rev 2007;18:CD004846.
3. Schwartzman RJ, et al. *Pain Med* 2009;10:401-412.

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

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Capsaicin 8% patch [package insert]. Ardsley, NY: Acorda Therapeutics, Inc.; 2013.

Muscular Pain

Diagnosis

- Clinical setting
  - Muscular injury
- Distribution
  - Muscle group
- Quality & timing
  - Aggravated by certain movement or position
  - Better at rest
  - Pulling, ripping, aching, spasm, cramping
- Physical findings
  - Limited ROM
  - Trigger points
  - Muscle tightness
  - Taut bands or knots

Drug Management

- Baclofen
- Tizanidine
- Other agents

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

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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

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III. Centrally-acting agents (spasmolytic drugs)

Muscle Relaxants (cont'd)

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

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1. Pharmacotherapy 2008;28(2):207–213. Principles of Pharmacology, 2nd edition
2. Skeletal Muscle Relaxants Quick Reference. Compiled by Nolan MJ and Fudin J.

Skeletal Muscle Relaxants

- 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

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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

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