PainWeek

Nonopioid Analgesics:
The Selection and Use of Adjuvant Therapies

Courtney Kominek, PharmD, BCPS, CPE

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Disclosure

- Courtney Kominek has nothing to disclose.
- This presentation was not a part of the presenter's official duties at the VA and does not represent the opinion of the VA
- The presentation will include "off-label" uses of some medications.

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Learning Objectives

- Describe where adjuvant analgesics act in the pain pathway and 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

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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 degenerative disc disease 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?

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Skeletal Muscle Relaxants

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Introduction

- 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

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Fudin J, Raouf M. Pract Pain Manage. 2016; 16(5):1-18.
See S, Ginzburg R. Skeletal muscle relaxants. Pharmacother. 2008;28(2):207-213.

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Spasticity vs. Spasms

Description	Spasticity	Spasms
Definition	Velocity-dependent increase in muscle tone because of increased excitability	Involuntary muscle contraction
Etiology	• Central • Upper motor neuron disorder	• Peripheral • Muscle sprain or injury • Nerve compression
Symptoms	• Stiffness • Hypertonicity • Hyperreflexia	• Jerks • Twitches • Cramps

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Spasticity vs. Spasms

Description	Spasticity	Spasms
Cause	• Multiple sclerosis • Cerebral palsy • Spinal cord injury • Traumatic brain injury • Motor neuron disease • Post-stroke syndromes	• Musculoskeletal pain • Fibromyalgia • Sciatica • Mechanical low back pain • Herniated disk • Spinal stenosis • Myofascial pain
FDA-approved medications	• Botulinum toxin • Baclofen • Dantrolene • Diazepam • Riluzole • Tizanidine	• Carisoprodol • Chlorzoxasone • Cyclobenzaprine • Metaxalone • Methocarbamol • Orphenadrine

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Neurotransmitters Involved in Muscle Spasticity and Spasm

Gamma-aminobutyric acid (GABA)
- Primary inhibitory neurotransmitter from interneurons

Glutamate
- Primary excitatory neurotransmitter from IA afferent fibers in descending corticospinal tract
- Binds AMPA, kainate, NMDA

Glycine
- Inhibitory and excitatory roles

Acetylcholine (Ach)
- Primary neurotransmitter for sending signals from neurons to muscles
- Changes Na+ and Ca2+

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Carisoprodol

- MOA
  - Centrally acting
  - Changes interneuronal activity in spinal cord and descending reticular formation of brain
  - Decreases pain perception
- Dosing
  - 350 mg PO QID
  - Max 1400 mg/day
- Avoid in children < 12 years (or EVERYONE)

Fudin J, Raouf M. Pract Pain Manage. 2016; 16(5):1-18.
See S, Ginzburg R. Skeletal muscle relaxants. Pharmacother. 2008;28(2):207-213.
Skeletal Muscle Relaxants. http://paindr.com/wp-content/uploads/2012/05/FINAL_skeletal-muscle-relaxants_2011-11-06.pdf. Accessed 2 June 2017.

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Carisoprodol

- ADE
  - Abuse potential
  - Drowsiness, headache, vertigo, insomnia
  - Respiratory depression particularly in combo
  - Seizures with overdose, excessive use, withdrawal
  - Idiosyncratic allergic type reactions
- Kinetics
  - Metabolized by CYP2C19 to meprobamate among others
    - Subject to pharmacogenetic differences

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See S, Ginzburg R. Skeletal muscle relaxants. Pharmacother. 2008;28(2):207-213.
Skeletal Muscle Relaxants. http://paindr.com/wp-content/uploads/2012/05/FINAL_skeletal-muscle-relaxants_2011-11-06.pdf. Accessed 2 June 2017.

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Chlorzoxazone

MOA	Dosing	ADE
• Acts at spinal cord and subcortical areas of brain • Inhibition of multisynaptic reflex arcs	• 500-75 mg PO TID-QID	• Dizziness, drowsiness, • Rare hepatoxicity (monitor LFTs periodically) • GI irritation or ulcer • Urine discoloration

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See S, Ginzburg R. Skeletal muscle relaxants. Pharmacother. 2008;28(2):207-213.
Skeletal Muscle Relaxants. http://paindr.com/wp-content/uploads/2012/05/FINAL_skeletal-muscle-relaxants_2011-11-06.pdf. Accessed 2 June 2017.

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Cyclobenzaprine

- MOA
  - Structurally related to tricyclic antidepressants (TCAs)
  - Not clear likely sedation
  - No direct activity on skeletal muscle
- Dosing
  - 5 mg PO TID
  - Increase up to 10 mg PO TID
  - Avoid longer than 3 weeks
- Kinetics
  - Metabolized by CYP3A4, CYP1A2, and CYP2D6
- ADE
  - Anticholinergic side effects
  - Avoid in patients with cardiac conduction abnormalities or arrhythmias

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See S, Ginzburg R. Skeletal muscle relaxants. Pharmacother. 2008;28(2):207-213.
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*All benzodiazepines have muscle relaxant properties

Diazepam

Approvals	• Spasticity • Muscle spasms
MOA	• GABA receptor agonist → increases chloride conductance → presynaptic inhibition of spinal cord
Dosing	• 2 mg PO BID-TID or 5 mg PO QHS • Target 40 mg/day divided

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See S, Ginzburg R. Skeletal muscle relaxants. Pharmacother. 2008;28(2):207-213.
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Diazepam

Kinetics:	• Elimination half-life 20-50 h • Active metabolites with half-life up to 100 h • Metabolized by CYP3A4 and CYP2C19
Avoid	• Elderly • Renal or hepatic impairment
ADE	• Abuse potential • Dizziness, drowsiness, confusion, amnesia • Withdrawal with abrupt cessation

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Skeletal Muscle Relaxants. http://paindr.com/wp-content/uploads/2012/05/FINAL_skeletal-muscle-relaxants_2011-11-06.pdf. Accessed 2 June 2017.

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Metaxalone

- MOA
  - Not established
  - No direct action on skeletal muscles or nerve fibers
- Dosing
  - 800 mg PO TID-QID
- Kinetics
  - Bioavailability increased with high fat meal
  - Metabolized by CYP1A2, CYP2D6, CYP2E1, and CYP3A4
- ADE
  - Dizziness, drowsiness (less compared to others), headache,
  - Respiratory depression in combination
  - Rare leukopenia and hemolytic anemia
  - Avoid < 12 yrs of age
  - Avoid in patients with renal or hepatic failures
  - Avoid in anemia

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See S, Ginzburg R. Skeletal muscle relaxants. Pharmacother. 2008;28(2):207-213.
Skeletal Muscle Relaxants. http://paindr.com/wp-content/uploads/2012/05/FINAL_skeletal-muscle-relaxants_2011-11-06.pdf. Accessed 2 June 2017.

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Methocarbamol

MOA

Centrally acting

Carbamate derivative of guaifenesin

Unknown mechanism of muscle relaxation, likely sedation

Dosing

1500 mg PO QID x 2-3 days, then 750 mg PO QID

ADE

Discoloration of urine (brown-black or green)

Altered mental status

Worsen myasthenia gravis

Fudin J, Raouf M. Pract Pain Manage. 2016; 16(5):1-18.
See S, Ginzburg R. Skeletal muscle relaxants. Pharmacother. 2008;28(2):207-213.
Skeletal Muscle Relaxants. http://paindr.com/wp-content/uploads/2012/05/FINAL_skeletal-muscle-relaxants_2011-11-06.pdf. Accessed 2 June 2017.

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Orphenadrine

- MOA
  - Anticholinergic agent
  - Structurally related to diphenhydramine
  - Inhibits antimuscarinic acetylcholine and N-methyl-D-aspartate receptors
- Dosing
  - 100 mg PO BID
- ADE
  - Anticholinergic
  - GI disturbances
  - Avoid elderly, glaucoma, cardiospasms, myasthenia gravis
- Contraindicated
  - Duodenal or pyloric obstruction or stenosing peptic ulcers

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See S, Ginzburg R. Skeletal muscle relaxants. Pharmacother. 2008;28(2):207-213.
Skeletal Muscle Relaxants. http://paindr.com/wp-content/uploads/2012/05/FINAL_skeletal-muscle-relaxants_2011-11-06.pdf. Accessed 2 June 2017.

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Tizanidine

MOA
- Structurally related to clonidine
- Centrally acting
- Inhibits presynaptic and postsynaptic α-2 motor neurons
- Potentiate glycine

Dosing
- Initial dose: 4 mg
- Increase by 2-4 mg q6-8h
- Max 36 mg/day divided

Fudin J, Raouf M. Pract Pain Manage. 2016; 16(5):1-18.
See S, Ginzburg R. Skeletal muscle relaxants. Pharmacother. 2008;28(2):207-213.
Skeletal Muscle Relaxants. http://paindr.com/wp-content/uploads/2012/05/FINAL_skeletal-muscle-relaxants_2011-11-06.pdf. Accessed 19 May 2019.

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Tizanidine

ADE
- Hypotension, sedation, asthenia, dry mouth
- Elevated liver function tests, hepatoxicity
  - Monitor baseline, 1, 3, and 6 months
- Withdrawal syndrome with abrupt discontinuation
- Avoid CrCl < 25 mL/min

Kinetics
- Bioavailability differs based on dosage form and food
- Metabolized by CYP1A2
  - Contraindicated with ciprofloxacin and fluvoxamine

Fudin J, Raouf M. Pract Pain Manage. 2016; 16(5):1-18.
See S, Ginzburg R. Skeletal muscle relaxants. Pharmacother. 2008;28(2):207-213.
Skeletal Muscle Relaxants. http://paindr.com/wp-content/uploads/2012/05/FINAL_skeletal-muscle-relaxants_2011-11-06.pdf. Accessed 19 May 2019.

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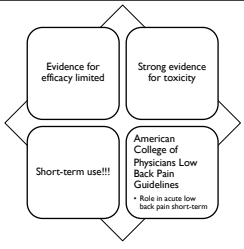
Antispamodics Place in Therapy



Qaseem et al. Ann Intern Med. 2017;166(7):514-530.
See S, Ginzburg R. Am Fam Physician. 2008;78(3):365-370.

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Tricyclic Antidepressants (TCA)

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Role in Pain Management

First-line for neuropathic pain	Second-line for neuropathic pain
• NICE • Canadian Pain Society Guidelines • Neuropathic Pain Special Interest Group of the International Association for the Study of Pain • European Federation of Neurological Societies	• American Academy of Neurology • American Diabetes Association

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Longson D, Bhojani I, Brandner B, et al. *National Institute for Health and Care Excellence: Clinical Guidelines*. 2013.
Moulin DE, Clark AJ, Gilron I, et al. *Pain Research and Management*. 2007;12(1):13-21.
Dworkin RH, O'Connor AB, Audette J, et al. *Mayo Clin Proc*. 2010;85(3 Suppl):S3-14.
Attal N, Cruccu G, Baron R, et al. *Eur J Neurol*. 2010;17(9):1113-e1188.

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Role in Pain Management

Effects independent of BH disorder	Low back pain	Migraine prophylaxis
Fibromyalgia	Effects independent of BH disorder	Lower doses compared to MDD

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Dharmshaktu P, Tayal V, Kalra BS. Efficacy of antidepressants as analgesics: a review. *J Clin Pharmacol*. 2012;52(1):6-17.

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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, Masters SB, Trevor AJ, eds. Basic & Clinical Pharmacology, 12nd ed. New York: McGraw-Hill; 2012. http://www.accesspharmacy.com/content.aspx?aID=5582584§. Accessed August 8, 2013.

Adapted from: DeBattista C. Chapter 30. Antidepressant Agents. In: Katzung BG, Masters SB, Trevor AJ, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 9th ed. New York: McGraw-Hill; 2011. http://www.accesspharmacy.com/content.aspx?aID=7466830. Accessed August 8, 2013.

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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
  - Use with caution in BPH, glaucoma, cardiac disease, and those at risk for suicide

Lancet Neurol 2015; 162–73.

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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

Gelenberg AJ, Freeman MP, Markowitz JC, et al. Treatment of Patients with Major Depressive Disorder. 2010. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed October 10, 2017.

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ADE

Anticholinergic → Elderly

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

Gelenberg AJ, Freeman MP, Markowitz JC, et al. Treatment of Patients with Major Depressive Disorder. 2010. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed October 10, 2017.

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ADE

- Withdrawal symptoms
- Suicide risk
- Seizure risk
- Histamine receptor antagonism → Sedation

Gelenberg AJ, Freeman MP, Markowitz JC, et al. Treatment of Patients with Major Depressive Disorder. 2010. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed October 10, 2017.

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Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

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Role in Pain Management

Duloxetine	• FDA-approved for • Diabetic peripheral neuropathy • FMS • Chronic musculoskeletal pain (LBP, OA) • Second-line in American College of Physician guideline on LBP
Milnacipran	• FDA-approved for FMS
Venlafaxine	• LBP • Diabetic peripheral neuropathy • FMS • Chemotherapy-induced neuropathy • Painful polyneuropathy • Headaches

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Lilly USA L. Cymbalta: highlights of prescribing information. 2016. http://pi.lilly.com/us/cymbalta-pi.pdf. Accessed 10/10/17.
Wyeth. Effexor XR: highlights of prescribing information. 2016. http://labeling.pfizer.com/showlabeling.aspx?id=100. Accessed 10/10/17.
Allergan USA I. Savella: highlights of prescribing information. 2016. https://www.allergan.com/assets/pdf/savella_pi. Accessed 10/10/17.

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ADE

Common
• Nausea • Somnolence • Dry mouth • Hyperhidrosis • Erectile dysfunction • Constipation

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Lilly USA L. Cymbalta: highlights of prescribing information. 2016. http://pi.lilly.com/us/cymbalta-pi.pdf. Accessed 10/10/17.
Effexor XR: highlights of prescribing information. 2016. http://labeling.pfizer.com/showlabeling.aspx?id=100. Accessed 10/10/17.

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ADE

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

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Lilly USA L. Cymbalta: highlights of prescribing information. 2016. http://pi.lilly.com/us/cymbalta-pi.pdf. Accessed 10/10/17.
Wyeth. Effexor XR: highlights of prescribing information. 2016. http://labeling.pfizer.com/showlabeling.aspx?id=100. Accessed 10/10/17.
Allergan USA I. Savella: highlights of prescribing information. 2016. https://www.allergan.com/assets/pdf/savella_pi. Accessed 10/10/17.

33

SNRI—Suicidality

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

Morrato EH, et al. *Am J Psychiatry*. 2008;165(1):42-50.
http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/UCM096273.
Accessed July 18, 2012.

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SNRI Bleeding Risk

- Block 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

Dalton SO, et al. *Arch Intern Med*. 2003;163(1):59-64.
Loke YK, et al. *Ailment. Pharmacol Ther*. 2008;27(1):31-40.
McCloskey DJ, et al. *Transl Res*. 2008;151(3):168-172.
de Abajo FJ, et al. *Arch Gen Psychiatry*. 2008;65(7):795-803.

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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
- Consider serotonin active herbal/OTC products!!!

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.

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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

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Lilly USA L. Cymbalta: highlights of prescribing information. 2016. http://pi.lilly.com/us/cymbalta-pi.pdf. Accessed 10/10/17.

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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

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Wyeth. Effexor XR: highlights of prescribing information. 2016. http://labeling.pfizer.com/showlabeling.aspx?id=109. Accessed 10/10/17.
Herndon C et al. Practical Pain Management. 2015;15(10).

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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

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

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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

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Allergan USA I. Savella: highlights of prescribing information. 2016. https://www.allergan.com/assets/pdf/savella_pi. Accessed 10/10/17.

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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

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VA/DoD clinical practice guideline for the management of posttraumatic stress disorder and acute stress disorder. 2017.
Treating patients with acute stress disorder and post-traumatic stress disorder a quick reference guide. American Psychiatric Association. 2004.

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Return to Patient Case

- 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

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Patient Case #2

- MP is a 68-year-old male with diabetic peripheral neuropathy. 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.

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Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

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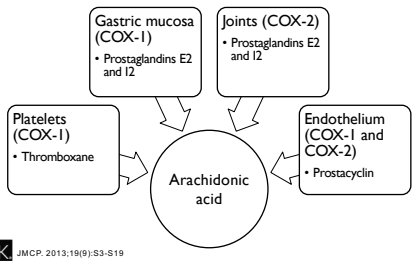
Mechanism of Action



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

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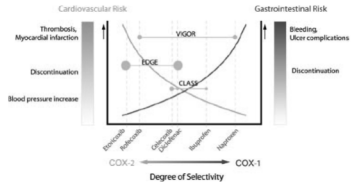
NSAIDs—COX Selectivity and Associated Risk



PainWeek Circulation. 2007;115:1634-1642.

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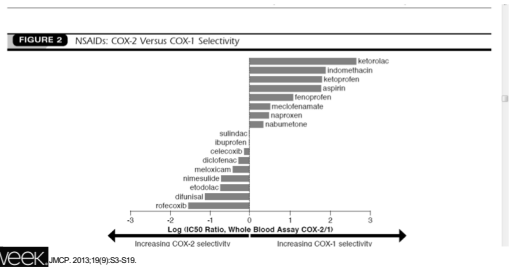
COX-1 and COX-2 Selectivity



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

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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.

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

48

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

PainWeek N Engl J Med 2016; :2519-2529.

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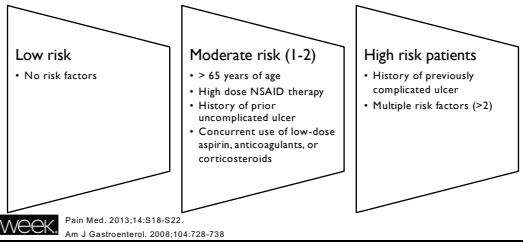
GI Adverse Events: Risk Factors



PainWeek Pain Med. 2013;14:S18-S22.
Am J Gastroenterol. 2008;104:728-738

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GI Adverse Events: Prevention

	Low GI Risk	Moderate GI Risk	High GI Risk
Low CV Risk	NSAID alone	NSAID + PPI or misoprostol	Alternative therapy or COX-2 + PPI or misoprostol
High CV Risk	Naproxen + PPI or misoprostol	Naproxen + PPI or misoprostol	Avoid NSAIDs or COX-2 inhibitors. Use alternative therapy

PainWeek Am J Gastroenterol. 2009;104:728-738.

51

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

PainWeek

Inker et al. Am J Kidney Dis. 2014;64(5):713-735.

52

NSAIDs and Renal Dysfunction

Sulindac and salsalate may have less renal hemodynamic changes	Limit dose and frequency
Topicals	Short-acting NSAIDs preferred

PainWeek

Am J Kidney Dis. 2014;64(5):713-735.
Clin Kidney J. 2017;10(5):688-697.

53

NSAIDs and Liver Dysfunction

Mild to moderate dysfunction

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

Avoid in patients with cirrhosis

PainWeek

Pract Pain Manage. 2013;13(9).
J Gastroenterol Hepatol. 2014;29:1356-1360
Drugs. 2012;72(12):1646-1669.

54

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

PainWeek

DRUGDEX System. MICROMEDEX 2.0, Greenwood Village, Colorado. 21 March 2014.
Circulation. 2014;129:907-916.
Arthritis Res Ther. 2013;15(Suppl 3):1-10.

55

Topical Products

PainWeek

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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

PainWeek

Pain Med. 2013;14:S35-S39

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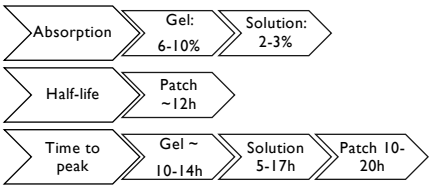
Topical NSAIDs: Place in Therapy

- 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

PainWeek BMC. 2014;15:1-5

58

Topical NSAIDs: Pharmacokinetics



PainWeek Packaging information.

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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 (5%)
- Lidocaine 5% patch applied directly to area of PHN
  - No more than 3 patches concurrently
  - 12 hours on, 12 hours off
- OTC lidocaine 4% patch
- IV infusion is a potential treatment option

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

60

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

PainWeek

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

61

Gabapentinoids

PainWeek

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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

PainWeek

Dworkin RH et al. Pain. 2007;1332:237-251.
Schifano F. CNS Drugs. 2014;28:491-496.
Micromedex 2.0 Online. http://www.micromedexsolutions.com/micromedex2/librarian.
J Clin Psychiatry. 2007 Mar;68(3):483-4

63

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

PainWeek

Addiction. 2016;111:1160-1174.
Neurology. 2011;76(20:1758-1765.
Diabetes Care. 2017;40(10:136-1584.
May Clin Proc. 2010;85(3 Suppl):S3-S14.

64

Role in Pain

Multimodal postoperative pain management	Acute or chronic sciatica	Nonspecific low back pain
Pain scores	No benefit for pregabalin	Ineffective
Opioid doses		Contribute to ADE
Opioid side effects		
Controversy around dosing and timing		

PainWeek

Spine. 2013;38(22):1947-1952.
NEJM. 2017;376(12):1111-1120.
Br J Anaesth. 2011;106(4):454-462.
Pain. 2007. 132;237-251.
PLoS Med. 2017;14(8):e1002369.
Medicine. 2017;96(21)e6982.
JAMA Surg. 2017;epub.

65

Off-label Uses

Pregabalin

- Bipolar disorder
- Alcohol/narcotic withdrawal
- Anxiety
- ADHD
- Restless legs syndrome
- Trigeminal neuralgia
- Non-neuropathic pain

Gabapentin

- Insomnia
- Neuropathic pain
- Drug and alcohol addiction
- Anxiety
- Bipolar disorder
- Migraines

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CNS Drugs. 2014;28:491-496.
Addiction. 2016;111:1160-1174.

66

Gabapentin

Gabapentinoid Medication	FDA-Approved Indications	Dosing	Renal Dose Adjustments
Gabapentin (Neurontin®)	• 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

PainWeek

Pfizer. Neurontin: highlights of prescribing information. 2017. http://labeling.pfizer.com/ShowLabeling.aspx?id=630

67

Gabapentin ER

Gabapentinoid Medication	FDA-Approved Indications	Dosing	Renal Dose Adjustments
Gabapentin (Gralise®)	• 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

PainWeek

Depomed. Gralise Full Prescribing Information. 2012. https://www.gralise.com/sites/default/files/GRALISE_PI_DEC2012.pdf. Accessed 5/19/18.

68

Gabapentin enacarbil

Gabapentinoid Medication	FDA-Approved Indications	Dosing	Renal Dose Adjustments
Gabapentin enacarbil (Horizant®)	• 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

PainWeek

Arbor Pharmaceuticals L. Horizant: Highlights of prescribing information. 2016.

69

Pregabalin

Gabapentinoid Medication	FDA-Approved Indications	Dosing	Renal Dose Adjustments
Pregabalin (Lyrica)	• 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

PainWeek

Pfizer. Lyrica: Highlights of prescribing information. 2016. http://labeling.pfizer.com/showlabeling.aspx?id=561. Accessed 10/10/17.

70

Pregabalin CR

Gabapentinoid Medication	FDA-Approved Indications	Dosing	Renal Dose Adjustments
Pregabalin CR	• 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

PainWeek

Pfizer. U.S. FDA approves Lyrica® CR (pregabalin) extended-release tablets CV [press release]. 2017. http://www.pfizer.com/news/press-release/press-release-detail/u_s_fda_approves_lyrica_cr_pregabalin_extended_release_tablets_cv . Accessed 10/12/17.

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Gabapentinoid Pharmacokinetics

Medication	F	Tmax	Half-life	Notes
Gabapentin IR (Neurontin)	900 mg 60% 1200 mg 47% 2400 34% 3600 33		5-7h	Bioavailability is not dose proportional
Gabapentin ER (Gralise)*		8h		Bioavailability is not dose proportional. Cmax increased 33-8% and AUC 33-118% with food depending on fat content. Absorbed from proximal small bowel by a saturable L-amino transport system.
Gabapentin enacarbil*	75%	7.3 h with food	5.1-6	Prodrug. Dose-proportional and extended exposure to gabapentin. Nonsaturable absorption
Pregabalin	90%		6.3 hours	Linear Cmax and AUC, independent of dose

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Gabapentin Increases Overdose Odds

- Population-based nested case-control study
- Cases (1,256 cases) were opioid users who died of an opioid-related cause matched with up to 4 controls (4,619 controls)
- Primary exposure was gabapentin use 120 days preceding index date
- 12.3% of cases and 6.8% of control were prescribed gabapentin
- Odds increased 49% if prescribed gabapentin + opioid
- High dose gabapentin (1800 mg/day) about 60% increased odds compared to moderate dose
- Very high dose (2,200 mg/day) associated with 2-fold increased odds

PainWeek PLoS Med. 2017;14(10:e1002396.

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Pregabalin Increases Overdose Odds

- Population-based, nested, case-control study in patients received opioid
- 1417 cases: died of an opioid-related cause, excluding suicide or homicide
- 5097 controls: matched on several characteristics
- Primary exposure: pregabalin 120 days prior to index date
- Case patients more likely to receive CNS depressants, more medications annually, and have more comorbidities
- Exposure to pregabalin 120 days prior increased odds of opioid-related death 1.68 (95% CI 1.19-2.26)
- High dose of pregabalin (> 300 mg/day) associated with 2.51 increased odds (95% CI 1.24-5.06)

PainWeek Ann Intern Med. 2018 Aug 21. epub ahead of print.

74

Gabapentinoid Abuse

- Prevalence
  - –General population 1.1%
  - –Opioid use disorder
    - 15-22% gabapentin misuse
    - 40-65% abuse of gabapentin with prescription
- Dosing – variety
  - –Therapeutic range – no prescription
  - –Supratherapeutic range
  - –3-20 times clinically used amounts
  - –Taken as one large dose

PainWeek Addiction. 2016;111:1160-1174. CNS Drugs. 2014;28:491-496. Drugs. 2017;77:403-426.

75

Gabapentinoid Abuse

- Typically ingested with other substances
- Often used to increase high or treat withdrawal
- 90% of fatalities involve opioids
- Withdrawal treatment involves tapering gabapentinoid

Drugs. 2017;77:403-426.
Brain Sci. 2018 Apr 22;8(4).
Psychother Psychosom. 2011;80(2):118-22.
CNS Drugs. 2014;28:491-496.
Addiction. 2016;111:1160-1174.
Guide to the management of gabapentinoid misuse. Available at:
https://www.prescriber.co.uk/article/guide-to-the-management-of-gabapentinoid-misuse/

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Role in Addiction Treatment

- Pregabalin
  - Alcohol withdrawal
  - Alcohol relapse prevention (abstinence similar to naltrexone)
  - Benzodiazepine/opioid withdrawal
  - Some evidence to prevent cocaine relapse
- Gabapentin
  - Evidence in opioid, THC, alcohol addictions
  - Gabapentin *suggested* in APA AUD Guidelines
    - Goal of reducing or abstaining from alcohol
    - Prefer topiramate or gabapentin or intolerant or did not respond to naltrexone or acomprosate
    - No contraindications

CNS Drugs. 2014;28:491-496.
Practice Guideline for the Pharmacological Treatment of Patients with Alcohol Use Disorder. APA.
https://psychiatryonline.org/doi/pdf/10.1176/appi.books.9781615371969

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Other Anticonvulsants

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Carbamazepine (CBZ) and Oxcarbazepine (OXCBZ)

- MOA: inhibit voltage-gated sodium channels and potentiate GABA
- Role
  - CBZ drug of choice for trigeminal neuralgia
  - OXCBZ
    - Trigeminal neuralgia
    - Specialist setting/4th line NICE neuropathic pain guidelines

Tegretol package insert. East Hanover, NJ: Novartis: 2018 March.
Trileptal package insert. East Hanover, NJ: Novartis: 2018 March.
Neurology. 2008;71:1183-1190.
Pain Research and Management. 2014;19(6):328-335..
Eur J Neurol. 2010;17(9):1113-e1188.
Neurosciences. 2015;20(2):107-114.
National Institute for Health and Care Excellence: Clinical Guideli
Institute for Health and Care Excellence: Clinical Guidelines. 201

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Carbamazepine and Oxcarbazepine

CBZ IR and XR	OXCBZ IR	OXBZ XR
• Initial: 100 mg PO BID • Titrate by 100 mg PO BID • Target dose 300-900 mg/day • Max dose: 1200 mg/day	• Initial: 150 mg PO BID • Titrate by 300 mg q3 days • Target: 300-600 mg PO BID • Max dose: 1800 mg/day	• Initial dose: 600 mg PO daily • Titrate by 600 mg/day weekly • Max dose: 2400 mg/day

Tegretol package insert. East Hanover, NJ: Novartis: 2018 March.
Trileptal package insert. East Hanover, NJ: Novartis: 2018 March.

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Carbamazepine and Oxcarbazepine

- CBZ
  - Metabolized by CYP3A4
  - Active metabolite carbamazepine 10,11, epoxide autoinducer
  - Induces CYP3A4, CYP1A3, CYP2B6, CYP2C9, CYP2C19
- OXCBZ
  - Keto-derivative of CBZ
  - Metabolized to active metabolite 10-monohydroxy oxcarbazepine which avoids CYP metabolism
  - May be better tolerated
  - 20-30% have cross-reactivity with OXCBZ if allergic to CBZ

Tegretol package insert. East Hanover, NJ: Novartis: 2018 March.
Trileptal package insert. East Hanover, NJ: Novartis: 2018 March.

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Carbamazepine and Oxcarbazepine

- Common ADE
  - Diplopia, abnormal vision
  - Fatigue
  - Dizziness
  - Somnolence
  - N/V
  - Ataxia
  - Headache
  - Nystagmus
  - Tremor
  - Abnormal gait
- Serious ADE
  - Hyponatremia
  - Allergic reactions
  - Pancytopenia
  - Agranulocytosis
  - Leukopenia
  - Serious dermatological reactions
    - HLA-B*1502 testing for those with Asian ancestry
  - Cardiac (BP, CHF, arrhythmias, AV block) (CBZ)
  - Elevation LFTS (CBZ)

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tol package insert. East Hanover, NJ: Novartis: 2018 March.
tol package insert. East Hanover, NJ: Novartis: 2018 March.

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Lamotrigine

- MOA: voltage-gated sodium channels
- Role
  - 4th line/specialist setting for neuropathic pain
  - 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 anti-retroviral therapy, and diabetic neuropathy
- Dosing
  - TITRATE DOSE SLOWLY
  - Initiate at 25 mg PO daily x 2 weeks then increase to 50 mg/day for 2 weeks
  - Then titrate by 50 mg/day q1-2 weeks
  - May need to titrate to 200-400 mg/day

PainWeek

Pain Research and Management. 2014;19(6):328-335.
Neuropathic Pain: The Pharmacological Management of Neuropathic Pain in Adults in Non-specialist Settings. National Institute for Health and Care Excellence: Clinical Guidelines. 2013.
Eur J Neurol. 2010;17(9):1113-e1188.
Lamictal package insert. Research Triangle Park: GlaxoSmithKline; 201 July.
Neurol Sci (2006) 27:S183–S189.

83

Lamotrigine

- Common ADE
  - Dizziness
  - Nausea
  - Insomnia
  - Somnolence
  - Fatigue
  - Diplopia
  - Ataxia
- Severe ADE
  - FATAL OR LIFE-THREATENING HYPERSENSITIVYT
  - Blood dyscrasias
  - Aseptic meningitis

PainWeek

amictal package insert. Research Triangle Park: GlaxoSmithKline; 2018 July.

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Topiramate

- MOA
  - Inhibits voltage-gated sodium channels
  - AMPA/kainate subtype of glutamate receptor
  - Carbonic anhydrase inhibitor
  - Increases activity at GABA-A receptor
- Role
  - Alcohol use disorder
  - Migraine prophylaxis
  - Neuropathic pain

PainWeek

The American Psychiatric Association Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder. https://psychiatryonline.org/guidelines
Pain Research and Management. 2014;19(6):328-335.
Neuropathic Pain: The Pharmacological Management of Neuropathic Pain in Adults in Non-specialist Settings. National Institute for Health and Care Excellence: Clinical Guidelines. 2013.
Trokendi XR package insert. Rockville, MD: Supernus Pharmaceuticals; 2018 Jan.
Topamax package insert. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2018 June.

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Topiramate

- Dosing
  - Topiramate IR
    - Initial dose: 25 mg po daily x 1 week
    - Titrate by 25-50 mg/day
    - Target dose
      - Migraine: 50 mg PO BID
      - Neuropathic pain 200-400 mg/day
  - Topiramate XR
    - Initial dose: 25 mg PO daily
    - Titrate by 25mg/day q week
    - Target dose: 100 mg/day

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Trokendi XR package insert. Rockville, MD: Supernus Pharmaceuticals; 2018 Jan.
Topamax package insert. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2018 June.

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Topiramate

- Dose-related ADE
  - Paresthesia
  - Fatigue
  - Nausea
  - Anorexia
  - Dizziness
  - Difficulty with memory
  - Diarrhea
  - Weight loss
  - Concentration/attention
  - Somnolence
- Caution
  - Secondary angle glaucoma
  - Metabolic acidosis
  - Hyperammonemia
  - Kidney stones
  - Oligohidrosis
  - Hypo/hyperthermia
  - Cognitive dysfunction
  - Renal adjustments CrCl < 70 mL/min

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Trokendi XR package insert. Rockville, MD: Supernus Pharmaceuticals; 2018 Jan.
Topamax package insert. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2018 June.

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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

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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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Learning Assessment Questions

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