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Smarter Pain Control: Leveraging Multimodal Strategies For Better Patient Outcomes

Dr. Lisa Luciani, Pharm.D., BCPS
Clinical Pharmacist Practitioner – Pain Management
Pain Management, Opioid Safety, and PDMP (PMOP) Coordinator
James E. Van Zandt VA Medical Center - Altoona, PA
drlisaluciani@gmail.com
https://www.linkedin.com/in/lisadragic

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Disclosure

I have a vested interest in or affiliation with a corporate offering financial support or grant monies for this continuing education activity or organization with any organization that has a specific interest in the therapeutic areas under discussion, as follows (within the last 12 months): Eli Lilly, Consultant

All relevant financial relationships have been mitigated.

The views and opinions expressed in this presentation are those of the authors and do not necessarily reflect the official policy or position of any agency of the United States government, including the Department of Veterans Affairs

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About Me

Lisa Luciani is the facility Pain Management and Opioid Safety Program Manager (PMOP) at the James E Van Zandt VA Medical Center in Altoona PA. Dr. Luciani specializes in complex and high-risk pain medication management. She obtained her doctorate from Temple University School of Pharmacy in Philadelphia, Pennsylvania. She completed her PGY-1 Pharmacy Practice Residency at the Albany Stratton VA Medical Center and her PGY-2 Pain and Palliative Care Pharmacy Residency at the Central Arkansas Veterans Healthcare System (CAVHS).

Lisa Luciani, PharmD, BCPS
Pain Management Clinical Pharmacist Practitioner
Facility PMOP Coordinator

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Presentation Objectives

Pharmacist Objectives:

1. Define multimodal pain management and describe its core principles in pain care.
2. Explain the pharmacologic and non-pharmacologic components commonly used in multimodal pain strategies.
3. Summarize the current evidence supporting multimodal pain management.
4. Apply evidence-based multimodal strategies to optimize individualized pain management plans in clinical practice.

Pharmacy Technician Objectives:

1. Define multimodal pain management and describe its core principles in pain care.
2. Review the pharmacologic and non-pharmacologic components commonly used in multimodal pain strategies.

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Disclaimer

- This presentation provides a high-level overview of pharmacotherapeutic approaches to pain management and is intended for educational purposes only.
- Due to time constraints and the breadth of the topic, not all medications, formulations, indications, disease states, adverse effects, contraindications, drug interactions, or clinical scenarios are discussed.
- Clinicians should consult current prescribing information, institutional policies, clinical practice guidelines, and primary literature when making patient-specific treatment decisions.
- Recommendations and perspectives presented herein reflect a synthesis of available evidence, clinical practice guidelines, published literature, and the speaker's professional experience and interpretation of the data.
- Therapeutic decisions should be individualized based on patient characteristics, comorbidities, goals of care, and evolving evidence.
- The content of this presentation should not be construed as establishing a standard of care, clinical protocol, or specific treatment recommendation for any individual patient.

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Background

- Chronic pain is the most common reason adults seek medical care.
- Linked to restrictions in mobility and daily activities, dependence on opioids, anxiety and depression, and poor perceived health or reduced quality of life (QOL).
- In 2023, an estimated 24.3% of U.S. adults experienced chronic pain, and 8.5% experienced high-impact chronic pain that frequently limited life or work activities.
- Chronic pain and high-impact chronic pain both increase with age and are more common among women, adults living in rural areas, individuals living in poverty, and those with public health insurance.
- The prevalence of chronic pain has increased from 20.4% in 2016 to 24.3% in 2023, highlighting the growing burden of pain in the United States.

Lucas JW, Sohi I. Chronic pain and high-impact chronic pain in U.S. adults, 2023. NCHS Data Brief, no 518. Hyattsville, MD: National Center for Health Statistics. 2024. DOI: https://dx.doi.org/10.15620/cdc/169631
Rikard SM, Strahan AE, Schmit KM, Guy GP Jr. Chronic Pain Among Adults — United States, 2019–2021. MMWR Morb Mortal Wkly Rep 2023;72:379–385. DOI: http://dx.doi.org/10.15585/mmwr.mm7215a1

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Background

- We have seen a 51.7% decrease in opioid prescriptions from 2012 to 2024
  - 260.5 million in 2012
  - 125.7 million in 2024
- Prescriptions for opioids have decreased every year since 2012
- Total morphine milligram equivalents have decreased by 65% from 2012 to 2024

Nguyen TD, Chua K, Jiao A, Bicket MC, Bohnert A, Lagisetty P. US Trends in Long-Term Opioid Therapy. JAMA. Published online April 08, 2026. doi:10.1001/jama.2026.3241
AMA Substance Use and Treatment Report. American Medical Association Substance Use and Pain Care Task Force Report. American Medical Association. Published 2024. Accessed May 14, 2026. https://www.ama-assn.org/system/files/ama-substance-use-and-treatment-report.pdf

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Background

Opioid dispensing rate declined steadily from a rate of 46.8 opioid prescriptions dispensed per 100 persons in 2019 to a rate of 37.5 opioid prescriptions dispensed per 100 persons in 2023

Acute pain is often caused by an event such as injury or surgery and usually lasts less than 3 months

Approximately 80 million adults are affected by acute pain in the US annually

Among patients who experience postsurgical pain, approximately two out of every three describe it as moderate to severe

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Acute to Chronic Use of Opioids

1 in 16 (6%) opioid-naïve surgical patients become chronic users

Longer initial exposure increases risk of long-term use

Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use — United States, 2006–2015. MMWR Morb Mortal Wkly Rep 2017;66:265-269. DOI: http://dx.doi.org/10.15585/mmwr.mm6610a1

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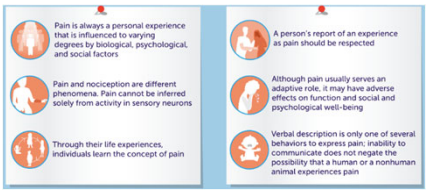
What is pain?

"An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.



International Association for the Study of Pain. IASP announces revised definition of pain. Published July 16, 2020. IASP Announces Revised Definition of Pain

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Types of Pain

- Nociceptive Pain:
  - Somatic
    - Skin, bone, joint, muscle, or connective tissue
  - Visceral
    - Internal organs
- Neuropathic Pain:
  - Pain caused by a lesion or disease of the somatosensory nervous system
  - Burning, tingling, radiating
  - Diabetic neuropathy, phantom limb pain
- Nociplastic

Cohen S, Vase L, Hooten W. Chronic pain: an update on burden, best practices, and new advances. The Lancet, 397, 2082-2097

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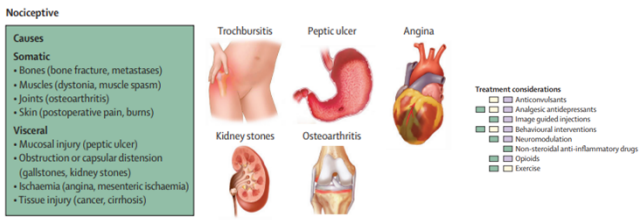
Nociceptive



Cohen S, Vase L, Hooten W. Chronic pain: an update on burden, best practices, and new advances. The Lancet, 397, 2082-2097

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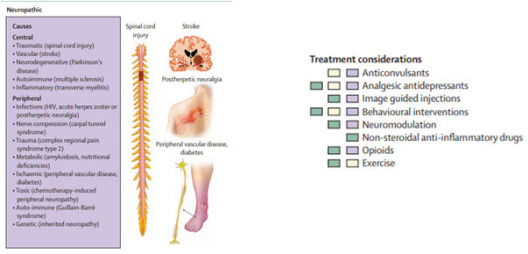
Neuropathic



Cohen S, Vase L, Hooten W. Chronic pain: an update on burden, best practices, and new advances. The Lancet, 397, 2082-2097

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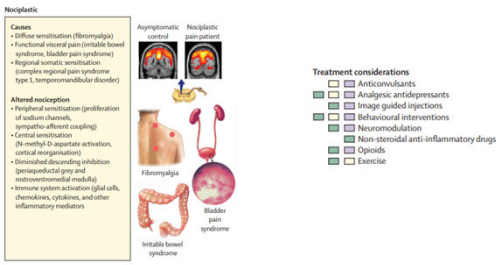
Nociplastic



Cohen S, Vase L., Hooten W. Chronic pain: an update on burden, best practices, and new advances. The Lancet, 397, 2082-2097

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NOCICEPTION

Nociceptors
- Respond to injury
- Chemical, mechanical, and thermal stimuli

Generate action potentials which travel via...

Conduction

Both A-δ and C fi… may be sensitize… multiple inflammatory…

Transmission

A-δ and C fibers synapse in...
- Dorsal horn
- Projection to higher…

Perception

Cerebral cortex
- What we think about pain

Limbic/reticular
- What we feel about pain

Inflamm…

Purpose: to modify, dampen, or augment nociception

Efferent pathways from the brain to the spinal cord …ulation …vels to...

Neurotransmitters involved
- Endorphins
- Serotonin
- Norepinephrine

…iboard" …rmation

allodynia

…herapy: A Pathophysiologic Approach; 2014.

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Acute versus Chronic

Characteristic	Acute Pain	Chronic Pain
Relief of pain	Highly desirable	Highly desirable
Dependence and tolerance to medication	Unusual	Common
Psychological component	Usually not present	Often present
Organic cause	Common	May not be present
Environmental/Family issues	Small	Significant
Insomnia	Unusual	Common
Treatment Goal	Pain Reduction	Functionality
Depression	Uncommon	Common

Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683a

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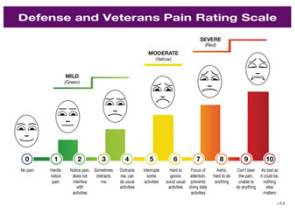
Assessing Chronic Pain



U.S. Department of Veterans Affairs. Defense and Veterans Pain Rating Scale (DVPRS): 2 Slides and References [PDF]. U.S. Department of Veterans Affairs Pain Management. Accessed June 2, 2026. https://www.va.gov/PAINMANAGEMENT/docs/DVPRS_2slides_and_references.pdf

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Assessing Chronic Pain

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Assessing Pain: PQRSTU

Precipitating and palliating	What brings on or worsens the pain? What relieves the pain? What the patient has taken (including breakthrough analgesics), what the response was, and if any side effects developed. What medications have been tried to treat the pain?
Quality	Can you describe the pain in your own words?
Region and Radiation	Where is the pain? Does it move anywhere? Is it deep inside or does it feel on the surface?
Severity	How would you rate your pain right now?
Temporal	Is the pain constant? Does it come and go? → how often? How long does it last?
Yo**u**	How is the pain affecting your life? How does it affect your ability to **sleep**, **mood**, appetite, ambulate?

McPherson ML. Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing. 2nd ed. Bethesda, MD: American Society of Health-System Pharmacists; 2018.

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Acute Pain Clinical Presentation	
General	• Obvious distress – trauma • Infants: changes in feeding habits and/or increased fussiness. • Dementia: changes in eating habits, increased agitation, calling out, and/or facial grimacing, mental/emotional factors that alter the pain threshold
Symptoms	• Sharp, dull, shock like, tingling, shooting, radiating, fluctuating in intensity, and varying in location
Signs ★	• Hypertension, tachycardia, diaphoresis, mydriasis, and pallor, but these signs are *not diagnostic* • In some cases there are no obvious physical signs • Comorbid conditions usually not present • Outcome of treatment generally predictable
Laboratory Tests	• Pain is always subjective • There are no specific laboratory tests for pain • Pain is best diagnosed based on patient description and history

Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683a

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Chronic Pain Clinical Presentation	
General	• Can appear to have no noticeable suffering. Mental/emotional factors may also alter the pain threshold, similar to acute pain.
Symptoms	• Sharp, dull, shock like, tingling, shooting, radiating, fluctuating in intensity, and varying in location
Signs ★	• Hypertension, tachycardia, diaphoresis, mydriasis, and pallor are **seldom** present. • In most cases, there are no obvious signs. • Comorbid conditions are often present (eg, insomnia, depression, and anxiety). • Outcome of treatment is often unpredictable.
Laboratory Tests	• Pain is always subjective • There are no specific laboratory tests for pain • Pain is best diagnosed based on patient description and history • General labs that may be considered include vitamin D, thyroid-stimulating hormone (generalized or widespread pain), and B_{12} (neuropathic pain).

Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683a

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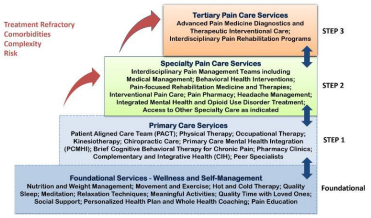
Stepped Care Model for Pain Management (SCM-PM)



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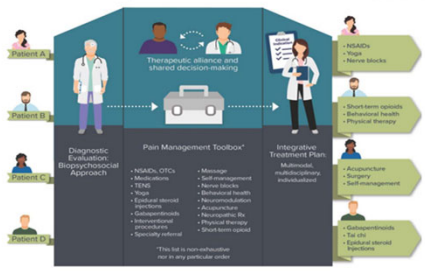

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Goals for Pain Management

- Treatment goal depends on the type of pain
- **Individualized**
- Acute post-operative pain:
  - Participation in physical therapy
  - Deep breathing to prevent pneumonia
- Chronic pain:
  - Improve patient's level of functioning
  - Decrease pain perception
  - Reduce use of medications when possible
  - Improve quality of life

Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683a

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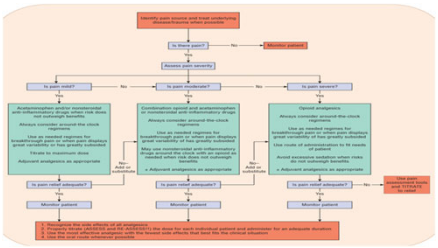
Algorithm for Acute Pain



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General Principles for Chronic Pain

- Nonopioid therapies are preferred
- Maximize nonpharmacologic and nonopioid pharmacologic therapies
- Only start opioids if expected benefits for pain and function are anticipated to outweigh risks
- Before starting opioids discuss with patients:
  - Realistic benefits and known risks
  - Establish treatment goals for pain and function
  - Exit strategy

Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1-95. DOI: http://dx.doi.org/10.15585/mmwr.rr7103a1

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Multimodal Analgesia

- Involves the use of more than one method or modality of controlling pain to obtain additive benefits, reduce side effects, or both
  - Non-opioids are combined with opioids to improve pain and reduce symptoms
- Synergistic
- Opioid sparing effect
- ★ Benefits:
  - Earlier oral intake, ambulation, and hospital discharge
  - Higher levels of participation in activities necessary for recovery
  - May reduce postoperative morbidity and mortality

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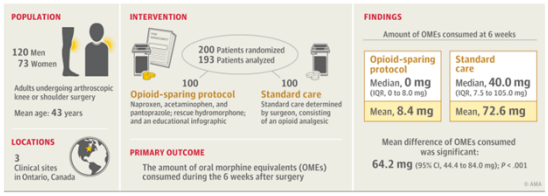
QUESTION Does a multimodal opioid-sparing postoperative pain protocol reduce postoperative opioid consumption compared with standard opioid prescribing after arthroscopic knee or shoulder surgery?

CONCLUSION Among patients who underwent arthroscopic knee or shoulder surgery, a multimodal opioid-sparing postoperative pain management protocol significantly reduced postoperative opioid consumption compared with standard opioid prescribing.



NO PAin Trial Investigators. Effect of a postoperative multimodal opioid-sparing protocol vs standard opioid prescribing on postoperative opioid consumption after knee or shoulder arthroscopy: a randomized clinical trial. JAMA. Published October 4, 2022. doi:10.1001/jama.2022.16844

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The Impact of Opioid-Sparing Analgesia on Postoperative Pain and Recovery: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

- Opioid-sparing strategies:
  - Reduced 24-h morphine requirement by ~9.5 mg (mean difference −9.47 mg; 95% CI −13 to −5.95)
  - Lowered pain scores (MD −0.72)
  - Increased patient satisfaction (MD +0.88).
  - Decreased postoperative nausea, vomiting (OR 0.73), and pruritus (OR 0.64), without extending hospital stay or affecting recovery quality

Zhang, Z., Wang, JJ., Ping, ZG. et al. The Impact of Opioid-Sparing Analgesia on Postoperative Pain and Recovery: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Pain Ther 14, 1473–1497 (2025). https://doi.org/10.1007/s40122-025-00762-2

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Interdisciplinary pain rehabilitation programs (IPRPs)

- Consist of multimodal, interdisciplinary provider teams with a shared "mission, philosophy, and set of objectives" to improve patient care using a biopsychosocial approach

Table 1. Summary of pain programs

		ABQ	CLE	PS	SF	TPA-IN	TPA-OUT
Program time commitment	Length of program	5 wk	12 wk*	8 wk	12 wk	5 wk	8 wk
	Days per week	2 d/wk	1 d/wk	1 d/wk	1 d/wk	1 d/wk	2 d/wk
	Hours per day	7 h/d	6 h/d	4 h/d	1.5 h/d	8.5 h/d	1 h/d
	Total treatment hours	70 h	72 h	64 h	126 h	127.5 h	80 h
Time points for outcomes collection	Pretreatment	✓	✓	✓	✓	✓	✓
	Midtreatment				✓		
	Posttreatment	✓	✓	✓	✓	✓	✓
	One month posttreatment		✓			✓	✓
	Three months posttreatment		✓	✓			
	Six months posttreatment		✓	✓	✓	✓	✓
	Twelve months posttreatment	✓	✓	✓		✓	✓
Sample program components	Behavioral therapy	✓	✓	✓	✓	✓	✓
	Medication management	✓	✓	✓	✓	✓	✓
	Physical therapy	✓	✓	✓	✓	✓	✓
	Biofeedback education	✓	✓	✓	✓	✓	✓
	Occupational therapy	✓	✓		✓	✓	✓
	Yoga and/or tai chi	✓		✓		✓	

ABQ = Albuquerque; CLE = Cleveland; PS = Puget Sound; SF = San Francisco; TPA = Tampa, IN = inpatient; OUT = outpatient.
Description of each program's respective time commitments and time points for outcomes collection.
*Flexible discharge time frame.

Murphy JL, Palyo SA, Schmidt ZS, Hollrah LN, Banou E, Van Keuren CP, Strigo IA. The Resurrection of Interdisciplinary Pain Rehabilitation: Outcomes Across a Veterans Affairs Collaborative. Pain Med. 2021 Feb 23;22(2):430-443. doi: 10.1093/pm/pnaa417. PMID: 33496787; PMCID: PMC8599775.

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Components of Multimodal Programs

Restorative therapies: Physical therapy, exercise, graded activity

Pharmacotherapy: NSAIDs, antidepressants (SNRIs), gabapentinoids, and judicious opioid use when other strategies fail

Behavioral treatments: Cognitive-behavioral therapy, acceptance and commitment therapy, pain neuroscience education

Procedural interventions: Nerve blocks, trigger point injections, neuromodulation when indicated

Complementary therapies: Acupuncture, massage, mindfulness-based approaches

Self-care strategies: Exercise, weight management, sleep hygiene, stress reduction

Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, Carter T, Cassidy CL, Chittenden EH, Degenhardt E, Griffith S, Manworren R, McCarberg B, Montgomery R, Murphy J, Perkal MF, Suresh S, Sluka K, Strassels S, Thirlby R, Viscusi E, Walco GA, Warner L, Weisman SJ, Wu CL. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain. 2016 Feb;17(2):131-57. doi: 10.1016/j.jpain.2015.12.008. Erratum in: J Pain. 2016 Apr;17(4):508-10. doi: 10.1016/j.jpain.2016.02.002. PMID: 26827847.
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Non-Pharmacologic

- Exercise
- Physical Therapy
- Nutrition
  - Anti-inflammatory
  - Elimination
- Weight loss
- Electroanalgesia: application of electrical stimulation to various areas that range from noninvasive to highly invasive
  - Noninvasive: transcutaneous electrical nerve stimulation (TENS)
  - Minimally invasive: percutaneous electrical nerve stimulation (PENS)
  - Highly invasive: spinal cord stimulation (SCS)
- Interventional approaches
- Cognitive behavioral therapy for chronic pain
- Multidisciplinary rehabilitation programs

Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, Carter T, Cassidy CL, Chittenden EH, Degenhardt E, Griffith S, Manworren R, McCarberg B, Montgomery R, Murphy J, Perkal MF, Suresh S, Sluka K, Strassels S, Thirlby R, Viscusi E, Walco GA, Warner L, Weisman SJ, Wu CL. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain. 2016 Feb;17(2):131-57. doi: 10.1016/j.jpain.2015.12.008. Erratum in: J Pain. 2016 Apr;17(4):508-10. doi: 10.1016/j.jpain.2016.02.002. PMID: 26827847.
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Complementary and Integrative Approaches

- Tai-Chi
- Yoga
- Acupuncture
- Massage
- Mindfulness, meditation, and relaxation
- Biofeedback
- Manipulation

Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L, eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683a

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Complementary and Integrative Approaches

Intervention	Description	Evidence	Safety
Tai Chi	Low impact; Mind body exercise; Started in China as a martial art; Slow mindful movement with attention to breathing and relaxation	Osteoarthritis; Chronic low back pain (CLBP); Fibromyalgia	Minor musculoskeletal aches and pains
Yoga	From India; Blend of meditation, breathing, and physical postures	Osteoarthritis; Rheumatoid Arthritis; Kyphosis; Fibromyalgia; Low back pain (LBP); Neck pain	Similar to musculoskeletal pain associated with PT; Discuss with provider/yoga instructor if glaucoma/osteoporosis
Acupuncture	Stimulation of certain body points with needle insertion into skin; East Asian	Acute: Post-surgical pain (reduced opioid dose); Migraine; Acute/subacute LBP; Ankle sprain. Chronic: CLBP; Osteoarthritis (knee, hip, general); TMD; Headache; Migraine; Neck pain; Shoulder pain; Peripheral neuropathy (diabetic, HIV, Bell's palsy, CTS); Fibromyalgia	Low risk; Minor: itching, relaxation, tired; Rare: pneumothorax, infections
Massage	Soft tissue manipulation	Acute: Postoperative pain. Chronic: CLBP; Neck and shoulder pain; Osteoarthritis; Heel pain; Epicondylitis; Fibromyalgia	Low risk for adverse effects
Mindfulness, meditation, and relaxation	A variety of mind-body practices to capitalize on body's calming response; Examples: mindfulness-based stress reduction (MBSR), cognitive behavioral therapy (CBT), pain-coping skills training (PCST), diaphragmatic breathing, progressive muscle relaxation (PMR), hypnosis, acceptance and commitment therapy (ACT), music therapy, guided imagery	Acute: Burn patients (music therapy); Acute/procedural pain (music therapy, hypnosis, guided imagery). Chronic: LBP (MBSR, CBT); Chronic pain (music therapy, CBT, guided imagery, ACT, relaxation); Headache (mindfulness and relaxation, MBSR); Fibromyalgia (relaxation, guided imagery); Knee pain (PCST); Osteoarthritis (PCST, guided imagery); Rheumatoid arthritis (PCST, guided imagery); Diabetic neuropathy (mindfulness/meditation); TMD (relaxation).	Rare adverse reactions (psychiatric patients, epilepsy, trauma history)
Biofeedback	Mind-body practice using devices that measure BP, HR, RR to alter thoughts and behaviors	Tension/migraine headache; CLBP; Fibromyalgia; Shoulder pain	No to low risk of adverse reactions
Manipulation	Treatment of spine and other joints	Osteoarthritis (hip, knee, ankle, plantar fasciitis, ankle, shoulder, epicondylitis); LBP; CTS; TMD	Musculoskeletal aches and pains; Rare but serious events (artery dissection, stroke, neck injury)

Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L, eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023.

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Pharmacologic Treatment

Nonopioid analgesics
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Acetaminophen
- Salicylates

Adjuvant agents (co-analgesics)
- Antidepressants
  - Tricyclic Antidepressants (TCAs)
  - Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)
- Anticonvulsants
- Muscle Skeletal Relaxants

Opioid analgesics

Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683a

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Principles of Adjuvant Analgesics

Assess complaint of pain, consider comorbidities

Avoid initiating several adjuvant analgesics concurrently

Start low and go slow!

Multiple MOA to treat pain

Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683a

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Choosing Analgesic Therapy

- What type of pain?
  - Nociceptive vs neuropathic vs mixed
  - Acute vs chronic
  - Severe vs mild
- What route should be used?
- What agent should be used?
  - Type, severity of pain
  - Patient characteristics – side effects, allergy, comorbid disorders, tolerance, previous agents used
  - Insurance, cost

Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683a

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Acetaminophen

- Reduces pain and fever
- MOA:
  - Inhibition of prostaglandin synthesis in CNS and reduced pain impulse
  - Inhibition of NMDA receptors
- Preparations:
  - Tablet, capsule, chewable, ODT, injection, suspension, suppository
- Maximum dose: 4000mg/day
- Boxed Warning: hepatotoxicity
- Caution in patients who drink
- Good for mild-moderate pain and bone pain

Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683a
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Acetaminophen Clinical Considerations

National Institute for Health and Care Excellence	• 2000 mg/day in cirrhotic patients
American College of Gastroenterology	• 2000 mg/day for severe liver disease (Child Pugh score >10)
American Liver Foundation	• 3000 mg/day in healthy individuals for any prolonged period
American Geriatric Society	• 2000-3000 mg/day in older patients with hepatic insufficiency or alcohol abuse history

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NSAIDs

- NSAIDs can be more effective than opioids and/or muscle relaxants for treating acute low back pain
- Effective in reducing swelling and pain caused by a muscle strain or sprain
- Compared to placebo or hydrocodone/ acetaminophen – NSAIDS required less rescue analgesics and had fewer adverse effects
- Can be given as "pre-emptive" analgesics for surgery as well as postoperatively in the elective setting

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NSAIDs

- Inhibit formation of varying prostaglandins produced in response to noxious stimuli, thereby decreasing neuronal pain transmission received by the CNS
- COX-1 versus COX-2
- Warnings:
  - GI Risk: Increase in risk of bleed, ulceration, and perforation of stomach and intestines
  - Cardiovascular Risk: Increase in thrombotic events, MI and stroke
- Effective for bone pain, inflammatory pain, narcotic-sparing effect
- Side Effects: GI, renal, hypertension, edema, reduced platelet activity, somnolence, CV events

Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683a

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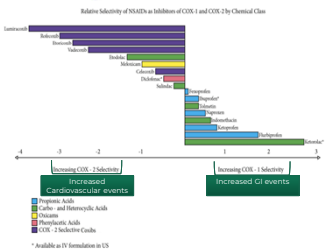

Fudin J. Relative Selectivity of NSAIDs as Inhibitors of COX-1 and COX-2 by Chemical Class.

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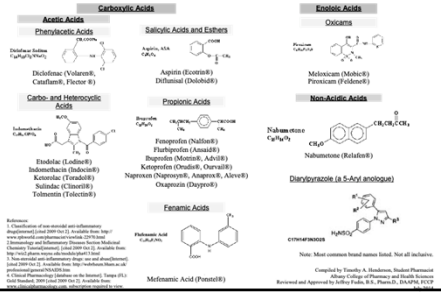
Chemical Classes of Non-Steroidal Anti-Inflammatories (NSAIDs) in US



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Who Should get NSAIDs?

YES	NO	CAUTION
Mild pain	Bleeding Disorder	Mild renal impairment
Inflammatory pain	Significant renal impairment	Uncontrolled HTN
Bone pain	Thrombocytopenia	ACE-I, ARB therapy
Osteoarthritis	Anticoagulants (Warfarin)	
Dysmenorrhea	Certain chemotherapy	
	Pregnancy	

Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683a

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Common NSAID Interactions

Class of Medication	Adverse Event
ACE Inhibitors/Angiotensin II receptor blockers	Increase in BUN/SCr
Loop diuretics	Increase edema, hypernatremia, hyperkalemia
Anticoagulants	Increase risk of bleeding
Selective Serotonin Reuptake Inhibitors	
Lithium	Increases blood level and toxicity
Methotrexate	Causes renal failure and pancytopenia
Aspirin	2 hours between ASA and NSAID

Fudin J. No perfect medicine: what you need to know about NSAIDs and opioids. MedCentral Pain Management. Published August 11, 2016. Accessed June 3, 2026. https://www.medcentral.com/pain/chronic/no-perfect-medicine-what-you-need-know-about-nsaids-opioids

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GI Prophylaxis with Oral NSAIDS

- Proton pump inhibitors (PPIs), misoprostol, and double-dose histamine-2 receptor antagonists (H2RAs) are effective in preventing chronic NSAID-related gastroduodenal ulcers

Risk Factors
Previous GI event
Concomitant use of anticoagulation
Age > 65
Corticosteroids
Low-dose aspirin use

Lanza, Frank L. MD, FACG1,2; Chan, Francis K.L. MD, FRCP, FACG3; Quigley, Eamonn M.M. MD, FACG4 Practice Parameters Committee of the American College of Gastroenterology. Guidelines for Prevention of NSAID-Related Ulcer Complications. American Journal of Gastroenterology 104(3):p 728-738, March 2009.

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GI Prophylaxis with Oral NSAIDS

Risk Factors
H. Pylori infection
Chronic debilitating disorders: cardiovascular disease, gastroesophageal reflux disorder (GERD), esophagitis, and diverticulitis. The symptoms that commonly occur with GERD and diverticulitis, for instance, can be increased with concomitant oral NSAID use
High-dose NSAID therapy

Patients are considered **high-risk** if they have more than 2 risk factors, or if they had a previously complicated ulcer, especially if recent

Patients are considered **moderate-risk** if they have 1-2 risk factors

Lanza, Frank L. MD, FACG1,2; Chan, Francis K.L. MD, FRCP, FACG3; Quigley, Eamonn M.M. MD, FACG4 Practice Parameters Committee of the American College of Gastroenterology. Guidelines for Prevention of NSAID-Related Ulcer Complications. American Journal of Gastroenterology 104(3):p 728-738, March 2009.

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Choosing an NSAID

	Low GI Risk	Moderate GI Risk	High GI Risk
Low CV Risk	NSAID alone (the least ulcerogenic NSAID at the lowest effective dose)	NSAID + PPI/Misoprostol	Alternative therapy if possible or COX-2 inhibitor + PPI/misoprostol
High CV Risk* (low-dose aspirin required)	Naproxen + PPI/Misoprostol	Naproxen + PPI/Misoprostol	Avoid NSAIDs or COX-2 inhibitors. Use alternative therapy.

*Gastrointestinal risk is stratified into low (no risk factors), moderate (presence of one or two risk factors), and high (multiple risk factors, or previous ulcer complications, or concomitant use of corticosteroids or anticoagulants).
High CV risk is arbitrarily defined as the requirement for low-dose aspirin for prevention of serious CV events. All patients with a history of ulcers who require NSAIDs should be tested for H. pylori, and if the infection is present, eradication therapy should be given.

Lanza, Frank L. MD, FACG1,2; Chan, Francis K.L. MD, FRCP, FACG3; Quigley, Eamonn M.M. MD, FACG4 Practice Parameters Committee of the American College of Gastroenterology. Guidelines for Prevention of NSAID-Related Ulcer Complications. American Journal of Gastroenterology 104(3):p 728-738, March 2009.

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Ketorolac

- ≤5 days management of moderate to severe acute pain requiring analgesia at the opioid level
- As effective as morphine in the management of surgical pain and pain related to cancer
- Opioid sparing effect
- Preparations: IM, IV, Oral
- Adjust dosage for patients 65 years and older, weighing less than 50 kg, and with moderately elevated serum creatinine.
  - Injection are not to exceed 60 mg/day

Jelinek GA. Ketorolac versus morphine for severe pain. Ketorolac is more effective, cheaper, and has fewer side effects. BMJ. 2000 Nov 18;321(7271):1236-7. doi: 10.1136/bmj.321.7271.1236. PMID: 11082068; PMCID: PMC1118998.
Pfizer Inc. Toradol (ketorolac tromethamine) [prescribing information]. New York, NY: Pfizer Inc. Revised 2013. Accessed June 2, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/019645s018lbl.pdf

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Topical vs Systemic NSAIDs

- Topical NSAIDs
  - Patch, cream, lotion, etc.
  - Range in application frequency from twice to four times daily
- Topical can provide NSAID relief at the site of inflammation without the systemic side effects
  - Topical NSAID products still contain the black box warning regarding serious cardiovascular and GI events based on the medication, not the formulation

Lin TC, Solomon DH, Tedeschi SK, Yoshida K, Kao Yang YH. Comparative Risk of Cardiovascular Outcomes Between Topical and Oral Nonselective NSAIDs in Taiwanese Patients With Rheumatoid Arthritis. J Am Heart Assoc. 2017 Oct 27;6(11):e006874. doi: 10.1161/JAHA.117.006874. PMID: 29079568; PMCID: PMC5721772.

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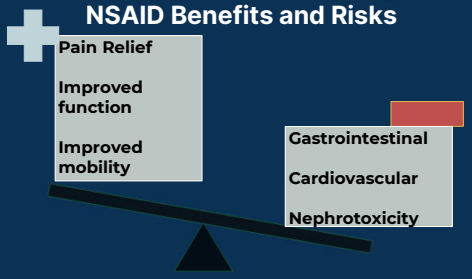
NSAID Benefits and Risks



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ANTICONVULSANTS

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Gabapentinoids – Gabapentin and Pregabalin

- Associated with reduced opioid requirements after major or minor surgical procedures, and some studies reported lower postoperative pain scores
- Effective when administered as a preoperative dose
  - Gabapentin: 600 or 1200 mg (maximum dose 3600mg)
  - Pregabalin: 150 or 300 mg
  - Administered 1–2 hours preoperatively
- Dose adjustments in renal impairment

Chou D, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, Carter T, Cassidy CL, Chittenden EH, Degenhardt E, Griffith S, Manworren R, McCarberg B, Montgomery R, Murphy J, Perkal MF, Suresh S, Sluka K, Strassels S, Thirlby R, Viscusi E, Walco GA, Warner L, Weisman SJ, Wu CL. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain. 2016 Feb;17(2):131-57. doi: 10.1016/j.jpain.2015.12.008. Erratum in: J Pain. 2016 Jun;17(6):748. PMID: 26827847.

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Gabapentinoids

- MOA: Bind α2δ1 subunit of voltage-gated calcium channels in CNS
- Gabapentin: postherpetic neuralgia
- Pregabalin: postherpetic neuralgia, painful diabetic peripheral neuropathy, fibromyalgia, NP associated with spinal cord injury
- Dosing
  - Gabapentin
    - 100-300mg at bedtime and titrate every 3 days; dosed 3-4 times a day
    - Target dose for NP: 1800mg-2700mg
    - Maximum Dose: 3600mg/day
  - Pregabalin
    - 75-150mg/day in 2-3 divided doses
    - Target dose for NP: 150-600 mg/day
    - Maximum Dose: 450-600mg/day
- Renal dose adjustment!
- AEs: edema, dizziness, drowsiness, headache, fatigue, weight gain, dry mouth, blurry vision

Uebbing EM, Zorn K, Fudin J. Treatment of Neuropathic Pain: The Role of Unique Opioid Agents. Pract Pain Manag. 2011;11(4). Updated 2022 May/June;(2023).
Pfizer Inc. Neurontin (gabapentin) [prescribing information]. New York, NY: Pfizer Inc.; 2013. Accessed June 2, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020235s054s055s056,020882s038s039s040,021129s035s036s037lbl.pdf
Lyrica (pregabalin) [prescribing information]. New York, NY: Upjohn US 2 LLC. Accessed June 2, 2026. https://labeling.pfizer.com/showlabeling.aspx?id=561

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Gabapentin vs Pregabalin?

Gabapentin
- Bioavailability: 27-60%
- Nonlinear, saturable absorption
- Slower onset
- Lower affinity for receptor
- Elimination:
- Renal: 76-81%
- ½ life: 5-7 hours

Pregabalin
- Bioavailability: >90%
- Linear, nonsaturable kinetics
- Faster onset
- Higher affinity for receptor
- Elimination:
  - Renal: 90%
  - ½ life: 6.3 hours

Chincholkar M. Gabapentinoids: pharmacokinetics, pharmacodynamics and considerations for clinical practice. Br J Pain. 2020 May;14(2):104-114. doi: 10.1177/2049463720912496. Epub 2020 Mar 13. PMID: 32537149; PMCID: PMC7265598.
Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. Clin Pharmacokinet. 2010;49(10):661-669. doi:10.2165/11536200-000000000-00000.
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Lyrica (pregabalin) [prescribing information]. New York, NY: Upjohn US 2 LLC. Accessed June 2, 2026. https://labeling.pfizer.com/showlabeling.aspx?id=561

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Gabapentin to Pregabalin Conversion

DAILY DOSE OF GABAPENTIN (MG/DAY)	DAILY DOSE OF PREGABALIN (MG/DAY) DIVIDE IN TWICE DAILY DOSING
0 -900	150
901 – 1500	225
1501-2100	300
2101-2700	450
2700 or higher	600

Studies show minimal benefit & more adverse effects when high Lyrica doses are used for diabetic neuropathy (>300 mg/day) and fibromyalgia (>450 mg/day)

Toth C. Substitution of gabapentin therapy with pregabalin therapy in neuropathic pain due to peripheral neuropathy. Pain Med. 2010 Mar;11(3):456-65. doi: 10.1111/j.1526-4637.2009.00796.x. Epub 2010 Jan 22. PMID: 20113408.

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Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

- MOA: Inhibit the reuptake of norepinephrine and serotonin
- Duloxetine, Venlafaxine
- Milnacipran
  - FDA approved for fibromyalgia
- AEs: nausea, headache, weakness, fatigue, insomnia, diaphoresis
- Caution in patients with:
  - Liver dysfunction
  - Uncontrolled hypertension
  - Moderate cardiovascular disease

Uebbing EM, Zorn K, Fudin J. Treatment of Neuropathic Pain: The Role of Unique Opioid Agents. Pract Pain Manag. 2011;11(4). Updated 2022 May/June;22(3).
Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683a

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Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

Duloxetine
- FDA approved:
  - Neuropathic pain associated with diabetic neuropathy
  - Fibromyalgia
  - Musculoskeletal pain (low back pain, osteoarthritis)
- More noradrenergic than venlafaxine
- Slight increase in blood pressure
  - Less significant than venlafaxine
  - Not a sustained effect
- Dose adjustment in renal impairment
  - Avoid use in eGFR <30ml/min
- Avoid use in hepatic impairment
  - Chronic liver disease or cirrhosis

Venlafaxine
- Evidence for neuropathic pain is less robust than duloxetine
- No FDA approval for pain indications
- Studied in: diabetic peripheral neuropathy, polyneuropathy, atypical facial pain, chemotherapy-induced peripheral neuropathy, migraine prevention, fibromyalgia, low back pain
- Analgesic effects generally seen at >150mg/day
- Dose-dependent increases in blood pressure
- Dosage adjustment required in renal/hepatic impairment
- Comes in XR formulation

Eli Lilly and Company. Cymbalta (duloxetine delayed-release capsules) [prescribing information]. Indianapolis, IN: Eli Lilly and Company; 2024. Accessed June 2, 2026. https://pi.lilly.com
Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683a
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Duloxetine Dosing

- Start at 20-30 mg daily x 1 week (2 weeks if an older patient)
  - Increase to 60 mg after ~1-2 weeks
- Can wait until follow up if concerns with compliance
- Target dose is 60 mg
- Doses above 60 mg not typically beneficial in pain management
- Dose Adjustments
  - CrCl<30 = Avoid per package insert, can consider lower doses (20-30 mg)
  - Child-Pugh Class A = Caution Use
  - Child-Pugh Class B or C = Avoid Use

Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683a
Eli Lilly and Company. Cymbalta (duloxetine delayed-release capsules) [prescribing information]. Indianapolis, IN: Eli Lilly and Company; 2024. Accessed June 2, 2026. https://pi.lilly.com

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What about SSRIs?

- Max et al
  - Diabetic neuropathy
  - Compared:
    - Amitriptyline (NE & 5-HT)
    - Desipramine (NE only)
    - Fluoxetine (5-HT only)
      - Responded poorly
- Cochran review in 2007 reviewed the literature regarding
  - Tricyclic antidepressants (TCA)
  - Select serotonin reuptake inhibitors (SSRI)
  - Serotonin norepinephrine reuptake inhibitors (SNRI)
- TCAs and venlafaxine have data which support their use in neuropathic pain
- There is limited evidence to suggest SSRIs are effective in managing neuropathic pain
  - They were better tolerated compared to TCAs relating primarily to side effect profile

Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med. 1992;326(19):1250-1256. doi:10.1056/NEJM199205073261904.
Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD005454. DOI: 10.1002/14651858.CD005454.pub2. Accessed 03 June 2026.

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Tricyclic Anti-Depressants (TCAs)

- MOA: inhibition of norepinephrine and serotonin reuptake
- Role in pain: fibromyalgia, low back pain, migraine prophylaxis, neuropathic pain
- Analgesic effects independent of antidepressant effects and lower doses needed for analgesic effects compared to MDD doses
- Higher dosing and longer treatment time needed for antidepressant effects
- QTc prolongation, orthostatic hypotension, arrhythmias, tachycardia
- Lots of drug-drug interactions
- Caution should be exercised in patients
  - With cardiac arrhythmias
  - Over the age of 65

Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683a

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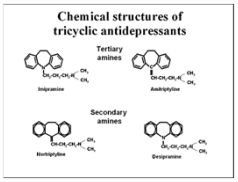
Anticholinergic Properties Among TCAs

- Tertiary amines are associated with more of the anticholinergic side effects compared to secondary amines
- Anticholinergic side effects include
  - Sedation
  - Dry mouth/ urinary retention
  - Postural hypotension
  - Arrhythmias or seizures



Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683a

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Selected Pharmacologic Treatments for Neuropathic Pain

Class	Medication	MOA	Comments
Anti-Convulsants	Carbamazepine & Oxcarbazepine	Inhibits voltage gated sodium channels, potentiate GABA	Significant drug–drug interactions Monitor CBC d/t aplastic anemia and agranulocytosis, LFTs, sodium level. Recommended testing HLA-B*1502 in patients with Asian ancestry d/t SJS/TEN
	Topiramate	Inhibits voltage gated sodium channels, AMPA/kainite subtype of glutamate receptor, and carbonic anhydrase; increases activity of GABAA receptor	Dosage adjusted in renal impairment; increase risk for kidney stones, weight loss
Topical Analgesic	Capsaicin	Transient receptor potential vanilloid1 receptor (TRVP1); Depletes and prevents accumulation of substance P in peripheral sensory neurons	Derived from chili pepper; skin irritation; must wash hands after application
Topical Analgesic	Lidocaine	Inhibits voltage gated sodium channels,	

Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683a

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SKELETAL MUSCLE RELAXANTS

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Spasticity

- Definition:
  - Velocity-dependent increase in muscle tone caused by the increased excitability of the muscle stretch reflex
- Symptoms:
  - Stiffness
  - Hypertonicity
  - Hyperreflexia
- Causes:
  - Multiple sclerosis
  - Cerebral Palsy
  - Spinal cord injury
  - Traumatic brain injury
  - Motor neuron disease
  - Post-stroke syndrome

Fudin J, Raouf M. A Review of Skeletal Muscle Relaxants for Pain Management. Pract Pain Manag. 2016;16(5).

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Spasms

- Definition:
  - Involuntary muscle contractions
- Symptoms:
  - Jerks
  - Twitches
  - Cramps
- Causes:
  - Musculoskeletal pain
  - Fibromyalgia
  - Sciatica
  - Mechanical low back pain
  - Herniated disk
  - Spinal stenosis
  - Myofascial pain

Fudin J, Raouf M. A Review of Skeletal Muscle Relaxants for Pain Management. Pract Pain Manag. 2016;16(5).

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Antispasmodics Vs. Antispastics

Antispasmodics

MOA: Blocks nerves from signaling **brain**

Conditions Treated: Spasms secondary to peripheral musculoskeletal conditions

Examples = **Injury, fatigue, and trauma**

Antispastics

MOA: Block nerve signaling from the **spinal cord** → Act directly on **skeletal muscle** to relax spasm

Conditions Treated: Spasticity secondary to upper motor neuron lesions

Examples = **Multiple Sclerosis, Spinal Cord Injury, Stroke, Cerebral Palsy, Infection**

Fudin J, Raouf M. A Review of Skeletal Muscle Relaxants for Pain Management. Pract Pain Manag. 2016;16(5).

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Treatment of Spasticity and Spasms

Spasticity:

- Baclofen
- Tizanidine
- Botulinum toxin
- Dantrolene
  - Hepatoxicity
- Diazepam
- Riluzole

Spasms:

- Methocarbamol
- Cyclobenzaprine
- Carisoprodol
  - Abuse potential, no longer recommended
- Metaxalone
- Chlorzoxazone
- Orphenadrine
- Diazepam

Fudin J, Raouf M. A Review of Skeletal Muscle Relaxants for Pain Management. Pract Pain Manag. 2016;16(5).

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SELECTED ANTISPASTICITY AGENTS

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Baclofen

- Indication
  - Spasticity associated with multiple sclerosis or spinal cord injury and other spinal cord diseases
- Mechanism of Action
  - Centrally acting: Inhibits monosynaptic and polysynaptic reflexes
- Dosing
  - 5 mg TID, increase by 5 mg TID every 3 days as needed
- Renal dosing:
  - CrCl 50-80: 5 mg Q12H
  - CrCl 30-50: 2.5 mg Q8H
  - CrCl <30: Avoid Use
- Also available intrathecally

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Baclofen

- Adverse Effects
  - Withdrawal can occur (hallucinations, seizures)
- Clinical Pearls
  - On Beers List for when eGFR<60
  - Intrathecal pump available to treat spasticity

Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683a

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Tizanidine

- Indication
  - For the management of spasticity
  - May also have some efficacy for acute musculoskeletal conditions (not FDA approved)
- Mechanism of Action
  - Centrally acting: Inhibits presynaptic and postsynaptic alpha 2 motor neurons
- Dosing
  - 2 mg Q6-8H (do not exceed 3 doses/24 hours)
  - Increase by 2-4 mg every 1-4 days
  - Max 36 mg/day
- Renal dosing for CrCl <25:
  - use with caution as clearance is reduced by more than 50%
  - International package inserts: start at 2 mg daily with slow titration

Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023.
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Tizanidine 4 mg Tablets Summary of Product Characteristics. Teva UK Ltd. Updated October 31, 2021. Accessed June 3, 2024. https://products.tevauk.com/media/download/25648

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Tizanidine

- Adverse Effects
  - **Hypotension**
  - QT prolongation
  - Very sedating
- Clinical Pearls
  - Not specifically mentioned on Beers list
  - **Structurally similar to clonidine**
  - **Taper off**
  - **Contraindicated with CYP1A2 inhibitors** (ciprofloxacin, fluvoxamine)
  - Food alters absorption

Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683a
Acorda Therapeutics, Inc. Zanaflex (tizanidine hydrochloride) tablets and capsules [prescribing information]. Ardsley, NY: Acorda Therapeutics, Inc.; 2013. Accessed June 3, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021447s011_020397s026lbl.pdf
Tizanidine 4 mg Tablets Summary of Product Characteristics. Teva UK Ltd. Updated October 21, 2021. Accessed June 3, 2026. https://products.tevauk.com/media/download/51645

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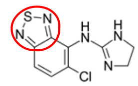
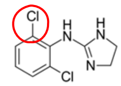
Tizanidine vs Clonidine



Tizanidine



Clonidine

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SELECTED ANTISPASMODIC AGENTS

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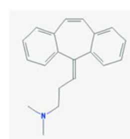
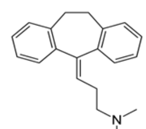
Who's who? Cyclobenzaprine versus Amitriptyline



Cyclobenzaprine



Amitriptyline

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Cyclobenzaprine

- Indication
  - Adjunct for treatment of acute, painful musculoskeletal conditions
- No direct activity on skeletal muscle
  - Sedative effects
- Similar to tricyclic antidepressants
  - Anticholinergic AEs
  - Tachycardia
  - Cardiac conduction disturbances

Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683a
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Cyclobenzaprine

- Mechanism of Action:
  - CNS depressant acting primarily at the brain stem level
  - Reduces excitability of alpha and gamma motor neurons
- Dosing:
  - 5 mg orally 3 times daily
  - May increase to 7.5 mg or 10 mg 3 times daily for 2-3 weeks
  - Elderly: 5 mg orally and less frequent dosing
- Dosage Adjustments for Renal and Hepatic:
  - Renal: NA
  - Hepatic:
    - Mild: 5mg daily
    - Moderate-Severe: Not recommended
- Adverse Effects:
  - Anticholinergic effects
  - Not recommended beyond 3 weeks
- Drug Interactions:
  - CYP1A2 substrate (major)
  - CYP2D6, CYP3A4 substrate (minor)

Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=266106683a
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Methocarbamol

- Indication
  - Adjunct as relief of discomfort due to acute painful musculoskeletal conditions
- Mechanism of Action:
  - Carbamate derivative of guaifenesin
  - Unknown mechanism but is thought to cause myorelaxation via sedation
- Dosing:
  - Initial dose: 1,500-2,000 mg orally 4 times daily for 2-3 days
  - Maintenance dose: 750-1,000 mg orally 3-4 times daily
- Dosage Adjustments for Renal and Hepatic:
  - Renal: NA
  - Hepatic: NA
- Adverse Effects:
  - Sedation, urine discoloration, hypotension, HA, confusion, seizure
- Drug Interactions:
  - CNS depression

Herndon CM, Kominek CM, Mullins AM. Pain Management. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L, eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 13th Edition. McGraw Hill; 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3091&sectionid=266106483s
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Corticosteroids

- Glucocorticoids reduce pain by:
  - Inhibiting prostaglandin synthesis
  - Reducing vascular permeability that results in tissue edema
- Short-term use
- Wide range of use:
  - Inflammatory neuropathic pain
  - Bone pain
  - Pain from bowel obstruction
  - Pain from headache associate with increased intracranial pressure
  - Stimulation of appetite
- Side Effects: weight gain, insomnia, GI upset, increase in blood glucose, psychiatric side effects

Haywood A, Good P, Khan S, Leupp A, Jenkins-Marsh S, Rickett K, Hardy JR. Corticosteroids for the management of cancer-related pain in adults. Cochrane Database of Systematic Reviews 2015, Issue 4. Art. No.: CD010756. DOI: 10.1002/14651858.CD010756.pub2. Accessed 03 June 2026.
National Comprehensive Cancer Network. Adult Cancer Pain (NCCN Clinical Practice Guidelines in Oncology). Version 1.2026. Updated January 23, 2026. Accessed June 3, 2026. NCCN website.

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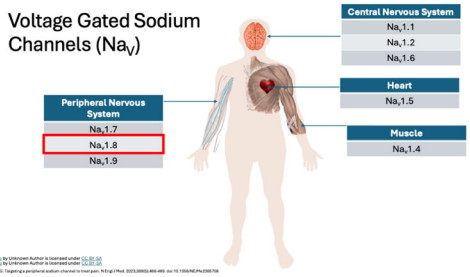
Voltage Gated Sodium Channels (Na_V)



Waxman SG. Targeting a peripheral sodium channel to treat pain. N Engl J Med. 2023;389(5):466-469. doi:10.1056/NEJMe2305708

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$Na_V1.8$ channels

Type of VG Na channels that play a role in nociceptive pain transmission	Transmembrane protein that controls regulation of membrane channel by controlling movement of Na ions across phospholipid bilayer of cells
$Na_V1.8$ channels are expressed in sensory neurons of the PNS	Expressed in dorsal root ganglion and trigeminal ganglion

Waxman SG. Targeting a peripheral sodium channel to treat pain. N Engl J Med. 2023;389(5):466-469. doi:10.1056/NEJMe2305708

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Suzetrigine

Mechanism of Action	• Selective inhibition of $Na_V1.8$, inhibiting transmission of pain signals from the PNS to the brain and spinal cord
Labeled Indications	• Moderate to severe acute pain in adults
Dosing	• Initial dose: 100 mg PO on an empty stomach 1 hour before or 2 hours after food to delay onset of action then 50 mg PO every 12 hours with or without food
ADEs	• Pruritus, muscle spasms, increased creatine phosphokinase, and rash
Contraindications	• Concomitant use with strong CYP3A4 inhibitors
Renal/Hepatic Considerations	• Avoid use in patients with eGFR < 15 mL/min • Avoid use in patients with Child-Pugh Class C hepatic impairment

Jones J, Correll DJ, Lechner SM, et al.; VX21-548-101 and VX21-548-102 Trial Groups: Selective inhibition of NaV1.8 with VX-548 for acute pain. N Engl J Med 2023; 389:393–405. doi:10.1056/NEJMoa2209870
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Mechanism of Action: Suzetrigine

- Selective blocker of NaV1.8 voltage-gated sodium channel
- Peripheral/DRG sodium channel blocker like local anesthetics but has a ≥ 31,000-fold selectivity ratio for NaV1.8
- Inhibits transmission of pain signals (action potentials) to the spinal cord and brain
- NaV1.8 channels are NOT expressed in the brain or spinal cord
  - In theory should not exhibit CNS side effects

Jones J, Correll DJ, Lechner SM, et al.; VX21-548-101 and VX21-548-102 Trial Groups: Selective inhibition of Na(V)1.8 with VX-548 for acute pain. N Engl J Med 2023; 389:393–405. doi:10.1056/NEJMoa2209870
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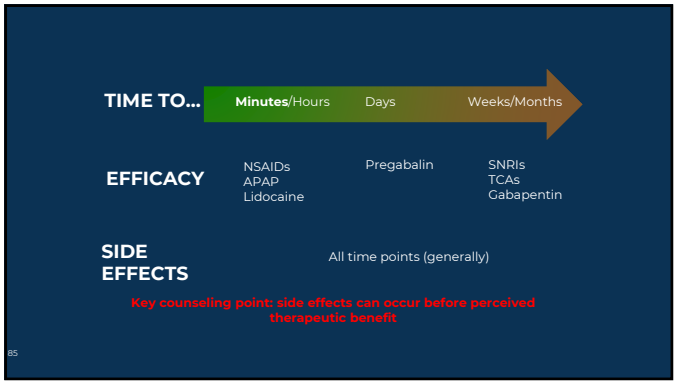

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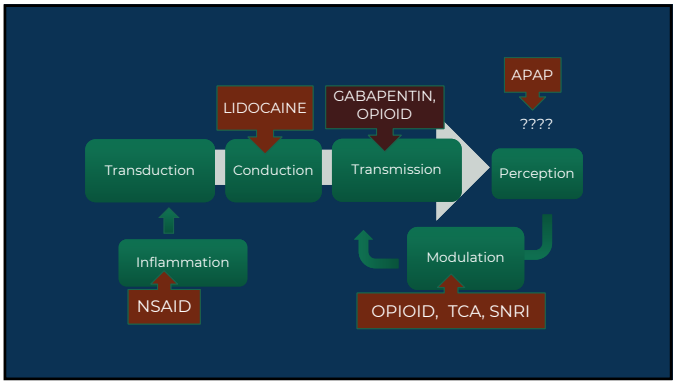

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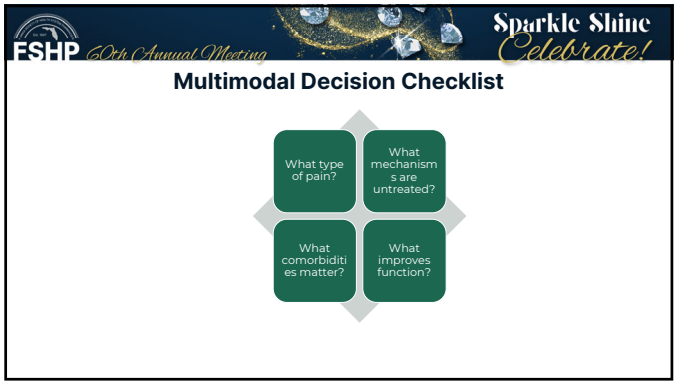

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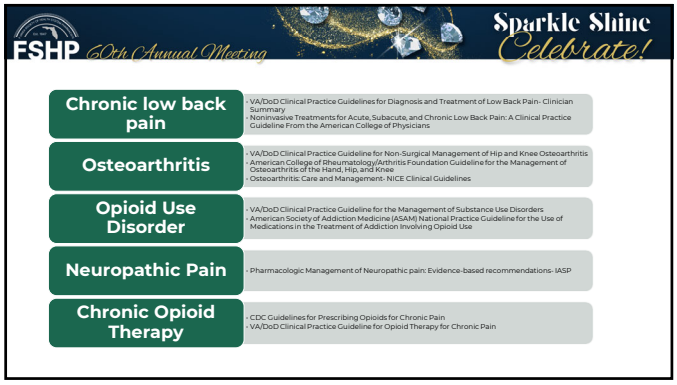

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Smarter Pain Control: Leveraging Multimodal Strategies For Better Patient Outcomes
Dr. Lisa Luciani, Pharm.D., BCPS
Clinical Pharmacist Practitioner – Pain Management
Pain Management, Opioid Safety, and PDMP (PMOP) Coordinator
James E. Van Zandt VA Medical Center - Altoona, PA
drlisaluciani@gmail.com
https://www.linkedin.com/in/lisadragic
Thank you!

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