2025 Early Career Scholar Program

An Intensive Multi-day Opioid REMS Initiative in Pain Management

CME OUTFITTERS

This activity is supported by an independent educational grant from the Opioid Analgesic REMS Program Companies.

Please see https://www.opioidanalgesicrems.com/Resources/Docs/List_of_RPC_Companies.pdf for a listing of REMS Program Companies. This activity is intended to be fully compliant with the Opioid Analgesic REMS education requirements issued by the U.S. Food and Drug Administration (FDA).

Multimodal Pain Management

Pharmacologic and Non-Pharmacologic Approaches

This activity may include discussions of products or devices that are not currently labeled for use by the FDA.

The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational uses (any uses not approved by the FDA) of products or devices. All identified conflicts of interest have been mitigated.

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Learning Objective

- Educate patients about multimodal pain management to optimize safe and effective, multimodal treatment plans

Patient Case: PP

55 y/o F, with fibromyalgia, rheumatoid arthritis, and depression

Current Medications:

- Hydrocodone/APAP 10/325mg PO TID prn
- Celecoxib 200 mg PO Qday
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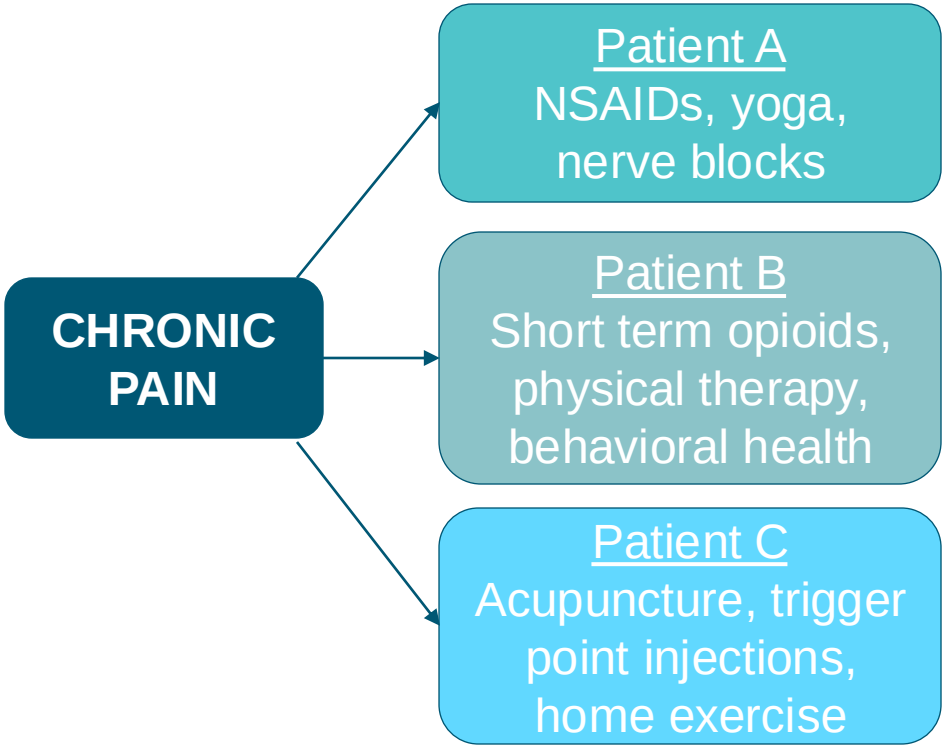
- Zolpidem CR 6.25mg PO QHS

APAP = acetaminophen; F = female; mg = milligram; PO = by mouth; prn = as needed; Qday = every day; QHS = every night at bedtime; QID = 4 times a day; TID = 3 times a day; XL = extra long.

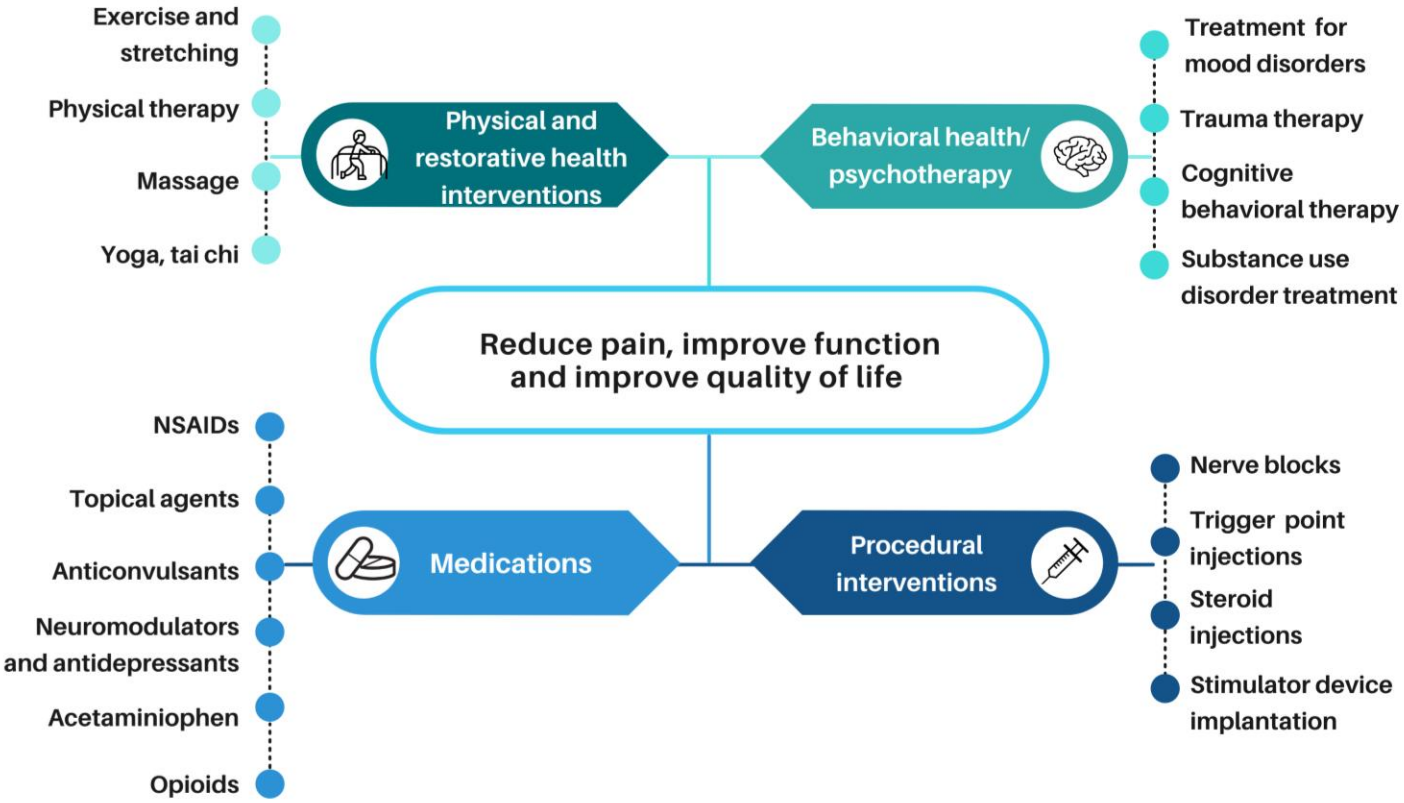
Patient-Centered Pain Care

- Patients with pain from the same condition can present differently and have different responses to the same treatment
- Building treatment plans based on unique patient factors improves patient satisfaction and outcomes



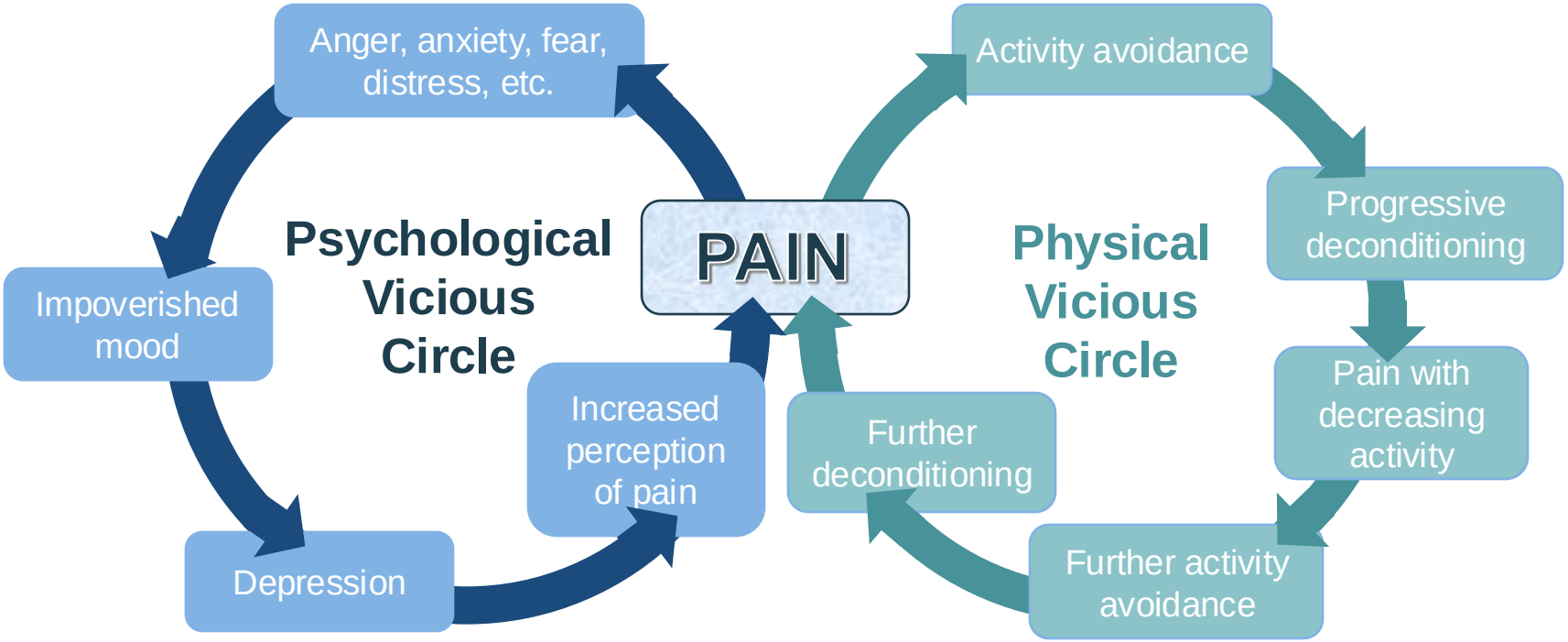
Centers for Disease Control and Prevention (CDC). National Archives Federal Register Website. 2022. https://www.federalregister.gov/d/2022-02802. Department of Health and Human Services [DHHS]. DHHS Website. 2022. https://www.hhs.gov/opioids/prevention/pain-management-options/index.html.

Multimodal Approach to Pain Care



Dale R, et al. *Med Clin North Am.* 2016;100(1):55-64. Dowell D, et al. *MMWR Recomm Rep.* 2022;71(3):1-95.

Psychological and Physical Circles of Pain



Cooper RG, et al. *Rheumatology (Oxford).* 2003;42(10):1133-1137.

Audience Poll

Do you receive pushback from patients or caregivers when non-opioid medications are prescribed?

A. Yes, most of the time
B. Yes, but it is usually manageable with education
C. No, not if it is part of a regimen that has opioids
D. No, it is rare that there is any pushback

Non-Opioid Pharmacotherapy for Pain

Medication or Drug Class	Condition for Use
Acetaminophen	Osteoarthritis (not recommended first line)
NSAIDs (oral and topical)	Chronic low back pain, osteoarthritis
SNRI antidepressants	Chronic low back pain, neuropathic pain, osteoarthritis, fibromyalgia
Tricyclic antidepressants	Neuropathic pain
Gabapentinoids	Post-herpetic neuralgia, neuropathic pain, fibromyalgia
Anticonvulsants	Neuropathic pain
Topical lidocaine or capsaicin	Neuropathic pain
Antispasmodics / muscle relaxants	Spasticity
Ensure dose optimization for all medication treatments	

NSAIDs = non-steroidal anti-inflammatory drugs; SNRI = serotonin-norepinephrine reuptake inhibitor.

Bates D, et al. *Pain Med.* 2019;20(Suppl 1):S2-S12. Cheng J, et al. *Pain Med.* 2020;21(1):1-3. Dowell D, et al. *MMWR Recomm Rep.* 2022;71(3):1-95. Duloxetine [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021427s055s057lbl.pdf. Milnacipran [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/022256Orig1s029lbl.pdf.

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Acetaminophen

Analgesic/Antipyretic: Not effective as an anti-inflammatory, mild-moderate pain without inflammation

- Mechanism of Action – Central inhibition of prostaglandin synthesis
- FDA max is still 4g/day
- Max 2g/day for pts on warfarin, have liver dysfunction, poor nutritional intake, or 3+ ETOH/day
- Precautions
  - Liver disease, use of hepatotoxic drugs, 3+ ETOH/day
- Safe in pregnancy & breastfeeding

ETOH = ethyl alcohol (3+ drinks/day); FDA = U.S. Food and Drug Administration.

Acetaminophen [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/019872Orig1s048lbl.pdf. Ong CK, et al. *Clin Med Res*. 2007;5(1):19-34. Zeng C, et al. *Osteoarthritis Cartilage.* 2021;29(9):1242-1251.

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NSAIDs

- For mild to moderate pain
- MOA: inhibit prostaglandin production
- Black Box Warning: CV risk-thrombotic events, MI, stroke
- GI risk-bleeding, ulceration, and perforation of the stomach
- Other ADRs - GI upset, fluid retention, increased bleeding
- Consider co-Rx of GI protective agent

ADRs = adverse drug reactions; CV = cardiovascular; GI = gastrointestinal; MI = myocardial infarction; MOA = mechanism of action; Rx = medical prescription.

U.S. Food and Drug Administration [FDA]. FDA Website. 2020. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/nonsteroidal-anti-inflammatory-drugs-nsaids . Marcum ZA, et al. *Ann Longterm Care.* 2010;18(9):24-27.

Comparison of NSAIDs

- Celecoxib
- Meloxicam
- Indomethacin
- Ibuprofen
- Naproxen
- Diclofenac
- Ketorolac

Amaechi O, et al. *Am Fam Physician.* 2021;104(1):63-72. Brune K, et al. *J Pain Res.* 2015;8:105-118.

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Antidepressants in Pain Management

- Data most supportive of:
  - Use of agents with mixed mechanism of action (inhibition of S & N reuptake)
    - TCAs, SNRIs
  - Treatment of neuropathic pain conditions and fibromyalgia
- Some good data to support use in:
  - Musculoskeletal pain (osteoarthritis, LBP)
  - Headache (migraine, chronic HA)
- Use of other antidepressants for concomitant depression (not pain)

HA = headache; LBP = low back pain; S & N = serotonin and norepinephrine; TCAs = tricyclic antidepressants.

Birkinshaw H, et al. *Cochrane Database Syst Rev.* 2023;5(5):CD014682.

Comparison of TCAs

Drugs	Relative Anticholinergic Effects	Relative Sedative Effects	Relative Norepinephrine Reuptake Inhibition	Relative Serotonin Reuptake Inhibition	Relative Orthostatic Effects
Tertiary Amino Side Chain Compounds					
Amitriptyline	++++	++++	++	++++	++
Imipramine	++	++	++	++++	+++
Secondary Amino Side Chain Compounds					
Nortiptyline	++	++	++	+++	+
Desipramine	+	++	++++	++	+

Adapted from Lipman AG. *Clin Geriatr Med.* 1996;12(3):501-515.

SNRIs

- Duloxetine
  - Efficacy established for depression, diabetic neuropathy, anxiety, fibromyalgia, musculoskeletal pain
  - ADRs
    - Nausea, increased BP, drowsiness, dizziness, anticholinergic effects
- Milnacipran
  - Approved for fibromyalgia
  - No CYP DDIs

BP = blood pressure; CYP = cytochrome P450; DDIs = drug-drug interactions.

Duloxetine [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021427s055s057lbl.pdf. Milnacipran [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/022256Orig1s029lbl.pdf.

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Anticonvulsants

- Primary uses
  - Neuropathic pain
  - Fibromyalgia
- Primary mechanisms
  - Blockade of voltage-gated Na^{+} channels
  - Modulation of voltage-gated Ca^{++} channels
- Other mechanisms
  - Blockade of GABA transporter
  - Modulation of SV2A receptors
  - Carbonic anhydrase inhibition

Ca^{++}= calcium ion; GABA = gamma-aminobutyric acid; Na^{+} = sodium ion; SV2A = synaptic vesicle glycoprotein 2A.
Finnerup NB, et al. *Physiol Rev.* 2021;101(1):259-301.

Anticonvulsants: Evidence for Use

Indication	Medication
Post-herpetic neuralgia	Gabapentin, pregabalin
Diabetic peripheral neuropathy	Oxcarbazepine, gabapentin, pregabalin
Trigeminal neuralgia	Carbamazepine
Fibromyalgia	Pregabalin
HIV Neuropathy	Gabapentin
Complex regional pain syndrome	Carbamazepine, gabapentin

Abd-Elsayed A, et al. *Ann Med.* 2024;56(1):2334398. Finnerup NB, et al. *Physiol Rev.* 2021;101(1):259-301. Schütz SG, et al. *HIV AIDS (Auckl).* 2013; 5:243-251.

Anticonvulsants: Gabapentin

- MOA: Modulation of α 2 δ subunits of voltage-gated calcium channels
- FDA-approved for PHN, used first-line for most types of NP
- Oral only
- Bioavailability decreases with increased doses
- Not metabolized, renally-eliminated
  - Dose adjustments required

NP = neuropathic pain; PHN = postherpetic neuralgia.

Gabapentin [package insert]. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=075694.

Gabapentin ADRs

- Somnolence
- Dizziness
- Ataxia
- Fatigue
- Weight gain
- Constipation
- Dry mouth
- Blurry vision
- Edema

Gabapentin [package insert]. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=075694.

Anticonvulsants - Pregabalin

- FDA-approved for PHN, DPN, FM, used first-line for most types of NP
- Same as gabapentin
  - MOA
  - Oral only
  - Negligible metabolism, renally eliminated
  - Side effects (but more mild)
  - Dosing (BID-TID)
- Different from gabapentin
  - 6x more potent binding
  - > 90% more bioavailable
  - Lower intersubject PK variability
  - Faster dose titration
  - Max 300mg/day DPN, 450mg/day FM, 600mg/day PHN

BID = twice a day; DPN = diabetic peripheral neuropathy; FM = fibromyalgia; PK = pharmacokinetic.

Gabapentin [package insert]. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=075694.
Pregabalin [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/021446s041,022488s018lbl.pdf.

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Topicals

- Capsaicin
- Lidocaine
- NSAIDs
  - Salicylates
  - Diclofenac
  - Ketoprofen
- Clonidine
- Gabapentin
- Muscle relaxants
- Menthol

Amaechi O, et al. *Am Fam Physician.* 2021;104(1):63-72. Dowell D, et al. *MMWR Recomm Rep*. 2022;71(3):1-95. Shahid M, et al. *BMC Pharmacol Toxicol.* 2019; 20(1):51.

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Antispasmodics/Muscle Relaxants

- No good comparative studies - choice based on ADR profile and cost
- Common ADRs
  - Drowsiness, dizziness, GI upset
  - Additive CNS depression with other CNS depressants (e.g., opioids)

- Cyclobenzaprine
- Carisoprodol
- Methocarbamol
- Metaxalone
- Baclofen
- Tizanidine

CNS = central nervous system.

Amaechi O, et al. *Am Fam Physician.* 2021;104(1):63-72. Dowell D, et al. *MMWR Recomm Rep*. 2022;71(3):1-95.

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Low-dose Naltrexone

- Daily dosage of naltrexone that are ~ 1/10th of the typical opioid addiction treatment dosage range
- Most research on 4.5mg QHS
  - Must be compounded
- Proposed mechanism
  - Small and transient blockade of opiate receptors causes upregulation of endorphins
  - Anti-inflammatory effects by antagonizing toll-like receptor 4 (TLR4)
- May be first glial cell modulating therapy for chronic pain
- Patients must not be taking opioids
  - Ok at the VLDN (0.5-1mg) and ULDN (100mcg) dosing

mcg = microgram; TLR4 = toll-like receptor 4; ULDN = ultra low-dose naltrexone/naloxone; VLDN = very low-dose naltrexone.

Younger J, et al. *Clin Rheumatol*. 2014;33(4):451-459.

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NMDA Receptor Antagonists

Rationale: glutamate action on NMDA receptors in the CNS contribute to pain pathways

- Off-label uses
- Ketamine
  - Approved for depression
  - 10% topical gel
  - 10-50 mg PO TID prn
  - 25 – 200 mg IV per day
- Memantine
- Amantadine
- Dextromethorphan
- Methadone

IV = intravenous; NMDA = N-methyl-D-aspartate.

Manikant L, et al. *Pain Physician.* 2023;26(7S):S7-S126. McDonagh MS, et al. *Nonopioid Pharmacologic Treatments for Chronic Pain.* 2020. https://www.ncbi.nlm.nih.gov/books/NBK556277/pdf/Bookshelf_NBK556277.pdf.

Suzetrigine

- First novel pain medication FDA-approved in 25 years
- MOA: selectively blocks sodium channels (NaV1.8) in the peripheral nervous system
- Indicated for the short-term treatment of moderate to severe acute pain in adults
- 50mg PO BID
- ADRs: nausea, headache, dizziness, constipation, and vomiting
- Precautions: kidney or liver disease, heart disease, and seizures

Osteen JD, et al. *Pain Ther.* 2025. U.S. Food and Drug Administration [FDA]. FDA Website. 2025. https://www.fda.gov/news-events/press-announcements/fda-approves-novel-non-opioid-treatment-moderate-severe-acute-pain.

Non-Pharmacologic Therapies for Pain

Treatment Category	Treatment Options
Lifestyle	Exercise, weight loss, nutrition/diet, sleep hygiene
Physical rehabilitation	Thermal therapies, physical and occupational therapy, massage, yoga, tai chi, postural support
Mind-body	Cognitive-behavioral therapy, muscle relaxation, hypnosis, meditation, music/art therapy, pain reprocessing therapy (PRT)
Complementary and alternative medicine	Acupuncture/acupressure
Device- and procedure-based	Surgery, transcutaneous electrical nerve stimulation, laser therapy, electromyography, biofeedback

Ashar YK, et al. *JAMA Psychiatry.* 2022;79(1):13-23. Department of Health and Human Services [DHHS]. DHHS Website. 2022. https://www.hhs.gov/opioids/prevention/pain-management-options/index.html.

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- Continued problems with sleep – zolpidem helping
- Recent 30 lb weight gain – considering a GLP-1
- Completed a year of occupational therapy 5 years ago
- Completed a year of physical therapy 5 years ago
- Currently seeing a pain psychologist monthly – incorporating biofeedback and relaxation exercises
- For myofascial pain - trigger point injections provide moderate relief, botulinum toxin injections provide minimal relief

GLP-1 = glucagon-like peptide-1; lb = pound.

SMART Goals

- Increase use of non-opioid pharmacologic treatments for pain management
- Educate patients on the benefits of multimodal pain care and how it can benefit them

Questions?

CME OUTFITTERS