Non-Opioid Pharmacologic Management of Pain

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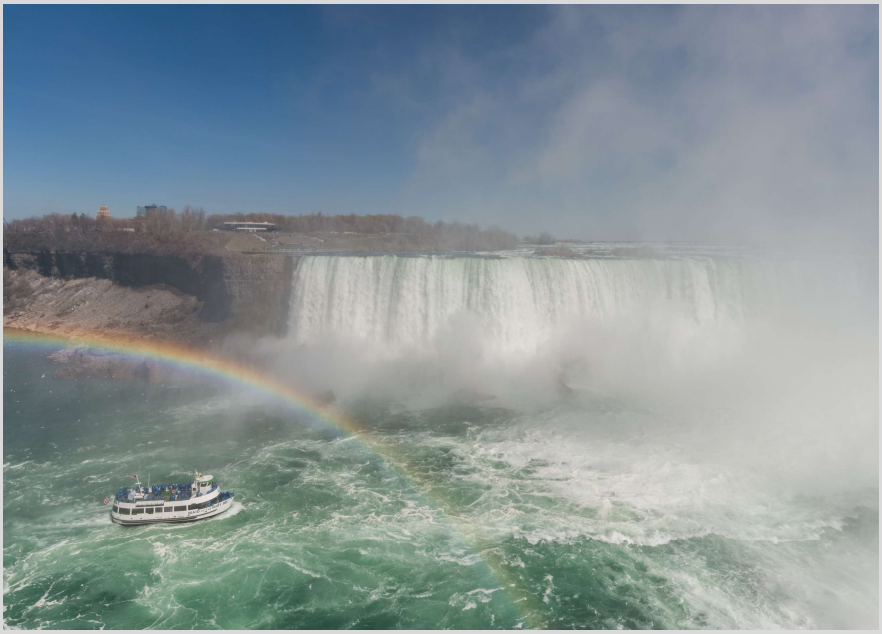
- None



Navigating Pain Management with Multiple Competing Goals

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Objectives

- Practical non-opioid treatment pa
- Focused pain assessment
- Current best practices
- Clinical case scenarios

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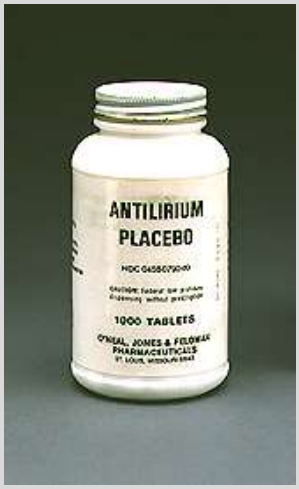
Non-opioid Medications



- Topical analgesics
- Local anesthetics
- Acetaminophen
- NSAIDs
- Muscle relaxants
- Antidepressants
- Antiepileptic Drugs (AEDs)
- Corticosteroids
- NMDA antagonists

https://commons.wikimedia.org/wiki/File:Antilirium_Placebo.jpg
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Journavx (Suzetrigine): Novel Non-opioid

FDA Approves January 30, 2025

- NaV1.8 Selective Na channel blocker
- Moderate to severe acute pain
- 2 RCTs acute surgical pain
- AEs: itching, muscle spasms, increased blood level of creatine phosphokinase, rash

https://www.fda.gov/news-events/press-announcements/fda-approves-novel-non-opioid-treatment-moderate-severe-acute-pain
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CDC Clinical Practice Guideline for Prescribing Opioids for Pain – United States, 2022 (Updated)[1]

- Non-opioid recommendations
- Determining whether or not to initiate opioids, then how to implement for **outpatients**

https://upload.wikimedia.org/wikipedia/commons/7/71/CDC_logo_2024.svg

Does NOT apply to[1]

- *Children <18 years*
- *Sickle cell disease*
- *Cancer*
- *Palliative*
- *End-of-life care*
- *Hospitalized, emergency, or observational setting that might transition to inpatient care*
- *Prescribing for opioid use disorder*

Comprehensive Evaluation to Improve Function

- Multimodal treatment:
  - Nonpharmacologic
  - Medication
  - Surgery
  - Early rehabilitation
- *Barriers:*
- *Resource allocation*
- *Insurance noncoverage*
- *Other (rural, transportation)*

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Pain Medication Targeted Assessment

- Where is the pain?
- Localized versus generalized?
- Character, quality, timing, duration?
- Medical comorbidities?
- Preexisting medications?
- Surgery / Procedure?
- Risks versus benefits?
- Physician / Patient preference?

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International Association for the Study of Pain (IASP) Definitions *Revised 2020*[2]

- **Nociceptive pain** is from actual or threatened damage to non-neural tissue (skin, musculoskeletal, certain soft tissues) and is due to the activation of nociceptors
  1. *somatic pain - skin, musculoskeletal, connective tissue*
  2. *visceral pain - internal organ*
- **Neuropathic pain** is direct consequence of a lesion or disease of the somatosensory nervous system
- **Nociplastic pain** is augmented central nervous system pain and sensory processing and altered pain modulation

AHRQ Agency for Healthcare Research and Quality

CDC U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION

- CDC funded AHRQ in 2018-2019 to conduct systematic reviews for updated 2022 CDC Opioid Prescribing Guidelines:
  - Evaluate effectiveness for medications for specific types of pain, considering function, QOL, AEs
  - **Nonopioid treatments for acute and chronic pain**[3,4]

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AHRQ Comparative Effectiveness Reviews[1]

- Data sources: Electronic databases (Ovid® MEDLINE®, Embase®, PsycINFO®, CINAHL®, Cochrane Central Register of Controlled Trials, and **Cochrane Database of Systematic Reviews)** through September 10, 2019
- Review methods: **Randomized controlled trials (RCTs)** of non-opioids in patients with pain
- Non-opioids for chronic pain: 185 RCTs and 5 systematic reviews

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework[1]

- **Magnitude** of effects: *Small, Moderate, or Large*
- Assessed **strength** of evidence
- Meta-analyses were conducted

- Reviewed
  - Study quality
  - Specific drug
  - Dose
  - Pain type

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The Data: Non-opioids for Chronic Pain:

7 Pain Conditions

- Neuropathic pain
- Fibromyalgia
- Osteoarthritis
- Inflammatory arthritis
- Low back pain
- Chronic headache
- Sickle cell disease

3 Time Durations

- Short term (1 to <6 months)
- Intermediate term (≥6 to <12 months)
- Long term (≥12 months)

Intermediate and long-term outcomes mostly not assessed

Pain Duration[1]

- Acute pain (<1 month)
- **Nonopioid therapies are effective for many types of acute pain**

- ***Nonopioid therapies preferred for subacute and chronic pain***
- Subacute pain (1-3 months)
- Chronic pain (>3 months)
- *Many patients do not experience benefit in pain or function from increasing opioid dosages to ≥50 MME/day but are exposed to more risk as dose increases*

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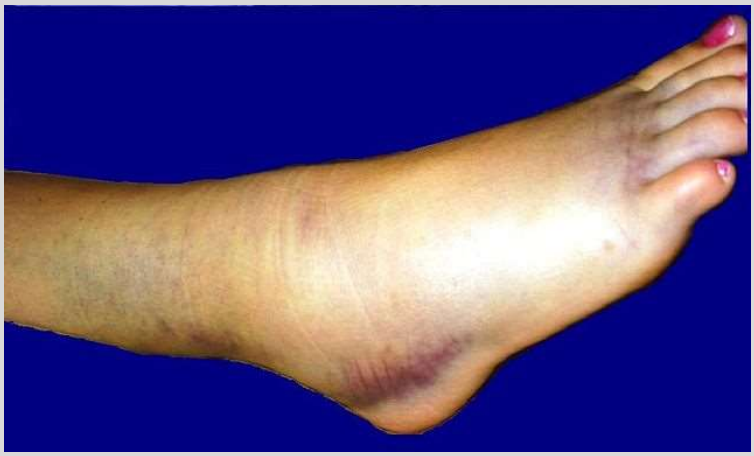
Recommendations for Nonopioids[1]



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NSAIDs for musculoskeletal pain *(not low back pain)*[1,4]

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Topical NSAIDs diclofenac +/- menthol gel first-line

then Oral NSAIDs +/- Acetaminophen

ACP American College of Physicians® Leading Internal Medicine, Improving Lives

AAFP American Academy of Family Physicians

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NSAIDs more effective than opioids for surgical dental pain[1,4]

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NSAIDs first-line

ADA

https://commons.wikimedia.org/wiki/File:American_Dental_Association.png
https://commons.wikimedia.org/wiki/File:Teeth_by_David_Shankbone.jpg
I, DavidShankbone, CC BY-SA 3.0, via Wikimedia Commons

NSAIDs or muscle relaxers for low back pain[1,4]

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NSAIDs similarly effective to opioids for LBP

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https://commons.wikimedia.org/wiki/File:Lower_back_pain.svg
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NSAIDs for nephrolithiasis pain[1,4]

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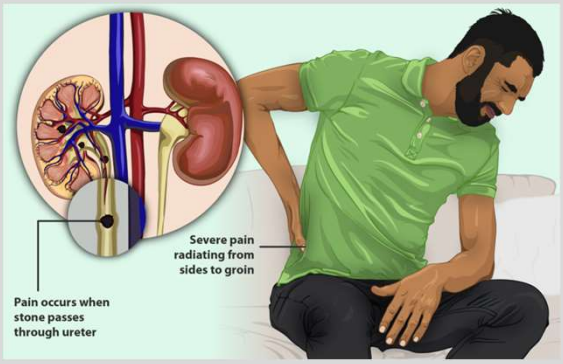

NSAIDs first-line

then acetaminophen

more effective than opioids

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Opioids for acute:

- low back pain
- postoperative pain

associated with increased likelihood of opioids long-term[1,4]

- NSAIDs & acetaminophen have decreased risk of short-term adverse events compared to opioids

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Worse Outcomes with Long-term Opioids[1]

- Osteoarthritis
- Nonspecific low back pain
- Headache
- Fibromyalgia

- *Limited evidence improved pain or function*

Patient perceptions

"Doctor, I need a prescription"

"OTC is not as effective"

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Common Non-opioid Medication Classes

Acetaminophen[1,5]

- Antipyretic, analgesic
- Well tolerated, less side effects
- MOA: Activates CNS descending serotonergic inhibitory pathways
- Inferior to NSAIDs improving knee and hip pain for OA
  - *No longer first-line for OA pain*

https://www.uptodate.com/contents/acetaminophen-paracetamol-drug-information

Topical Analgesics Acute and Chronic Pain[6]

Good Evidence at least 50% relief	Low Quality Evidence
• NSAIDs • Capsaicin • Lidocaine	• Rubefacients (Salicylates) • Clonidine

https://upload.wikimedia.org/wikipedia/commons/9/9d/Cochrane-logo.jpg

Topical NSAIDs[7]

- Acute muscle or joint injuries: sprains, strains
- Osteoarthritis = single or few joints near the surface of the skin
- Little systemic uptake, plasma concentrations are only a fraction (usually much less than 5%) compared to oral
- Topical NSAID levels high enough to inhibit COX-2

Topical NSAIDs[7]

- Primary outcome >50% pain relief compared to placebo
- Topical diclofenac is equivalent to oral NSAIDs in knee and hand osteoarthritis (joints close to skin surface)
- Formulation can influence efficacy
- Topical NSAIDs reduce GI adverse events compared with oral NSAIDs

Topical Capsaicin[1]

- RCT studies using high-concentration (≥5%) topical
  - Postherpetic neuralgia
  - Painful HIV-neuropathy
  - Peripheral diabetic neuropathy

- Moderate quality evidence that high-concentration (8%) capsaicin patches gives > moderate pain relief to a minority of people with postherpetic neuralgia
- Low quality evidence that it benefits those with HIV-neuropathy and peripheral diabetic neuropathy

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Topical Lidocaine[1]

- Neuropathic pain: PHN or traumatic nerve injury
- Minimal systemic side effects
- MOA: sodium channel & N-methyl-d-aspartate (NMDA) receptor blockage
- Formulations: cream, gel, patch, spray, solution
- Oral, intranasal, transdermal

https://commons.wikimedia.org/wiki/File:Drugs_and_Treatments_-_Patch_--_Smart-Servier.png
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NSAIDs

- Analgesic, antipyretic, and anti-inflammatory effects
- Inhibition of cyclooxygenase (COX), which impairs

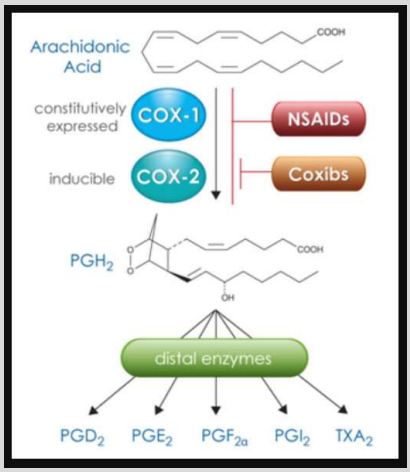
arachidonic acid → prostaglandins, prostacyclin, thromboxanes

  - COX-1 is expressed in most tissues; "housekeeping" enzyme, regulating normal cellular processes
  - COX-2 expression is increased in inflammation

- Significant cardiovascular, renal, GI consequences

https://www.uptodate.com/contents/overview-of-cox-2-selective-nsaids

Oral NSAIDs lowest effective dose, shortest duration



Major coronary events
- Heart failure
- Myocardial infarction

Stroke

GI bleeding / perforation

Renal failure

https://upload.wikimedia.org/wikipedia/commons/2/2a/Tipus_de_prostaglandines.jpg

COX selectivity of common NSAIDs

- Nonselective COX-1 inhibitors: ibuprofen, naproxen
- "More" selective for COX-2 inhibitors: meloxicam, diclofenac, etodolac

- Selective COX-2 inhibitor: celecoxib

https://www.uptodate.com/contents/overview-of-cox-2-selective-nsaids

CAUTION Systemic NSAIDs[8]

- Older adults
- Previous GI bleeding / risk for peptic ulcer disease
  - *(COX-2 inhibitor or + proton pump inhibitor)*
- Renal insufficiency / failure
- Cardiovascular comorbidities

NSAIDs for Acute LBP[9]

- NSAIDs are effective for low-back pain without sciatica
  - *moderate evidence*
- NSAIDs are similarly effective to opioids
- Various types of NSAIDs = COX-1 versus COX-2 NSAIDs, are **equally effective** for acute low-back pain
- COX-2 NSAIDs had statistically significantly less side-effects

NSAIDs for Chronic LBP[10]

- **Short-term use** only
- NSAIDs are more effective than placebo

NSAIDs for Sciatica

- For acute sciatica, no difference between NSAIDs and placebo

- *Rasmussen-Barr E, Held U, Grooten WJA, Roelofs PDDM, Koes BW, van Tulder MW, Wertli MM. Non-steroidal anti-inflammatory drugs for sciatica. Cochrane Database of Systematic Reviews 2016, Issue 10. Art. No.: CD012382. DOI: 10.1002/14651858.CD012382. Accessed 05 February 2025*
- *Hansueli Krapf, CC BY-SA 3.0 <https://creativecommons.org/licenses/by-sa/3.0>, via Wikimedia Commons*

Corticosteroids for Sciatica

- **Systematic review of three studies found some benefit but only**
  - **short term (>2 weeks but <3 months)**
- No significant leg pain difference in intermediate term **> 3 months**
- Patients receiving steroids had more adverse effects, including epigastric symptoms, mood changes, and hyperglycemia

Pinto RZ, Maher CG, Ferreira ML, Ferreira PH, Hancock M, Oliveira VC, McLachlan AJ, Koes B. Drugs for relief of pain in patients with sciatica: systematic review and meta-analysis. BMJ. 2012 Feb 13;344:e497. doi: 10.1136/bmj.e497. PMID: 22331277; PMCID: PMC3278391

Muscle Relaxants Clinical Practice Guideline[11]

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CDC U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION

- **Patient population: acute, subacute, or chronic low back pain**
- Most patients with acute, subacute low back pain improve over time *regardless of treatment:* **recommend NONPHARMACOLOGIC first line**
- Recommendation SECOND line: select NSAIDS or **skeletal muscle relaxants *(moderate evidence; strong recommendation)***

Muscle Relaxer Clinical Outcomes		
↑ pain relief	**↓ work disability**	**↑ patient satisfaction**
↑ function and QOL	**↓ # of back pain episodes**	**AEs: drowsiness**

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Antidepressants for Chronic Pain: SNRIs/TCAs[12]

- Tricyclic antidepressants (TCAs) and serotonin norepinephrine reuptake inhibitors (SNRIs) have **analgesic effects independent of antidepressant effects**
- MOA: inhibits reuptake of serotonin and norepinephrine at descending inhibitory pain pathways in spinal cord
- TCAs: sodium channel modulation in periphery & NMDA antagonism → enhances dorsal root inhibition and reduces peripheral sensitization

SNRIs for Chronic Pain[12]

- **Duloxetine standard dose (60 mg) showed a small to moderate effect for substantial pain relief, *moderate certainty evidence***
- For pain intensity, **milnacipran standard dose (100 mg)** also showed a small effect, *moderate certainty evidence*
- Duloxetine showed a small effect on mood (*moderate certainty evidence*)
- Common side effects mild: fatigue, somnolence, nausea, and dizziness, mild GI distress

Duloxetine for Chronic Pain[13]

- **Diabetic peripheral neuropathy: 60 mg-120 mg daily** effective
  - *moderate quality*
- **Fibromyalgia: 60 mg** daily improves pain, mental & mood symptoms
  - *low-moderate quality*
  - Minor side effects are common with duloxetine 60 mg and particularly with 120 mg daily, than 20 mg daily, but serious side effects are rare

Venlafaxine for Neuropathic Pain[14]

- some third-tier evidence of benefit, little compelling evidence to support use
- In the largest RCT by Rowbotham, 2004, 56% of participants receiving venlafaxine 150 to 225 mg achieved at least a 50% reduction in pain intensity versus 34% of participants in the placebo group

Tricyclic Antidepressants[15]

- Tertiary amines more sedation = antihistaminic and anticholinergic side effects, more potent inhibiting reuptake **5-HT** compared to NE

  - *amitriptyline, doxepin, imipramine*

- Secondary amines more potent inhibiting reuptake **NE** > 5-HT

  nortriptyline, and desipramine

- Caution against use >65yrs: delirium, orthostatic hypotension, falls
- Decreased seizure threshold, sexual dysfunction, diaphoresis, and tremor
- Dangerous in overdose by suicidal patients (age <25yrs)

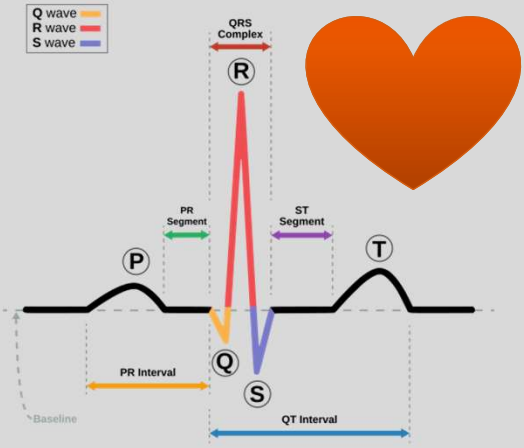
TCA Cardiac CAUTION[15]

- Increased risk of cardiac side effects, contraindicated in heart failure, cardiac conduction blocks, FHx sudden death

  - Increased risk of sudden cardiac death at higher doses (>100mg)

- Patients > age 50 years baseline electrocardiogram (ECG)

- contraindicated QTc > 500ms



https://www.uptodate.com/contents/tricyclic-and-tetracyclic-drugs-pharmacology-administration-and-side-effects
https://commons.wikimedia.org/wiki/File:SinusRhythmLabels.svg
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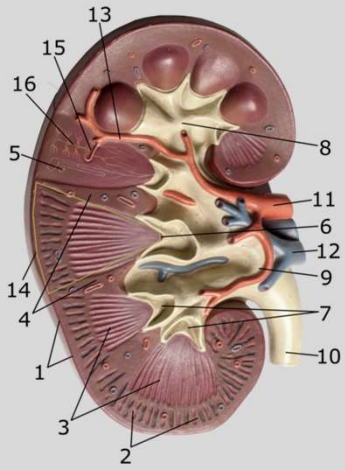
Amitriptyline for Neuropathic Pain[16]

- One or more condition & > moderate pain:
  - painful diabetic neuropathy
  - postherpetic neuralgia
  - trigeminal neuralgia
  - phantom limb pain
  - postoperative/traumatic neuropathic pain
  - complex regional pain syndrome
  - cancer-related neuropathy
  - Guillain Barré
  - HIV neuropathy
  - spinal cord injury

- Only third-tier evidence
- Historically first-line successful treatment for neuropathic pain for decades
- Continue to be useful

Antiepileptic Drugs[1]



- First-line therapies for neuropathic pain
  - *Gabapentin and pregabalin*
- Alpha-2-delta subunit of voltage-sensitive calcium channels → reduces release of excitatory neurotransmitters glutamate, substance P, and calcitonin gene-related peptide
- Caution: lower dose for renal disease

https://commons.wikimedia.org/wiki/File:Didactic_model_of_a_mammal_Kidney_with_numbered_parts.png
Origin: Museum of Veterinary Anatomy FMVZ USP Photographer: Wagner Souza e Silva Modified: D6194c-1cc, CC BY-SA, via Wikimedia Commons

Gabapentin[17]

- Gabapentin at doses of 1200 mg to 3600 mg daily may provide good levels of pain relief for **postherpetic neuralgia** and **peripheral diabetic neuropathy**
- Around 3 or 4 out of 10 participants had at least 50% pain intensity reduction; improved QOL & function
- Over half of those treated with gabapentin will not have worthwhile pain relief
- AEs: dizziness (19%), somnolence (14%), peripheral edema (7%), and gait disturbance (14%), blurry vision, weight gain, cognitive effects

Pregabalin[18]

- Efficacy for **postherpetic neuralgia & painful diabetic neuropathy**
  - *(moderate quality)*
- Absence of efficacy in HIV neuropathy
  - *(moderate quality)*
- Some people will derive substantial benefit (at least >50% pain reduction)
- More will have moderate benefit at least (>30% pain reduction)
- But many will have no benefit or will discontinue treatment
- Higher doses = greater AEs

- Cohort study: rotation to pregabalin in patients who were gabapentin responders (≥30% relief on a visual analog scale) or gabapentin nonresponders after prolonged GBP use; compared with patients receiving continuous GBP therapy
- Both gabapentin responder and non-responder groups had >25% neuropathic pain relief following rotation to pregabalin after 6 and 12 months
- Improved QOL was identified in the gabapentin non-responder group
- Conclusion: pregabalin may provide additional pain relief and QOL compared to gabapentin

Other Antiepileptics

- topiramate: side effect weight loss
- oxcarbazepine, lacosamide
- *carbamazepine, lamotrigine (US Boxed warning: life-threatening skin reactions)*
- increased risks / side effects

https://commons.wikimedia.org/wiki/File:Lose_weight_now.jpg
Alan Cleaver, CC BY 2.0, via Wikimedia Commons

$$$ **DAILY** Antiepileptic Drugs: Less Sedating! $$$

GENERIC Extended-release	BRAND NAME Extended-release	MANUFACTURER COUPON? *(Private insurance only)*	CHEAPER ONLINE PHARMACY? (TEXT COUPON)	GENERIC FORMULATION AVAILABLE?
extended release gabapentin	GRALISE®	**YES**	**N**	**YES**
topiramate ER	QUDEXY® XR TROKENDI XR®	**NO** **YES**	**YES**	**YES**
pregabalin CR	LYRICA® CR	**NO**	**NO**	**NO**

Strategies for Drowsiness

- **Extremely slow titrations may help, ER formulations**
- AEDs, Muscle Relaxers: only take at night
  - *Daytime alert & still have pain, but sleep better*
  - Nighttime only dosing as long as brain fog/hangover feeling in AM
  - Take evening dose earlier (7pm) to avoid morning hangover feeling
- Instead of BID dosing;
  - try TID dosing = divide morning dose into half = take AM + afternoon; followed by PM dosing
- **Schedule reminders** to space medication

N-methyl-D-aspartate (NMDA) Antagonists Reverse Central Sensitization

- Nonopioid drugs include:
  - ketamine
  - dextromethorphan
  - memantine
- *Others: methadone, TCAs, phencyclidine (PCP)*

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NMDA Antagonists: Ketamine[20]

- Continuous ketamine IV infusion reduces/reverses CNS hyperexcitability = "windup" amplification of noxious & non-noxious stimuli
- Improves pain, function, QOL
- Greatest reduction in pain scores**: high-dose ketamine therapy** or **complex regional pain syndrome patients**
- AEs: sedation, dysphoria, and dissociative episodes

Ketamine Infusions for Chronic Pain[20]:

- **Helps all types of pain, all medical conditions**
- Three RCTs reported significant analgesic benefit favoring ketamine
  - **(at least >30% or at least >50% pain relief)**
  - Even small effect up to 2 weeks after the infusion (mean difference in pain scores, -1.83 points on 0-10 scale)
  - Proportion with a positive outcome was greater in the ketamine than in the placebo group (51.3% vs 19.4%)

Low-dose Naltrexone for Neuropathic Pain[21,22,23]

- MOA: anti-inflammatory effect cells in brain/spinal cord (glial cells modulation)
- Chronic pain conditions: CRPS, IBD, Fibromyalgia, low back pain, RA, PDN
- 2021 RCT: Low-dose naltrexone (to 4mg) exhibited similar efficacy and a superior safety profile compared with amitriptyline (25/50mg) in **painful diabetic neuropathy**
- 2013 RCT: low-dose naltrexone (4.5mg) improved **fibromyalgia** pain, QOL, mood, sleep, fatigue
- Side effects MINIMAL: sleep disturbance/unusual dreams, headache, decreased appetite, nausea and fatigue

Common Pain Syndromes

https://commons.wikimedia.org/wiki/File:Exam_room_in_a_doctor%27s_office.jpg
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Root Cause Analysis to Optimize Functional Health

- Healthy weight, proper nutrition
- Reduce toxins: sugar, alcohol, cigarettes, chemicals
- Identify poor posture/body mechanics; repetitive injury risks
- Prevent neuropathy progression with tighter glucose control
- Immune-modulating agents for rheumatoid arthritis, autoimmune
- Stress management

Fibromyalgia[1]

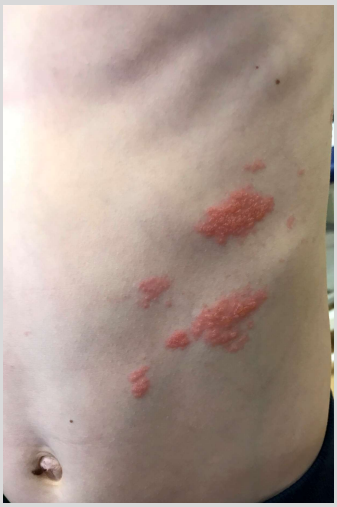
OFF-LABEL	DRUG CLASS	FDA-APPROVED
TCAs - amitriptyline - nortriptyline - doxepin	ANTIDEPRESSANTs *Benefits patient with co-occuring PAIN/DEPRESSION/ANXIETY*	SNRIs - duloxetine - milnacipran
gabapentin topiramate	ANTIEPILEPTICs	pregabalin
low-dose naltrexone	OPIOID-ANTAGONIST	
	NSAIDs = topical,systemic	
ketamine (topical) memantine	NMDA Antagonists	
clonidine (patch, pill, topical)	Alpha-2 agonist (sympatholytic)	
tizanidine (alpha-2 agonist)	MUSCLE RELAXERS	
Vitamin D; Magnesium	micronutrients	

Central Sensitization / Abdominal Pain / Pelvic Pain

BEHAVIOR MODIFICATION	TREATMENTS
nutrition/elimination diet/water intake	Opioids less than ideal
AVOIDANCE OF pelvic floor dysfunction • *Excess idle time on toilet* • *Prolonged sitting on perineal region* • *Constipation*	Avoid chronic systemic NSAIDs
Healthy weight	TCAs, SNRIs, AEDs
Minimize stress; rehab psych; CBT, EMDR	Low-dose naltrexone
Regular exercise/outdoors/good sleep	

Postherpetic Neuralgia
Ounce of prevention worth a pound of cure

- Vaccination for varicella-zoster virus
- Prompt antiviral for herpes zoster (shingles)
- Topicals: capsaicin, lidocaine
- Antiepileptic drugs
- SNRIs (duloxetine), TCAs
- Early aggressive multimodal pain management



https://commons.wikimedia.org/wiki/File:Zonaz_(herpes_zoster).jpg
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Conclusions:[1]

- High quality evidence/research may not be available, expert opinion helpful
- Favorable evidence for duloxetine for diabetic peripheral neuropathy, fibromyalgia
- Consider duloxetine for chronic low back pain; autoimmune, OA & inflammatory arthritis; central sensitization; as opioid sparing, NSAID sparing technique
- Cannabis evidence is limited, AEs may limit use

Conclusions: Go case-by-case[1]

- **Opioids should not be first-line or routine therapy for subacute or chronic pain**
- ***HOWEVER some clinical contexts: opioids are appropriate first-line for serious illness:***
  - *e.g., patient with poor prognosis*
  - *contraindications to other therapies*
  - *physician/patient agreement that overriding goal is patient comfort*
- In other situations (e.g., headache, fibromyalgia), expected benefits of initiating opioids are unlikely to outweigh risks regardless of previous therapies

Opioids are not a failure; NSAIDs harmful too!

- Severe cerebrovascular or cardiovascular disease (CVA, MI, PVD)
- Renal disease
- Severe gastrointestinal bleeding presence or risk
- Chronically anticoagulated patient
- Certain pain populations (elderly, cancer, palliative, end-of-life)
- No surgical solution; no “easy” fix
- Procedure harm outweighs benefit
- Noncoverage of other “superior” medications or therapies
- If no contraindication, and if other treatments ineffective…

Are opioids causing a moral dilemma?

- Patients/physicians need to consider options, both of their preferences, for greatest benefit
- Set treatment goals early and often
- Identify barriers to treatment
- Bridge the gap from lack of awareness (implicit bias) to ability to recognize bias in ourselves and others
- Results in equitable, quality, & patient-centric care

Final thoughts:

- Caution to avoid synergistic risks of medications
- Combinations of medications that depress CNS = such as an opioid with gabapentin, have increased risk for overdose compared with either medication alone
- Dose reductions may lessen AEs and still have pain relief
- Start low and go slow

Goals of Care Improve Function MORE (treat pain less)

- Pain is a warning sign
- Take one pill and get two new side effects?
- Are side effects worse than actual problem?
- Medication may be a bridge to a fuller life
  - Purpose-driven life in the foreground…pain in background

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"Do the best you can until you know better. Then when you know better, do better."

- Maya Angelou

Thank You

https://commons.wikimedia.org/wiki/File:V%C3%A4imela_Alaj%C3%A4rv_2012_08.jpg
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