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How the Program Works



- Web-based program, CME, CNE, and CPE credit available
- Two parts, with a post-test after each part (note: ★ in upper right-hand corner of slides indicate post-test content)
- Brief polling questions periodically in each part
- Certificate available upon completion of post-test and evaluation
- Additional resources, tools, and supplemental educational activities available at www.scopeofpain.org

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Faculty



Faculty members have no relevant financial relationships to disclose.

This activity does include discussion of the off-label use of certain formulations of buprenorphine to treat pain. These formulations are approved to treat opioid use disorder but not to treat pain. This presentation does include discussion of the off-label use of clonidine and tizanidine to treat opioid withdrawal symptoms. Clonidine and tizanidine are not FDA approved for this use.

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Partnership & Opioid Analgesic REMS



National Partner

- Federation of State Medical Boards

Opioid REMS

- Content dictated by FDA
"Blueprint for Prescriber Education"
- FDA requires opioid analgesic manufacturers to fund CME-certified education by approved providers

Grant Support

Independent educational grant from Opioid Analgesic REMS Program Companies

https://opioidanalgesicrems.com/Resources/Docs/List_of_RPC_Companies.pdf

This activity is intended to be fully compliant with the Opioid Analgesic REMS education requirements issued by the US FDA

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About the Program



Through the case presented in this program, you will learn how to:

- Quantify pain and functional impairment using validated tools
- Formulate individualized, multimodal pain treatment plans using a risk-benefit framework
- Counsel patients on the therapeutic limitations of opioids and risk mitigation strategies
- Monitor opioid therapy continuously for efficacy, safety, and adverse outcomes
- Diagnose and manage opioid use disorder in patients with or without concurrent pain
- Use interprofessional, team-based care for comprehensive pain management

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Purpose of the Training



- Covers strategies for pain management including safer use of opioids by reviewing **best practices** and sharing **clinical pearls**
- Counts towards the **2023 DEA education requirement** of the **Medication Access and Training Expansion (MATE) Act**
- Aligns with the **2022 CDC Clinical Practice Guideline for Prescribing Opioids for Pain**
- Does NOT cover palliative care or end of life pain management

Alford DP, et al. *Pain Med.* 2016
 Dowell D et al. *MMWR* 2022
https://deaddiversion.usdoj.gov/pubs/docs/MATE_Training_Letter_Final.pdf

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Introduction: Setting the Stage

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Pain: “An Unpleasant Sensory and Emotional Experience”



Acute Pain

Life sustaining symptom

Adaptive to minimize harm and allow healing

Chronic Pain

Pain persisting beyond expected healing (~3 months)
No evolutionary benefit, can be a disease in and of itself

- **Maladaptive** disorder influenced by genetics and epigenetics
- Classification influences work-up, treatment, and prognosis
 - **Nociceptive**: actual or threatened tissue damage - **somatic** (e.g., bones, joints, muscle), **visceral** (e.g., mucosal injury, obstruction, ischemia)
 - **Neuropathic**: disease or injury of the somatosensory nervous system - **central** (e.g., traumatic, vascular), **peripheral** (e.g., compression)
 - **Nociplastic**: abnormal pain processing without evidence of discrete pathology - **diffuse sensitization** (fibromyalgia), **regional sensitization** (complex regional pain syndrome), **visceral pain** (irritable bowel syndrome)
 - **Mixed Pain**: combination of different types of pain, occurring simultaneously in the same area

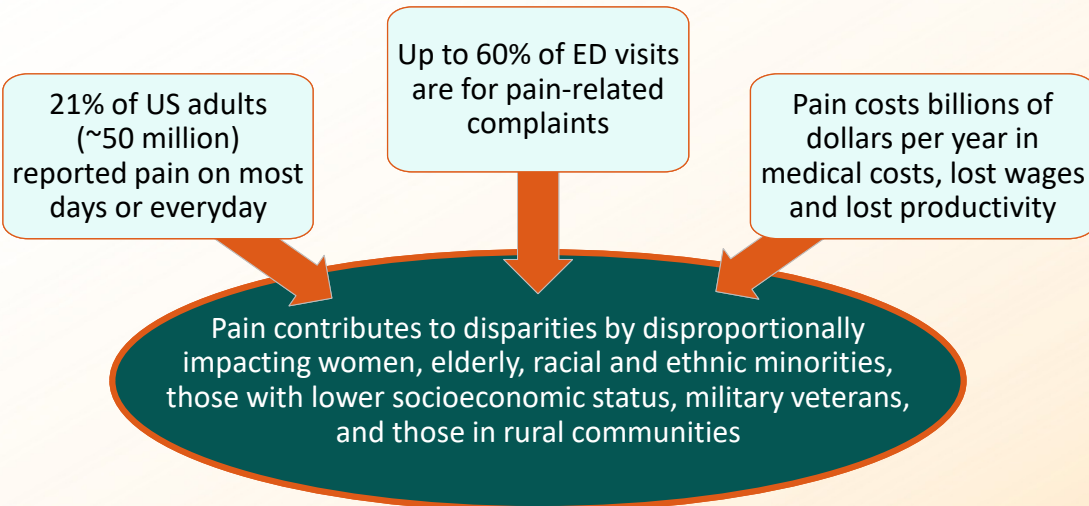
Raja SN, et al. *Pain*. 2020
Cohen SP, et al. *Lancet*. 2021
Fitzcharles MA et al. *Lancet*. 2021
Treede RD et al. *Pain*. 2019

Clauw DJ et al. *Postgrad Med*. 2019
Freynhagen R et al. *Curr Med Res Opin*. 2020

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State of Pain



Yong R et al. *Pain* 2022
Cordell WH, et al. *Am J Emerg Med*. 2002

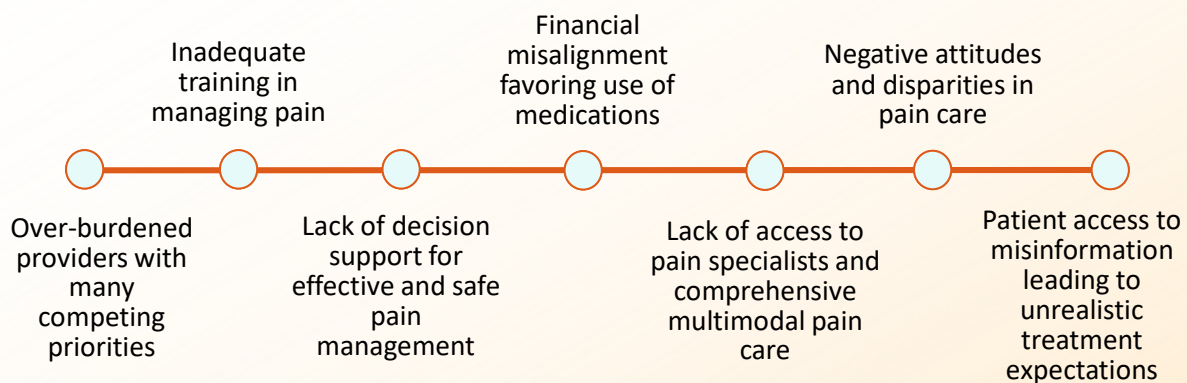
Gaskin DJ, Richard P. *J Pain* 2012

Dahlammer J et al. *MMWR* 2018
Mills SEE et al. *Br J Anaesth*. 2019

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Barriers to Optimal Pain Care



AMA J Ethics. 2020
Laferton JAC et al. *JAMA*. 2025
Hadi MA, et al. *BMJ Open*. 2017

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State of Opioids



• Opioid prescribing

- Opioid analgesic prescribing increased in the 1990s, peaked in 2012
- National opioid prescriptions fell more than 44% over last decade



• Opioid overdoses

- In 2025 opioid overdose deaths dropped to 44,564 (down from 55,296 in 2024), 3rd consecutive year of national decline
- Illicit fentanyl drive most opioid deaths along with poly-substances including cocaine, methamphetamine, and/or adulterants like xylazine

www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

www.cdc.gov/overdose-prevention/data-research/facts-stats/opioid-dispensing-rate-maps.html

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Part 1:

Assessing and Managing Pain

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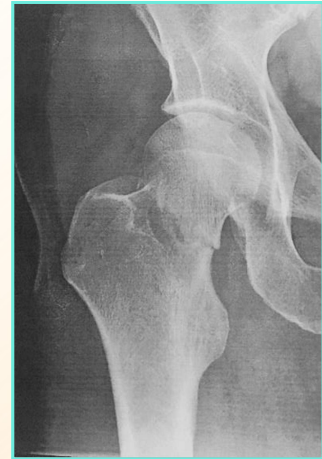
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Case Study – Michelle Jones – 36 yo female



Medical History

- 36-year-old female with no past medical history
- Displaced right femoral neck fracture after a motor vehicle crash
- Underwent internal fixation
- Perioperative pain managed with nerve blocks and parenteral hydromorphone



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Assessing Acute Pain

S	Site
O	Onset
C	Character
R	Radiation
A	Associations
T	Time course
E	Exacerbating/relieving factors
S	Severity

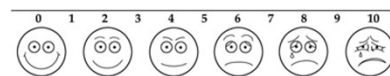
He S, et al. *JAMA*. 2022
 Oken BS. *Brain*. 2008
 Breivik H, et al. *Br J Anaesth*. 2008
 Mason ST, et al. *Handbook of Pain Assessment*. 2011

“Many factors influence self-reported pain including gender, social support, clinician characteristics, trust.”

~ Barry S. Oken, MD, PhD

Pain intensity scales include:

- Visual Analogue Scales (VAS)



- Emoji-based VAS



- Numerical Rating Scales (NRS) 10-point scale



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Risk: Developing Chronic Postsurgical Pain



- Alterations in expression of neurotransmitters, receptors, and ion channels
- Changes to neuron structure, connectivity, and survival

Patient-related

- Younger
- Female
- History of
 - Anxiety
 - Depression
 - Catastrophizing
 - Pre-existing pain syndrome
 - Preoperative opioid use

Persistent Pain

Intraoperative variables

- Surgical procedure
- Nerve ligation/injury
- Ischemia

Postoperative pain

- Uncontrolled severe pain
- Longer duration of postop pain

Voscopoulos C, Lema M. *Br J Anaesth.* 2010
 Pozek JP, et al. *Med Clin North Am.* 2016

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Risk: Acute to Chronic Musculoskeletal Pain

STarT MSK Screening Tool

- Helps identify modifiable risk factors for chronic musculoskeletal pain disability
- Score stratifies risk:
 - Low (0-3)
 - Medium (4-7)
 - High (8-9)

Characteristics

Catastrophizing

Last 2 weeks...(disagree [0] or agree [1])

1. ...troublesome joint or muscle pain in more than one part of your body?
2. ...only been able to walk short distances because of your pain?
3. ...dress more slowly than usual because of your pain?
4. ...other important health problems?
5. ...feel it is unsafe...to be physically active?
6. ...worrying thoughts about your pain a lot of the time?
7. ...your pain condition will last a long time?
8. ... stopped enjoying all the things you usually enjoy?
9. How bothersome has your pain been...
(not at all, slightly, moderately, very much, extremely)

Campbell P, et al. *J Pain Res.* 2016
 Beneciuk JM, et al. *J Pain.* 2024

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Case Study – Michelle Jones – 36 yo female



What is the correct amount of opioid to discharge this patient on?



Discharge Home

- Orthopedic follow-up in 1 week
- Physical therapy referral
- Prescriptions
 - Ibuprofen 600 mg every 8 hours prn pain
 - Oxycodone (5 mg) 1-2 tablets every 4-6 hours prn pain (**#40 tablets**)



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Opioid Overprescribing for Acute Pain



Overprescribing

- Postoperatively over 70% of patients took half or less of their opioids
- After ED visit (renal colic, fracture/dislocation) 93% of patients had leftover pills, 52% of pills were unused

Overprescribing Risk

- 31% of prescription opioids misused obtained from family & friends
- 3-5% of opioid-naïve patients receiving an opioid became long-term (>3 months) opioid users (*risk factors: male, over 50, mental illness, substance use disorder*)

Since 2012, fewer *new* opioid prescriptions for more than 7 days

Bartels et al. *Plos One*. 2016
Dayer LE, et al. *J Surg Res*. 2025

SAMHSA. (2025). 2024 NSDUH
Sun EC, et al. *JAMA Intern Med*. 2016
McCarthy DM, et al. *Pain Med*. 2021

Riva JJ, et al. *Ann Intern Med*. 2020
Deyo RA, et al. *J Gen Intern Med*. 2017
Zhu W et al. *N Engl J Med*. 2019

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Treating Acute Pain



Acute Dental Pain

Molar extractions:
NSAID + APAP more effective versus oxycodone alone or in combination with APAP

Acute Musculoskeletal Pain

No significant difference in pain reduction
NSAID + APAP versus opioid alone or in combination with APAP

Acute Pain Guidelines

Multimodal, individualized approach
Minor surgeries: NSAIDs +/- APAP or limited opioids then transition to NSAIDs +/- APAP

CDC Recommendations 1 & 6

- Acute pain: maximize non-pharm and non-opioids
- Only consider opioids if benefits > risks
- Discuss realistic benefits and known risks
- Prescribe no greater quantity than needed for expected duration of severe pain

Dowell D, et al. MMWR. 2022

Moore RA, et al. *Cochrane Library* 2015
Chang AK, et al. *JAMA* 2017
Jones CMP, et al. *Lancet* 2023

Joshi GP. *Curr Pain Headache Rep.* 2023
Qaseem A, et al. *Ann Intern Med* 2020

Fiore JF, et al. *Lancet* 2022
Mariano ER et al. *Reg Anesth Pain Med.* 2022
Rech MA, et al. *Am J Emerg Med.* 2022

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Ketamine Suzetrigine

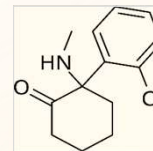
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Ketamine for Acute Pain

Dissociative Anesthetic developed in 1960s



- NMDA receptor antagonist provides analgesia at subanesthetic doses
- Analgesic without respiratory depression
- Low oral bioavailability - parenteral use (IV, IM) as analgesic in ED and perioperative settings
 - Low dose (0.3-0.5 mg/kg) reduces pain more rapidly but less sustained than morphine
 - Decreases opioid requirements ("opioid-sparing")
- Oral, sublingual and intranasal formulations being studied for efficacy and safety for refractory severe chronic pain
- Dose-dependent adverse effects - hallucinations, agitation, anxiety, dysphoria, euphoria
- Misuse potential due to psychoactive effects

Faisco A, et al. *Cureus*. 2024

Pickering G, et al. *CNS Drugs*. 2026

Phan JH, et al. *Ann Pharmacother*. 2026

Duong HG, et al. *Pain Manage*. 2026

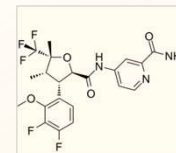
Guo J, et al. *Am J Emerg Med*. 2024

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Suzetrigine for Acute Pain

1st Nonopioid Analgesic in over 25 Years



- Oral systemic selective Na channel blocker for short-term treatment of moderate to severe **acute pain** in adults
- For postoperative pain more efficacious than placebo but not hydrocodone/APAP
 - Only available as oral formulation: dosage 100 mg once followed by 50 mg BID
- In clinical trials, well-tolerated, over 80% of participants still required rescue NSAIDs
- Alternative when NSAIDs or opioids are ineffective or the risk of adverse effects with their use is too high
- Efficacy and safety for treatment of subacute or chronic pain is being investigated

Med Lett Drugs Ther. 2025

Yuan S, et al. *J Pain Palliat Care Pharm*. 2026

Divito AE et al. *Cleve Clin J Med*. 2026

Courtney D et al. *Am J Health-Syst Pharm*. 2026

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Case Study – Michelle Jones – 36 yo female



Postoperative Course

- Completed physical therapy
- Occasionally performed recommended home exercises
- Hip pain and range of motion improved over time
- She ended up with 15 unused oxycodone tablets, which she threw away

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Case Study – Michelle Jones – 54 yo female



What is the most efficient way to screen for psychiatric conditions?



18 Years Later...

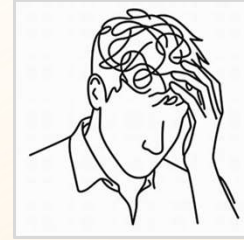
- Presents for primary care, at age 54, after previous PCP retired
- Chief complaint: **"I need my pain med refilled today. My feet and hip are killing me! It is making me so depressed!"**
- Past medical history:
 - Type 2 diabetes mellitus (A1C 7%)
 - Painful diabetic neuropathy
 - Diabetic nephropathy (Stage 3a, GFR 50)
 - Hypertension
 - Hyperlipidemia
 - Obesity (BMI 32)
 - Post-traumatic osteoarthritis of right hip

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Psychiatric Co-Morbidities

- Almost every psychiatric diagnosis in the DSM-5 is also associated with increased rates of chronic pain
 - Major depressive disorder
 - Generalized anxiety disorder
 - Personality disorder
 - Sleep disorder
 - PTSD
 - Substance use disorder
- Bidirectional relationship
 - Psychiatric conditions make pain worse
 - Pain makes psychiatric conditions worse
- Should assess for psychiatric conditions and attempt to co-manage



Johnston KJA, Huckins LM. *Complex Psychiatry*. 2023

25

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Brief Screenings for Co-Morbidities

Depression	→ PHQ-2 (Patient Health Questionnaire), 2-items. <i>If positive PHQ9</i>
Anxiety	→ GAD-2 (Generalized Anxiety Disorder), 2-items, <i>if positive GAD-7</i>
PTSD	→ PC-PTSD-5 (Primary Care PTSD Screen for DSM-5), 5-items
Sleep Disorder	→ ISI-3 Insomnia Severity Index, 3-items
Suicidality	→ ASQ (Ask Suicide-Screening Questions), 4-items
Substance Use	→ TAPS (Tobacco, Alcohol, Prescription Meds, & Other Substance Use) Tool SISQ (Single Item Screening Question – Alcohol, Drugs) <i>if positive *AUDIT +/- **DAST or ^DSM-5 for substance specific use disorder</i>

Kroenke K, et al. *Med Care*. 2003
Kroenke K, et al. *Ann Intern Med*. 2007
Prins A, et al. *J Gen Intern Med*. 2016
Thakral M, et al. *Sleep Med*. 2021

McNeely J, et al. *Ann Intern Med*. 2016
Horowitz LM, et al. *Psychosomatics*. 2020
Smith PC, Saitz R. *J Gen Intern Med* 2009
Smith PC, Saitz R. *JAMA Intern Med* 2010

*Alcohol Use Disorders Identification Test
**Drug Abuse Screening Test
^Diagnostic & Statistical Manual of Mental Disorders, 5th Ed

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Case Study – Michelle Jones – 54 yo female



Screening Results

- Positive for depression: PHQ9 = 5 (mild depression)
- Positive for anxiety: GAD7 = 8 (mild anxiety)
- Negative for insomnia
- Negative for substance use disorder

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Case Study – Michelle Jones – 54 yo female



Medications

Metformin, Empagliflozin,
Lisinopril, Atorvastatin

Pain Medications

Oxycodone 10 mg 4x/day (60 MME*)
Gabapentin 300 mg 3x/day

Previous Pain Medications

NSAIDs (ibuprofen, naproxen)	Diabetic nephropathy and GI upset
Acetaminophen	Inadequate pain relief
Tricyclic antidepressants (TCA) (amitriptyline)	Inadequate pain relief and dry mouth
Tramadol	Inadequate pain relief
Acetaminophen with codeine	Inadequate pain relief and nausea

*Morphine Milligram Equivalents

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Case Study – Michelle Jones – 54 yo female



Social History

Paralegal law office 20 hours/week

Married, no children

Substance Use History

No tobacco use

Alcohol use: 1 glass of wine on special occasions

No illicit drug or cannabis use

Family History

Father being treated for lung cancer

Mother died from complications of alcohol-associated cirrhosis

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Case Study – Michelle Jones – 54 yo female



Pain Medications

- Spacing out oxycodone to avoid running out
- Took last oxycodone this morning
- Best pain relief with oxycodone 10 mg every 6 hours
- Current pain is more severe due to less frequent oxycodone
 - “My pain pills don’t last. I’m suffering. It’s almost impossible to go to work.”
- Presents with some medical records from previous PCP

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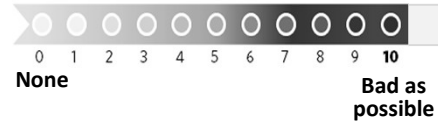
Case Study – Michelle Jones – 54 yo female



Pain Assessment

- **Moderate right hip pain**
 - Constant deep, aching pain radiating to the right groin
 - Exacerbated with activity and relieved with rest
- **Severe bilateral foot pain**
 - Burning, numbness and tingling
 - Pain worse at night, trouble sleeping because of pain

On a scale of 0-10



Michelle states
her pain is **"20"!**

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Building Trust: Patient Issues

Patients may assume that you do not believe the severity of their pain complaints



Demonstrated by **exaggerating pain scores** and **functional limitations**

Upshur C et al, *Pain Med.* 2010

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Building Trust: Clinician Issues

After completing a thorough pain hx, focused exam, and appropriate diagnostic testing...

Show empathy...clinician empathy is associated with better chronic pain outcomes

"I hear how much this pain is affecting your life."

"I can see how hard you are trying to manage this pain."

Validate that you believe the patient's pain and suffering is real...

"I hear how much pain you are in, and I believe you."

"Your pain is real; we will figure this out together."

Believing the severity of a patient's pain report
does not mean opioids are indicated

Licciardone JC et al. *JAMA Network Open*. 2024
Lozano PM et al. *J Pain*. 2025

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Chronic Pain Assessment



Unidimensional Scales

- ☐ (e.g., Numeric rating) are of limited value for assessing chronic pain

Multidimensional Instruments

- ☐ McGill Pain Questionnaire
 - ☐ Graded Chronic Pain Scale
 - ☐ Brief Pain Inventory
- Impractical for use in most primary care settings

Brief Multidimensional Tool

Pain, Enjoyment, General Activity (PEG) Scale

1. What number best describes your <u>pain on average</u> in the past week:										
0	1	2	3	4	5	6	7	8	9	10
No pain						Pain as bad as you can imagine				
2. What number best describes how, during the past week, pain has interfered with your <u>enjoyment of life</u> ?										
0	1	2	3	4	5	6	7	8	9	10
Does not interfere						Completely interferes				
3. What number best describes how, during the past week, pain has interfered with your <u>general activity</u> ?										
0	1	2	3	4	5	6	7	8	9	10
Does not interfere						Completely interferes				

Breivik H, et al. *Br J Anaesth*. 2008
Salaffi F, et al. *Best Pract Res Clin Rheumatol*. 2015

Krebs EE, et al. *J Gen Intern Med*. 2009
Reed II DE, et al. *J Pain*. 2024

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Case Study – Michelle Jones – 54 yo female



In the past week...

PEG Scale Assessment

Pain on average?

0 1 2 3 4 5 6 7 8 9 10

No pain As bad as you can imagine

Pain interfered with Enjoyment of life?

0 1 2 3 4 5 6 7 8 9 10

Does not interfere Completely interferes

Pain interfered with General activity?

0 1 2 3 4 5 6 7 8 9 10

Does not interfere Completely interferes

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Case Study – Michelle Jones – 54 yo female



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How will you manage this patient's chronic pain?

Physical Examination

- No acute distress
- Normal vitals, weight 193 lbs (BMI 32)
- Musculoskeletal exam normal except right hip with decreased internal rotation
- Neuro-motor exam normal except absent Achilles tendon reflex bilaterally
- Diabetic foot exam:
 - No lesions, normal pulses
 - Loss of protective sensation by monofilament test

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Goals of Care and Multimodal Approach



***Self-management** is a patient-centered, multimodal approach (physical, emotional, and cognitive strategies) that reduces the impact of pain and improves function by transitioning patients from passive treatment recipients to active partners of their care.

Hestmann R, et al. *BMC Health Serv Res.* 2023
Kang Y, et al. *BMJ.* 2024

Henry SG, et al. *Clin J Pain.* 2017
Elbers S, et al. *Eur J Pain.* 2022

Connell NB, et al. *J Gen Intern Med.* 2022
Wang Y, et al. *Cell Rep Med.* 2025

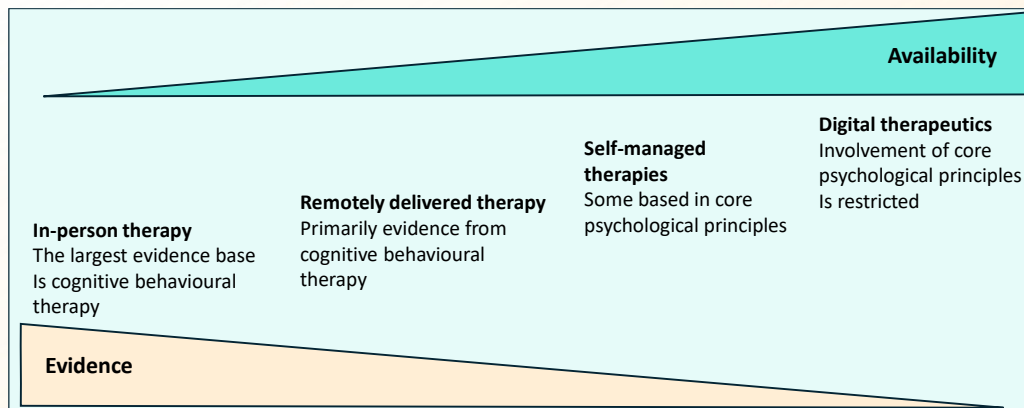
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Behavioral Interventions

CBT, ACT, Mindfulness-Based Stress Reduction, Pain Reprocessing, Biofeedback & Relaxation

- Targets cognitive, emotional, and behavioral factors contributing to pain
- Mitigate psychological distress: reframe maladaptive pain beliefs, reduce catastrophizing/rumination, correct somatic misinterpretations, and downregulate central threat perception



Vase L, et al. *Lancet.* 2025

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Behavioral Interventions

CBT, ACT, Mindfulness-Based Stress Reduction, Pain Reprocessing, Biofeedback & Relaxation



- High-quality evidence demonstrate reduced pain, catastrophizing, and emotional distress, improvements in functioning and coping that match or exceed the benefits of many medications

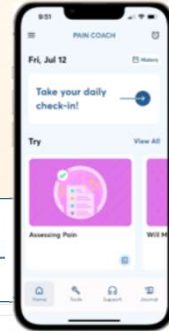


- Mobile health apps (e.g., mindfulness, relaxation, reframing, pacing, goal setting), many free (e.g., *VA Pain Coach app*, *Manage My Pain app*), some require subscription or paid version with more features
- Finding health psychologists: hospital-affiliated clinics, insurance plan, Psychology Today (www.psychologytoday.com/us), Society of Behavioral Medicine



Psychology Today

Therapists City, Zip or Name



Kerns RD, et al. *Pain Med.* 2022
Vase L, et al. *Lancet.* 2025
Kang Y, et al. *BMJ.* 2024

Ziadni MS, et al. *J Pain.* 2026
APA. *Clinical Practice Guideline.* 2024

Skelly AC, et al. *AHRQ.* 2020
Eagle H, et al. *Clin J Pain.* 2026

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Physical and Restorative Approaches

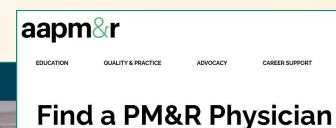
Physiatrists (PM&R), Osteopathic Physicians, PT, OT, Chiropractors



- Mechanical interventions to optimize neuromusculoskeletal function targeting physical forces, tissue manipulation, and biomechanical training
- Evidence for improving pain and function: strongest with therapeutic structured exercise, moderate evidence for spinal manipulative therapy, and weaker evidence for standalone passive treatments (e.g., massage)



- Use professional medical directories and search tools dedicated to each specific practice type, insurance plans



Find a Board-Certified Physical Therapist Specialist

Skelly AC, et al. *AHRQ.* 2020
Trager RJ, et al. *J Clin Med.* 2024
González-Gómez L, et al. *Eur J Pain.* 2025

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Integrative Medicine Approaches

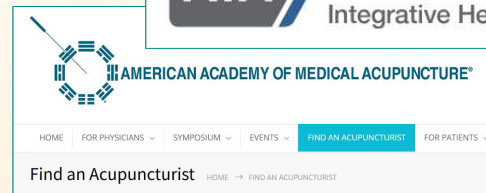
Acupuncture, Mind-Body Practices, Movement Therapies (Tai Chi, Qigong, Yoga)



- Whole-person approaches to address the biological, psycho-social, and environmental factors contributing to a patient's pain experience
- Systematic reviews and meta-analyses of RCTs show moderate, clinically meaningful improvements in pain and function with strong safety profile



- Hospital departments of Integrative Medicine, local licensed acupuncturists, board-certified integrative physicians, insurance plans



Nahin RL, et al. JAMA. 2024
Seal KH, et al. JAMA. 2026

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Case Study – Michelle Jones – 54 yo female



How will you respond to her concerns about nonpharmacologic approaches?



Plan of Care

- You discuss the importance of self-management and the benefits of nonpharmacologic treatments.
- She responds by saying...
 - “You don’t believe me, you think my pain is all in my head”
 - “I have tried these other things and they didn’t work...some made my pain worse...they were a waste of time”

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Discussing Nonpharmacologic Options

- “Seeing a psychologist doesn’t mean that your pain is not real, pain changes the nervous system, making the brain’s ‘amplifier’ too sensitive, and this therapy will teach the brain how to quiet down pain signals. Psychologists are experts in the brain.”
- “Carefully guided movement actively repairs your body, so the soreness you feel during rehab is actually a safe sign that your body is adapting and getting stronger—not causing damage. You can use quick relief options like ice or heat to ease any discomfort and to help you get moving.”
- “Exploring integrative treatments does not mean your pain isn’t serious, nor does it mean conventional medicine is giving up on you. Instead, these therapies work hand-in-hand with your medications and other treatments to help your body heal and become stronger.”



Braverman MT, Volmar KM, Govier DJ. *Am J Health Promot.* 2023

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Case Study – Michelle Jones – 54 yo female



What are your medication options for treating her chronic pain?



- She reluctantly agrees to read about self-management strategies and see a psychologist for behavioral approaches
- You tell her that you will review the medications she is taking and those she has tried in the past to determine if there are any improvements that can be made

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Non-Opioid Pharmacotherapies

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

- Nonselective and selective COX-2 inhibitor (celecoxib)
- Anti-inflammatory, analgesic, antipyretic
- Adverse effects (GI, renal, CV) especially at high doses

Acetaminophen (APAP)

- Analgesic, antipyretic
- Less effective than full dose NSAIDs in relieving chronic pain
- Fewer adverse effects than NSAIDs

General Considerations

- Ceiling analgesic effects
- No known analgesic tolerance
- Additive role (NSAID+APAP)
- Some patients may respond better to one NSAID than another

Med Lett Drugs Ther. 2022
Finnerup NB. N Eng J Med. 2019

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Non-Opioid Pharmacotherapies

• Analgesics with primary indication other than pain

- **Antidepressants** (TCAs, SNRIs)
- **Anticonvulsants** (gabapentinoids, carbamazepine)
- **Antispasmodics/muscle relaxants**
- **Local anesthetics** (lidocaine)

} Mainstay of pharmacologic treatments for neuropathic and nociplastic pain syndromes



Caution:

- Misuse and addiction potential with:
 - Gabapentinoids (gabapentin, pregabalin)
 - Muscle relaxants (carisoprodol metabolizes into meprobamate (barbiturate-like drug))
- Additive burden of anticholinergic side effects (e.g., TCAs, cyclobenzaprine)

Med Lett Drugs Ther. 2022
Finnerup NB. N Eng J Med. 2019

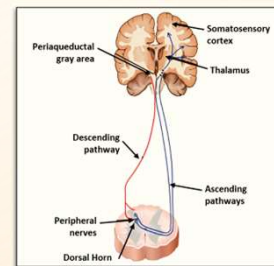
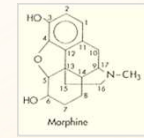
Evoy KE et al. Drugs. 2021
Hill J, Alford DP. Semin Neurol. 2018

46

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Opioid Analgesics

- **Classification**
 - **Opiates** (e.g., morphine, codeine)
 - **Semisynthetic opioids** (e.g., oxycodone, hydrocodone, buprenorphine)
 - **Synthetic opioids** (e.g., fentanyl, methadone)
- **Analgesic mechanisms of action**
 - Turn on descending inhibitory systems (periaqueductal gray) and prevent ascending transmission of pain signal
 - Inhibit activation of C-fibers and the peripheral nociceptors
- **Activate the reward pathway → euphoria**
- **Not all patients respond to the same opioid in the same way**
 - Variability driven by μ -receptor polymorphisms and single nucleotide polymorphisms (SNPs) influencing metabolism, transport, and receptor kinetics
 - Pharmacogenomic (PGx) profiles not routinely used due to cost and lack of coverage

Ren Z et al. *Pain Physician*. 2015Somogyi AA, et al. *Anaesth Intensive Care*. 2022Crews KR, et al. *Clin Pharmacol Ther*. 2021

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Opioid Tolerance & Physical Dependence



Both tolerance and physical dependence are physiological adaptations to chronic opioid exposure



Tolerance:

- Increased dosage needed to produce specific effect
 - Develops readily for CNS and respiratory depression
 - Less so for constipation
 - **Unclear about analgesia**



Physical Dependence:

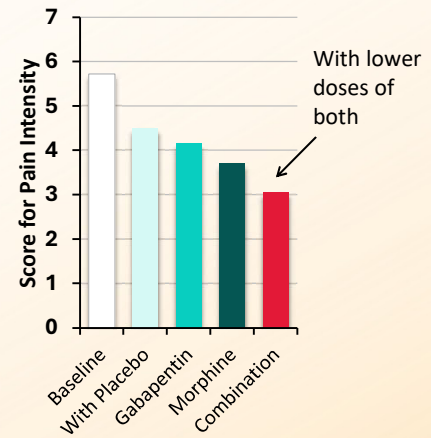
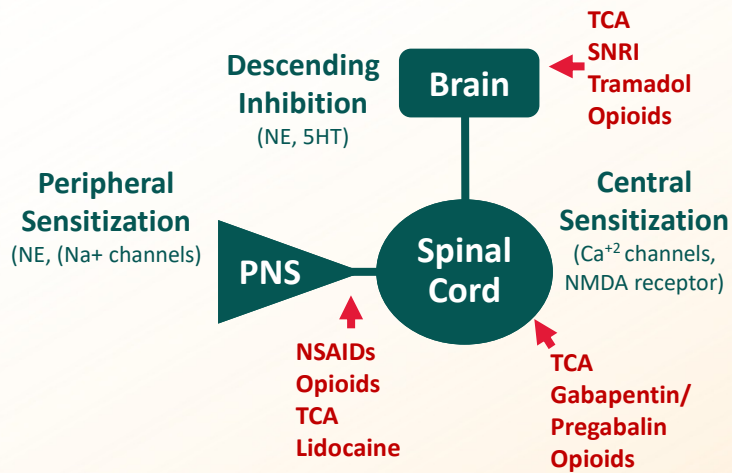
- Signs and symptoms of withdrawal by abrupt opioid cessation, rapid dose reduction or exposure to an opioid antagonist (e.g., naloxone, nalmefene)

48

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Rational Polypharmacy

Exploit Synergism



Finnerup NB. *N Eng J Med.* 2019
Woolf CJ. *Ann Intern Med.* 2004

Gilron I, et al. *N Engl J Med.* 2005

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Opioid Efficacy and Safety

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Opioid Efficacy for Chronic Pain



Meta-analyses (3-6 m f/u)

- **Opioids vs placebo**
(high-quality studies)
Opioids with statistically significant, but small, improvements in pain^{1,2} and physical functioning²
- **Opioids vs nonopioids**
(low-mod quality studies)
Similar benefits²

1. Meske DS, et al. *J Pain Res.* 2018
2. Busse JW, et al. *JAMA.* 2018

RCT³ found opioids **not superior** to nonopioids for improving musculoskeletal pain-related function over 12 months

*Limitations to generalizability:*⁴

- Excluded patients already on long-term opioids

3. Krebs EE, et al. *JAMA.* 2018
4. Webster L. *Pain Med.* 2019

Two longer term follow-up studies found **44.3%** on chronic opioids for chronic pain had **at least 50% pain relief**⁵

5. Noble M, et al. *Cochrane Syst Rev.* 2010

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Opioid Safety and Risks

Allergies: Rare

Immunosuppression

Animal models, opioid induced immuno-suppression

Humans increased risk invasive pneumococcal disease, and community acquired pneumonia

Diaso PD, et al. *Eur J Pain.* 2019
Wiese AD, et al. *Ann Intern Med.* 2018
Edelman EJ, et al. *JAMA Intern Med.* 2019
Kotlińska-Lemieszek, A et al. *Drug Des Devel Ther.* 2024

Organ Toxicities

Suppression of the hypothalamic-pituitary-gonadal and adrenal axes

- Menstrual irregularities, reduced fertility, erectile dysfunction
- Osteoporosis, fatigue
- Obesity, metabolic syndrome

Adverse Effects

Nausea, sedation, urinary retention, sweating

Constipation: (hypodynamic bowel, dry stool)

Pruritus (histamine release)

Respiratory depression → Death

Report AE to FDA 1-800-FDA-1088, www.fda.gov

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Managing Opioid Adverse Effects

Nausea and Vomiting

- Usually resolves in a few days
- Antiemetics, switch opioids

Sedation

Mostly during initiation or change in dose

- **Decrease dose**

Constipation

Most common and should be anticipated

- Stool softeners, osmotic stimulants
- Peripherally-acting opioid antagonists
- Switch opioids, avoid bulking agents

Pruritus

- Switch opioids
- Antihistamines

Urinary Retention

- Switch opioids

Paul AK, et al. *Pharmaceuticals*. 2021
Hanson B et al. *Gastroenterology*. 2019

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Opioids & Patient Considerations

Age



- Decline in therapeutic index and predisposition to adverse drug effects
- Fall risk, worsening cognitive function

Medical Co-morbidities



- **Liver disease:** decreased opioid clearance
 - Morphine, oxycodone, hydromorphone: reduce doses and prolong dosing intervals



- **Kidney disease:** decreased opioid excretion
 - Preferred are hydromorphone, fentanyl, buprenorphine, methadone
 - Caution with oxycodone, morphine due to active metabolites

Pregnancy



- Risk of neonatal opioid withdrawal syndrome (NOWS)
- All opioids transfer into human milk to some degree

Hamilton JP. *Gastroenterol Hepatol*. 2023
Rajput K, Ng J, et al. *Anesthesiol Clin* 2023

Esposito DB, et al. *JAMA Network Open*. 2022
Odoma VA, et al. *Cureus*. 2023

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Opioids: Drug-Drug Interactions (DDI)

- Significant DDI can occur between opioids and drugs that affect the opioid metabolism
- DDI often arise due to inhibition or induction of **cytochrome P450** (CYP450)
 - **Opioids metabolized by CYP450:** DDIs can reduce or increase opioid effects (e.g., codeine, oxycodone, hydrocodone, fentanyl, tramadol, methadone)
 - **Opioids not metabolized by CYP450:** fewer DDIs (e.g., morphine, hydromorphone)
- CNS depressants (benzodiazepines, alcohol, cannabis, other sedatives, hypnotics, TCAs) may potentiate opioid effect on sedation and respiratory depression
- Alcohol may rapidly release opioid (dose dump) or increase drug levels w/out dose dumping



Recommendation 11

Use caution when concurrently prescribing opioids and benzodiazepines (and other CNS depressants)

Dowell D, et al. MMWR. 2022

Kotlinska-Lemieszek A, et al. *Drug Des Devel Ther.* 2015
Coates S, Lazarus P. *J Pharmacol Exp Ther.* 2023

55

55

Problematic Opioid Use

Systematic review and meta-analysis

- 148 studies, 4.3 millions participants - chronic pain treated with long-term opioids
- Settings: pain clinics, primary care, other specialty clinics

Aberrant Behavior: 29.6%

(95%CI: 22.1% - 38.3%)

Worrisome behaviors including early refills, repeated dose escalations, lost prescriptions, seeking meds from multiple prescribers, unexpected urine drug test results

Opioid Use Disorder: 9.3%

(95% CI: 5.7% - 14.8%)

Based on DSM or ICD diagnostic criteria/codes

Thomas KH, et al. *Addiction.* 2024

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Collateral Opioid Risk



Risks

- Young children's ingestion and overdose*
- Adolescent experimentation leading to overdose and addiction
- Other household contacts (family, visitors)

Mitigating risk

- Safe storage (e.g., lock box)
- Child resistant packaging
- Mail-back envelopes: REMS Program Companies to provide pre-paid drug mail-back envelopes to pharmacies and other dispensers
- Safe disposal www.deadiversion.usdoj.gov/drug_disposal/
- Overdose education and naloxone distribution www.prescribetoprevent.org



Gaither JR, et al. *JAMA Pediatr.* 2016
 Beletsky L, Rich JD, Walley AY. *JAMA* 2012
 SAMHSA *Opioid Overdose Prevention Toolkit* 2018
 Bonomo Y, Hogg M. *Pain Manag Today.* 2023



Recommendation 8

Use strategies to mitigate risk including naloxone co-prescribing

Dowell D, et al. *MMWR.* 2022

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Higher Dose Opioids

Lack of high-quality evidence about the efficacy of high-dose opioids for chronic pain

Higher doses associated w/:

- Immunosuppression
- Hyperalgesia
- Reduced function
- **Overdose risk increased**
 - 2X at 20-49 MME (Morphine Mg Equivalent)
 - Up to 9X at ≥ 100 MME

Patient on high doses...

- Manage as higher risk
- Increase monitoring and support



Recommendation 4

- When starting, prescribe lowest effective dosage
- Use caution at any dosage
- Carefully evaluate benefits and risks when considering increasing dosage
- Avoid increasing dosage above levels w/ diminishing benefit relative to risk

Dowell D, et al. *MMWR.* 2022

Els C, et al. *Cochrane Reviews* 2023
 Kobus AM, et al. *J Pain.* 2012
 Huxtable CA, et al. *Anaesth Inten Care.* 2011
 Brush DE. *J Med Toxicol.* 2012

Lee M, et al. *Pain Physician.* 2011
 Braden JB. *Arch Intern Med.* 2010
 Paulozzi LJ. *Pain Med.* 2012
 Edelman EJ, et al. *JAMA Int Med.* 2019

Dunn KM, et al. *Ann Intern Med.* 2010
 Bohnert AS, et al. *JAMA.* 2011
 Zedler B et al. *Pain Med.* 2014
 Gomes T, et al. *Open Med.* 2011

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Opioid-Related Harms

?

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Risk Factors for Opioid-Related Harm

(misuse, overdose, addiction)



Medication Factors	Patient Factors
Higher opioid dose	Mental health disorder (e.g., depression, anxiety)
Long-term opioid use (>3 months)	Substance use disorder (SUD) (e.g., alcohol, tobacco, illicit and prescription drug)
Extended release/long-acting (ER/LA) opioid	Family history of SUD
Initial 2 weeks after starting ER/LA opioid	History of opioid overdose
Combination opioids and sedatives (e.g., benzodiazepines)	Sleep-disordered breathing

Liebschutz JM, et al. *J Pain*. 2010
Weiner SG, et al. *JAMA Network Open*. 2022
Han B, et al. *J Clin Psychiatry*. 2024

Volkow ND, et al. *N Engl J Med*. 2016
Kendler KS, et al. *Psych Med*. 2023
Thomas AT, et al. *Pain Physician*. 2022

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Screening for Sleep-Disordered Breathing

STOP-BANG Questionnaire

STOP

- Do you **SNORE** loudly?
- Do you often feel **TIRED**, fatigued, or sleepy during daytime?
- Has anyone **OBSERVED** you stop breathing during your sleep?
- Do you have or are you being treated for high blood **PRESSURE**?

BANG

- BMI** more than 35?
- AGE** over 50?
- NECK** circumference (males: 17+ inches; females: 16+ inches)?
- GENDER** male?



Sleep Apnea Risk	Total Score
High Risk	5-8
Intermediate Risk	3-4
Low Risk	0-2

Chung F et al. *Anesthesiology* 2008
Feltner C et al. *JAMA*. 2022

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Assess for Opioid Misuse Risk Prior to Prescribing

Check for Prior History of Opioid Misuse

Check medical records and speak to prior PCP and co-care providers for any history of loss of control, compulsive use, continued use despite harm

Verify Substance Use and Medication History

Check urine drug test and prescription drug monitoring program

Screening Tools

(no gold standard, lack of high-quality evidence supporting use)

ORT: Opioid Risk Tool
DIRE: Diagnosis, Intractability, Risk, Efficacy
SOAPP: Screener and Opioid Assessment for Patients with Pain
STAR: Screening Tool for Addiction Risk
STORM: VA Stratification Tool for Opioid Risk Mitigation
BRQ: Brief Risk Questionnaire
PMQ: Pain Medication Questionnaire
Others...

Moore TM, et al. *Pain Med*. 2009
Klimas J et al. *JAMA Network Open*. 2019

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Case Study – Michelle Jones – 54 yo female



What are your medication options for treating her chronic pain?



- Michelle screened negative for sleep disorder breathing
- She has several opioid misuse risk factors including:
 - Long-term opioid therapy
 - Personal history of depression and anxiety
 - Family history of substance use disorder

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Opioid Therapy from Previous Clinician

“Legacy Patients” “Opioid Orphans”

- Review the patient history from medical records and with the former clinician, if possible
- Review prescription history (e.g., Prescription Drug Monitoring Program)
- Assess the patient for opioid use disorder and treat or refer to specialty care, if indicated
- Consider a therapeutic bridge for the patient until a plan of care is determined given the risks associated with stopping opioid therapy abruptly
- Document rationale for treatment plan and next steps

Coffin PO, et al. *N Engl J Med.* 2022



Recommendation 5

For patients already on opioids, carefully weigh benefits and risks

- If benefits > risks, continue opioids and optimize other therapies
- If risks > benefits, optimize other therapies, gradually taper opioids to lower dosages
- Unless life-threatening issue (i.e., impending overdose), do not abruptly reduce opioids from higher dosages

Dowell D, et al. *MMWR.* 2022

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Case Study – Michelle Jones – 54 yo female

PDMP showed
oxycodone 10 mg
#120 tablets per
month with one
prescriber and one
pharmacy, last filled
7 weeks ago



At 1st visit

- Sent urine drug test (UDT)
- Obtained release to contact previous PCP
- Prescribed oxycodone 10 mg 4x/day x 2 weeks (#56)
- Continued gabapentin 300 mg 3x/day
- Added APAP 500 mg 4x/day to be taken with the oxycodone
- Referred to a local psychologist, given self-management handout

Before 2nd visit

- Reviewed previous medical records
 - Problem and medication lists reconciled
 - Inadequate documentation about benefits (e.g., pain, function) or monitoring (e.g., UDT) BUT no evidence of worrisome behaviors (e.g., early refills)

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Questions for Next Visit



Clinician Concerns:

- Should I continue the opioid?
- Should I change the opioid dose?
- Should I change to an ER/LA opioid?
- What about any other adjuvant medications or therapies?
- What sort of treatment plan should I develop for her chronic severe pain including co-managing her depression and anxiety?

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Summary Part 1



- Focus on reducing pain, improving coping, restoring function, cultivating wellbeing, and maximizing quality of life
- Build strong therapeutic alliance to improve treatment adherence and clinical outcomes
- Utilize validated, multidimensional instruments to evaluate the full impact of chronic pain
- Use self-management strategies with nonpharmacologic therapies and targeted combined pharmacologic options
- Routinely assess and comanage co-occurring mental health conditions
- Prescribe opioids judiciously while assessing all patients for opioid misuse risk

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Part 2: Safer Opioid Prescribing

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Case Study – Michelle Jones – 54 yo female



Should opioids be
continued?
If so, should the
opioid be changed?



In the interim...

- Unable to contact previous PCP who retired
- UDT positive for oxycodone only (as expected)

Office Visit 2

- PEG scores:
 - “6 out of 10” after oxycodone dose
 - “9 out of 10” right before next oxycodone dose
- Denied sedation
- Completed 2-week oxycodone prescription on schedule
- Did not make appointment with psychologist

2

2

When Might Opioids be Indicated?



Opioids should not be first choice

- Pain is severe and has significant impact on function and quality of life
- Expected benefits for pain and function outweigh the potential severe risks
- Pain type is potentially opioid-responsive (e.g., nociceptive > nociplastic)
- Patient agreeable to safety monitoring and risk mitigation practices
- Non-pharmacological and non-opioid therapies have proven insufficient
- **If already taking opioids, is there documented benefit and absence of harm**



Recommendation 2

- Maximize non-pharmacologic and non-opioid therapies
- Only consider opioids if expected benefits (pain/function) > risks
- Before starting opioids discuss realistic benefits and known risks
- Establish treatment goals and how opioids will be discontinued if benefits < risks

Chou R, et al. *Ann Intern Med.* 2015
 Dowell D et al. *N Engl J Med.* 2022
 Reuben DB, et al. *Ann Intern Med.* 2015
 Volkow ND, McLellan T. *N Engl J Med.* 2016

Dowell D, et al. *MMWR.* 2022

3

3

Opioid Choices

Immediate Release/ Short-acting (IR/SA)

- Morphine
- Hydrocodone
- Hydromorphone
- Oxycodone
- Oxymorphone
- Tramadol
- Tapentadol
- Buprenorphine (buccal)
- Fentanyl (transmucosal)
- Codeine

Extended Release/ Long-acting (ER/LA)

- Morphine
- Hydrocodone
- Hydromorphone
- Oxycodone
- Oxymorphone
- Tramadol
- Tapentadol
- Buprenorphine (transdermal)
- Fentanyl (transdermal)
- Methadone

Product-specific information: <http://dailymed.nlm.nih.gov/dailymed>; pharmacy medication guide;
www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass

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Choosing IR/SA vs ER/LA Opioids



IR/SA Opioids

- No opioid tolerance/opioid naïve
- Intermittent or occasional pain (PRN dosing)



Recommendation 3

When starting opioids, use IR/SA instead of ER/LA opioids

Dowell D, et al. MMWR. 2022

ER/LA Opioids

- Opioid tolerance exists
- Constant, severe, around-the-clock pain (scheduled dosing)
- To stabilize pain relief when patient using multiple doses of IR/SA opioids
- **MUST NOT be broken, chewed or crushed**

Uncertainties about comparative effectiveness and safety (IR/SA vs ER/LA)

- Choose option that best meet patient's needs

Always
start low
and
go slow

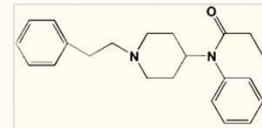


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Transdermal Fentanyl

- 100 times more potent than morphine, dosed in mcg
- Slow peak onset (12-24h) and delayed offset (12-24h)
- Sustained release requires predictable blood flow and adequate subcutaneous fat
 - Applied to intact, clean and healthy skin (chest, back, arms)
 - Absorption increased with fever or broken skin
 - Absorption decreased with edema
- Replace patch q72h to a different location
- Fully used patches contain 20-60% of original dose requiring safe disposal (FDA: fold with sticky sides together, flush them down a toilet)
- May need to remove before MRI, some with metal foil backing causing burns



Fentanyl

- Every 72 hours
- Dosages (mcg/hr): 12, 25, 37.5, 50, 62.5, 75, 87.5, 100

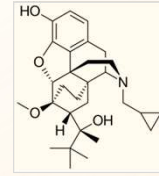
Fu Q, et al. *Drug Des Devel Ther.* 2024
Taylor KP, et al. *StatPearls.* 2023

6

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Buprenorphine for Pain

- Formulations approved for pain (mcg) or opioid use disorder (mg)
- 25-40 times more potent than morphine
- Poor oral bioavailability due to hepatic first pass metabolism
- Mu opioid receptor agonist
 - High affinity and slow dissociation can precipitate opioid withdrawal if full opioid agonist highly bound
 - Partial agonist w/ ceiling effect on respiratory and CNS depression
 - Acts as full agonist for analgesia
- Kappa and delta opioid receptor antagonism:
 - Antihyperalgesia and anxiolytic effects
- Can prolong QTc interval
- Less effects on cognitive/psychomotor function and hypogonadism compared to other opioids



Taper prior opioid to <30 MME before starting buprenorphine

Buccal film 75-900 mcg q12-24

- Do not cut, chew or swallow

Transdermal patch 5-20 mcg/hr q 7 days, 72 hrs to achieve steady state

- (mcg/hr): 5, 7.5, 10, 15, 20 (max)
- Rotate sites wait min 3 wks before using same site

Vu PD et al. *Curr Pain Headache Rep.* 2023
Spinella S, McCarthy R. *Am J Med.* 2024

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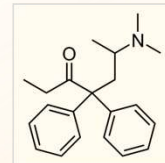
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Methadone for Pain

- Complex pharmacology causing unique risks
- Long, variable, unpredictable $t_{1/2}$ - extensive plasma protein binding
 - Analgesia 6-8 hours while serum $t_{1/2}$ 20-120 hours
- QTc prolongation, risk of torsades de pointes

Some possible advantages:

- NMDA receptor antagonist resulting in reduced hyperalgesia and analgesic tolerance
- Inhibits serotonin and norepinephrine reuptake making it efficacious for neuropathic pain
- No active metabolites
- Inexpensive, small dosage units (scored 5mg tablets)



Hanna V, Senderovich H. *J Pain.* 2021
Brown P, et al. *Health Psychol Res.* 2025

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Dual Mechanism Opioids

Norepinephrine and Serotonin reuptake inhibition

Tramadol

Weak μ -opioid receptor agonist
Minimal norepinephrine effect
Prominent serotonin effect

Tapentadol

Stronger μ -opioid receptor agonist
Prominent norepinephrine effect
Minimal serotonin effect



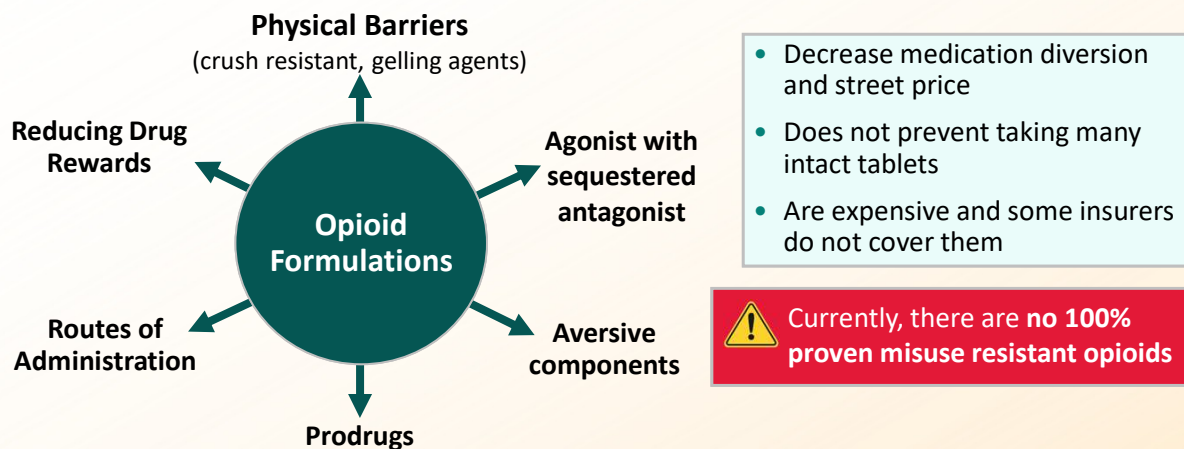
Seizure risk
Physical dependence
Serotonin syndrome
Controlled substances with addiction potential

Zavaleta-Monestel E, et al. *Cureus*. 2024
Seidmohammadi K, et al. *J Pain Palliat Care Pharmacother*. 2025

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Formulations with Abuse Deterrent Properties



Updated list of abuse-deterrent opioids: www.fda.gov/drugs/drugsafety

Webster L, Gudlin J. et al. *J Pain Res*. 2024

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Individualizing Opioid Choice

- Duration and onset of action
 - Consider pattern of pain: intermittent vs. constant
- Patient's prior experience (effects & side effects)
 - Mu-opioid receptor polymorphisms and differences in opioid metabolism
- Patient's level of opioid tolerance (always assess before starting ER/LA opioid formulations)
- Age, other medications and health conditions
- Route of administration
- Cost and insurance issues



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Case Study – Michelle Jones – 54 yo female

Over the ensuing months patient reported better pain control



Change Opioid Regimen

- Tolerates IR oxycodone 10 mg 4x/day (60 MME) but...
 - Periodicity of effects (on-off) may be causing inadequate pain control due to "withdrawal-mediated pain"
 - Analgesia may improve with more stable blood levels using ER/LA oxycodone requiring a lower daily dose (15 mg 2x/day) (45 MME)
 - Don't assume need for breakthrough medication
- Reviewed, signed Patient Provider Agreement (PPA)
- Re-reviewed importance of self-management and behavioral therapy for her pain
- Referred to PT for chronic right hip pain
- Counseled on weight loss

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Universal Precautions



Predicting opioid risk and misuse is imprecise

Consistent application of precautions reduces stigma and standardizes care

Precautions include:

- Assess and document pain diagnosis(es) and opioid misuse risk
- **Prescribe opioids as a test or trial**; continued, modified or discontinued based on risks/benefits (e.g., every 1-3 months)
- State maximum number of tablets to be taken per day
- Use Patient Prescriber Agreements written at 5th grade level, without coercive language
- Monitor for adherence, misuse, and diversion



Recommendations 7 & 10

Evaluate benefits and risks 1-4 weeks of starting opioids or after dose escalation and then regularly

Use strategies to mitigate risk including toxicology testing

Dowell D, et al. MMWR. 2022

Gourlay DL, Heit H. *Pain Med.* 2005
Chou R, et al. *J Pain.* 2009

Franklin GM. *Neurology.* 2014
Laks J, et al. *J Gen Intern Med.* 2021

FSMB 2024 www.fsmb.org/opioids/

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Patient Provider Agreement (PPA)



Informed Consent

Realistic Goals

- Reduce (*not eliminate*) pain
- Improve function

(SMART goals):

Specific
Measurable
Action-oriented
Realistic
Time-sensitive

Potential Risks

- Adverse effects and DDI
- Over-sedation, impairment (esp. during dose adjustments)
- Misuse
- Overdose & Death
- Risk of neonatal opioid withdrawal syndrome
- Hyperalgesia
- Victimization by others

Plan of Care

- Engage in other treatments as directed
- Safer opioid use: take as directed, don't double dose if dose missed, safe storage/disposal, no sharing
- No illicit drugs, avoid/minimize sedatives
- Report other meds, adverse effects
- Discuss pregnancy plans, risks and monitor

Tobin DG, et al. *Cleve Clin J Med.* 2016
Nicolaidis C. *Pain Med.* 2011
Paterick TJ, et al. *Mayo Clin Proc.* 2008

Mailis-Gagnon A, et al. *Clin J Pain.* 2012
Cheatle MD, Savage SR. *J Pain Symp Manage.* 2012
Tolia VN, et al. *N Engl J Med.* 2015

Schumacher MB, et al. *Psychopharm.* 2017
Hale TW, Krutsch K. *Clin Pharmacol Ther.* 2021

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Monitoring: Urine Drug Testing

Objective data

- Information on therapeutic adherence
- Information on use of illicit drugs



- Document time of last medication use
- Discuss urine drug testing openly with patient → "If I send your urine now, what will I find in it?"
- Discuss unexpected findings with open-ended questions → "Your urine had 'x' please tell me about it?"
- One medical data point to integrate with others
- **Urine drug screen** usually immunoassays (quick, inexpensive, risk of false negatives and false positives)
- **Definitive testing** w/ *GC-MS or LC-MS (know opioid metabolites e.g., hydrocodone→hydromorphone)

*Gas Chromatography (GC) or Liquid Chromatography (LC), and Mass Spectroscopy (MS)

Contact lab toxicologist for questions regarding unexpected results

Argoff CE, Alford DP, Fudin J et al. *Pain Med.* 2018
Nagpal G et al. *JAMA.* 2017

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Monitoring: Medication Count & Prescription Drug Monitoring Program (PDMP)

Medication Count

Information on

- Medication adherence
- Possible diversion

28-day (vs 30-day) decreases risk of running out on weekends and medication hoarding



Recommendation 9

Use strategies to mitigate risk including reviewing PDMP data

Dowell D, et al. MMWR. 2022

PDMP

Information on

- Harmful polypharmacy
- Multiple prescribers

Some states:

- require utilization of PDMP
- allow delegating access to others
- have interstate data sharing

Methadone administered or dispensed at opioid treatment programs not routinely included

Insufficient evidence that PDMPs increase or decrease opioid overdoses

Fink DS, et al. *Ann Intern Med.* 2018

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Monitoring Based on Risk

Universal precautions applied individually to match risk

- Review personal and public health (community) risks of opioids
- Discuss monitoring is to protect patient from harm

One example: (www.opioidresources.org)

Opioid Misuse Risk Level	Visits/year	UDT & PDMP checks/year
Low-Moderate Risk	4	2-4
High Risk	6	6

- State laws may mandate certain levels of monitoring
- Monitoring more intensive during first 6 months of therapy and after change in treatment plan

Liebschutz JM, et al. *JAMA Intern Med.* 2017

17

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Documentation

Study using National Ambulatory Medical Care Survey data found that in visits when an opioid was prescribed, **30% had no pain diagnosis**

Six A's

Analgesia

Activities

Adverse effects

Aberrant behaviors

Affect

Adherence

Include:

- **Subjective reports** from patient, co-care providers, caregivers, "reliable" family members (beware of those with secondary gain for giving inaccurate information)
- **Objective information** (observations, PEG scores, drug tests, pill counts, PDMP)
- **24-hour inventory** "Tell me how you are taking your medications." "Do you miss doses on some days?" "On average how many doses do you take per day?"

Sherry TB, et al. *Ann Intern Med.* 2018

Passik SD, et al. *Clin Ther.* 2004

Know federal and state guidelines and regulations: www.deadiversion.usdoj.gov/pubs/manuals/index.html
 Templates in Resources at: www.scopeofpain.org and www.opioidresources.org

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Safer opioid prescribing is a lot of work!

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What is the Clinician's Role?

Use a risk-benefit
framework

Judge the opioid treatment,
not the patient



NOT



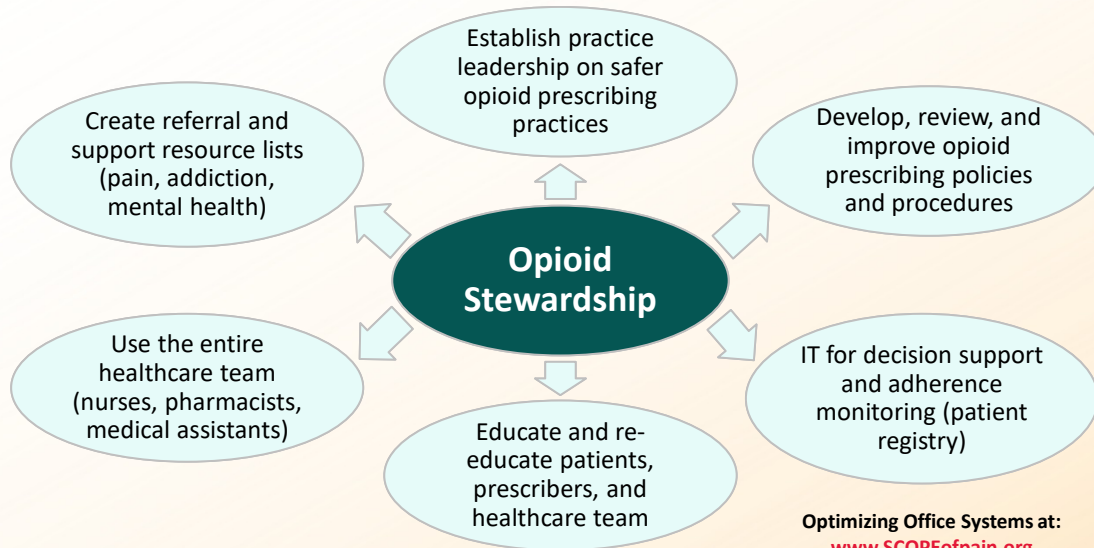
Nicolaidis C. *Pain Med.* 2011

20

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Implementing Opioid Stewardship

Prescribing opioids safely, correctly, and under the right circumstances



MacIntyre PE, et al. *JAMA Surg.* 2022

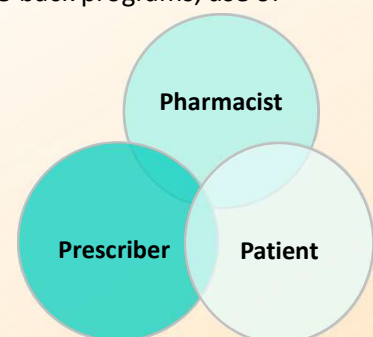
Optimizing Office Systems at:
www.SCOPEofpain.org
 click on: Supplemental Training

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Community Pharmacist

- Pharmacist must ensure that prescriptions are for “legitimate medical purpose”
- Help with medication choices, doses and substitutions
- Interact with patients
 - Educate on risks, proper use, storage and disposal, drug take-back programs, use of naloxone
 - Check PDMP, monitor for worrisome behaviors
 - Identify potential drug-drug interactions
 - Assist with formularies and prior authorizations
- Prescribers can help by including:
 - Diagnosis or indication on prescription
 - Parameters for when script should be filled
 - Maintain open lines of communication (direct phone lines)



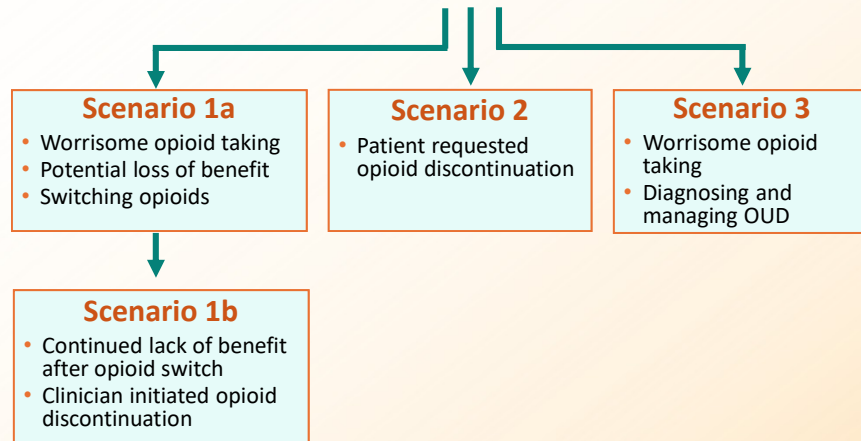
Compton WM et al. *Res Soc Adm Pharm.* 2019

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Case Study – Michelle Jones – 54 yo female

Did well on regimen of ER/LA oxycodone 15 mg bid with gabapentin 300 mg 3x/day for 11 months...

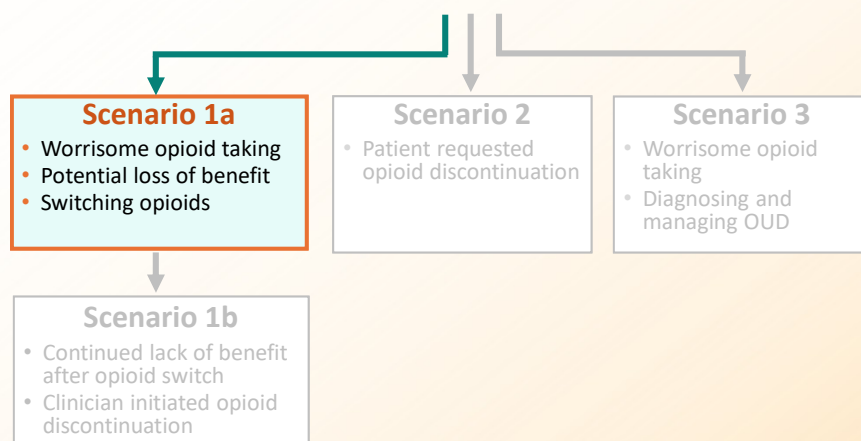


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Case Study – Michelle Jones – 54 yo female

Did well on regimen of ER/LA oxycodone 15 mg bid with gabapentin 300 mg 3x/day for 11 months...



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Case Study – Michelle Jones – 54 yo female



Scenario 1a

- She then went to the ED of her local hospital, **requesting early refill** of her oxycodone
- ED physician noted that she was in moderate opioid withdrawal and gave her enough ER/LA oxycodone to last until her next PCP appointment in one week
- ED physician left a message with the PCP office regarding patient visit and follow-up plan

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Case Study – Michelle Jones – 54 yo female

Post ED Follow-up



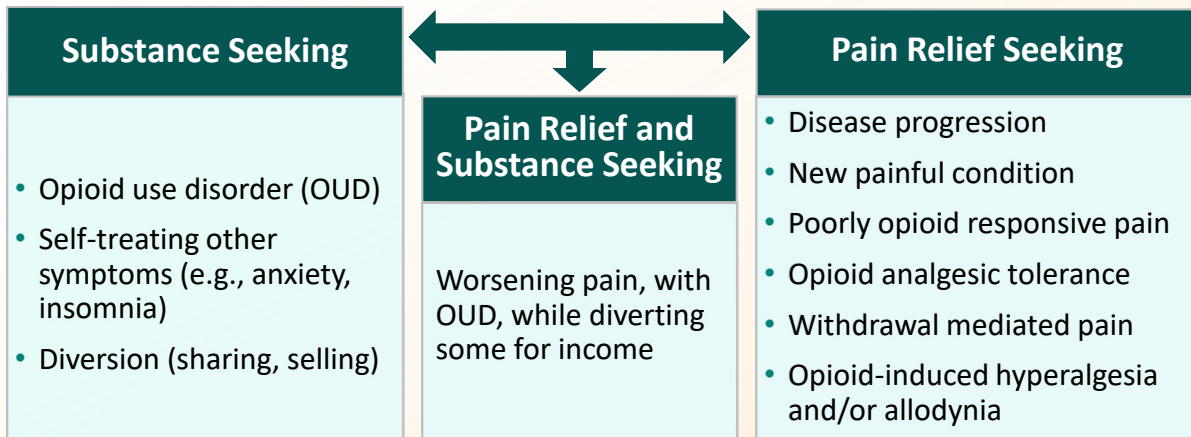
History since last visit

- Foot pain worse in past month “10 out of 10 most days”
- Extra oxycodone in the afternoon and ran out early
- Concerned “body has become used to current dose”; doesn’t seem to work all day anymore
- Requests increase in her dose
- Husband says she has become “addicted”
- Difficult to go to work due to severe pain
- Missed first appointment with pain psychologist, attended one session with physical therapist
- She is re-educated about risks including death of self-escalating her opioid dose and the benefits of physical and behavioral therapies

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Worrisome Medication-Taking Behaviors: Differential Diagnosis



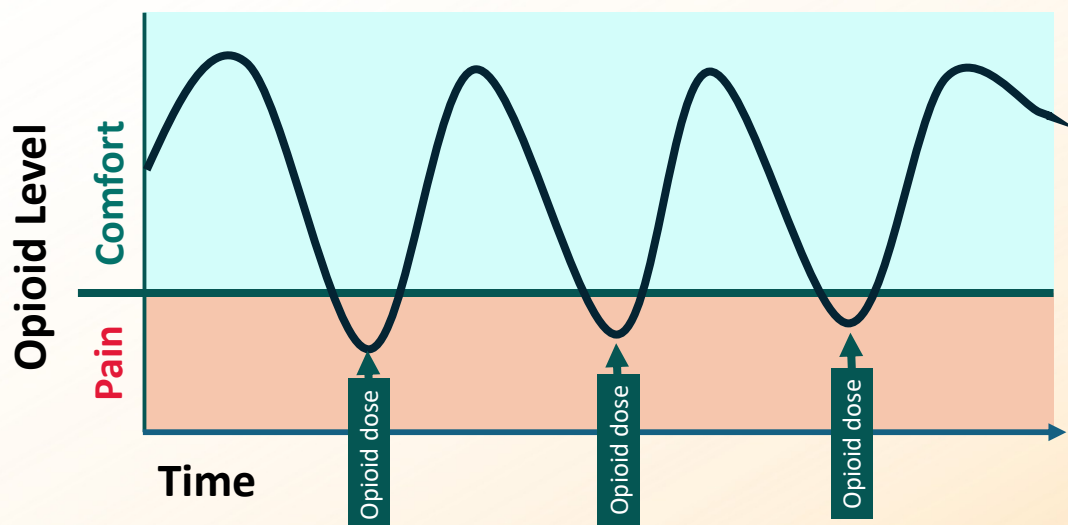
Maumus M, et al. *Ochsner J.* 2020

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Opioid Withdrawal Mediated Pain

In patients with physical dependence, a drop in blood-opioid levels causing opioid withdrawal can increase pain sensitivity



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Opioid-Induced Hyperalgesia and Allodynia

- Paradoxical worsening pain despite an increase in the opioid dose with neural hyperexcitability causing increased sensitivity to painful (i.e., hyperalgesia) and nonpainful (i.e., allodynia) stimuli
- Underlying pathophysiology unclear, but experiments demonstrate NMDA-mediated increased pain sensitivity after prolonged opioid exposure
- True incidence is unknown, most studies report in patients on high dose opioids
- No validated diagnostic criteria but clinically pain is generalized, diffuse, ill-defined, beyond the site of original pain and is refractory to opioid dose increase
- When suspected it can be managed with a reduction or discontinuing opioid, or switch to an alternative opioid



Guichard L et al. *Clin J Pain*. 2022

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Lack or Loss of Benefit

What are the next steps?

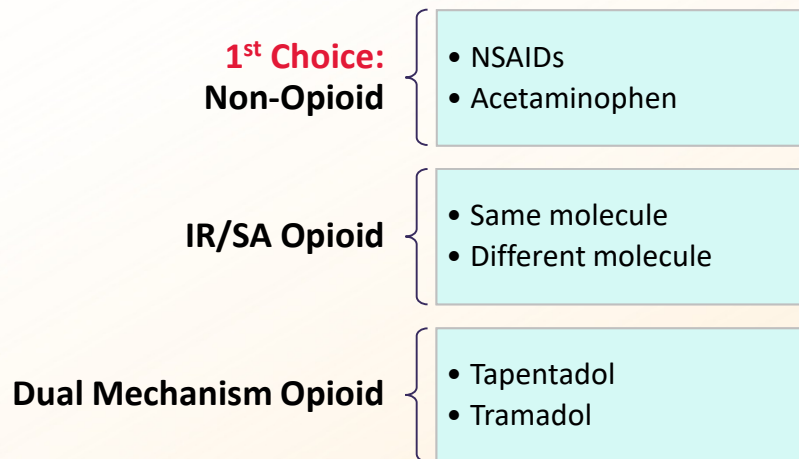


- Reassess factors affecting pain
- Re-attempt to treat underlying disease and co-morbidities
- Consider...
 - Add or increase non-opioid and non-pharmacologic treatment
 - Add breakthrough medications
 - Switch to a different opioid ("rotation")
 - **Avoid dose escalation to "high" dose opioids due to increase risks**

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Consider Breakthrough Medication

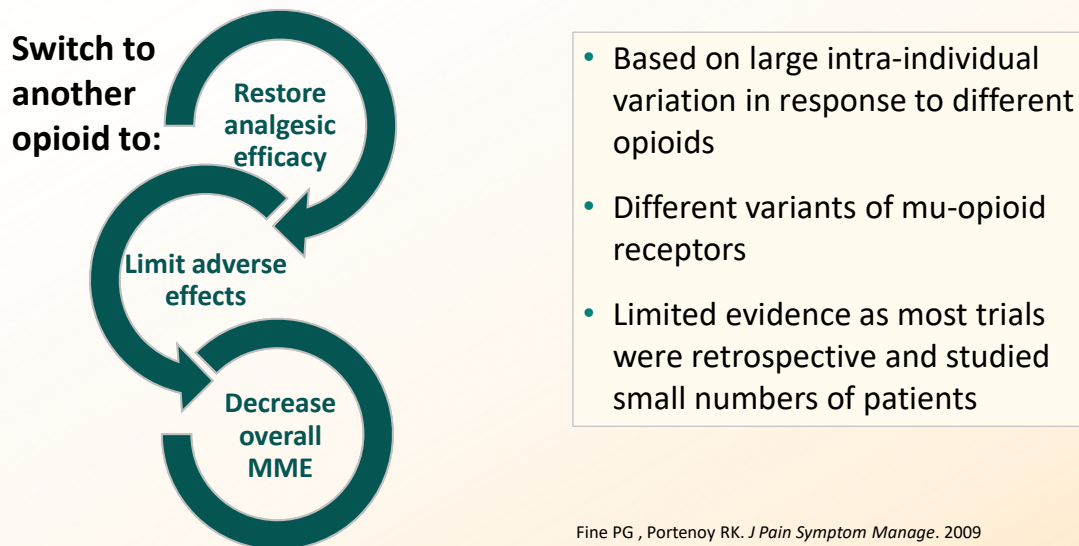


Davies AN, et al. *Eur J Pain*. 2009

31

31

Consider Switching Opioids



Fine PG, Portenoy RK. *J Pain Symptom Manage*. 2009
 Smith HS, Peppin JF. *J Pain Res*. 2014
 Treillet E, et al. *J Pain Res*. 2018

32

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Opioid Conversion Tables

- Derived from relative potency ratios using single-dose analgesic studies in opioid-naïve patients
- Based on limited doses or range of doses
- Does not reflect clinical realities of chronic opioid administration
- Are not reliable due to individual pharmacogenetic differences
- Most tables do NOT adjust for incomplete cross-tolerance

Fudin J, et al. *J Pain Res* 2018
Webster LR, Fine PG. *Pain Med*. 2012
Adams, MCB, *Pain*, 2025

Opioid	NIH 2024 Conversions
Morphine (mg)	1
Hydrocodone (mg)	1
Oxycodone (mg)	1.5
Buprenorphine tablet/film (mg) sublingual	38.8
Buprenorphine film (mcg) buccal	0.039
Buprenorphine patch (mcg/hr) transdermal	2.2
Codeine (mg)	0.15
Fentanyl patch (mcg/hr)	2.4
Hydromorphone (mg)	5
Methadone (mg)	4.7
Oxymorphone (mg)	3
Tapentadol (mg)	0.3
Tramadol (mg)	0.2

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Case Study – Michelle Jones – 54 yo female

<https://globalrph.com/medcalcs/opioid-pain-management-converter-advanced/>

Scenario 1a Switching Opioids



Rotated off
ER/LA oxycodone
15 mg bid
(45 MME)

Converted to
ER/LA morphine
15 mg bid
(30 MME)

ADVANCED OPIOID CONVERTER	
Converting from:	
First selection:	Oxycodone PO
Daily dose:	30 mg
Additional drugs to convert if present:	
2nd Selection:	0
Daily dose:	mg
3rd Selection:	0
Daily dose:	mg
Reduction for incomplete cross tolerance:	
Reduction factor:	33 %
— RESULTS —	
Final opiate chosen (Converting TO): Morphine chronic PO	
Equivalent dosage of FINAL opiate:	➡ 30.15 mg

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Case Study – Michelle Jones – 54 yo female

Over the next 18 months after switching to morphine



Scenario 1a

- Medication management
 - Continued ER/LA morphine 15mg 2x/day (30 MME)
 - Continued acetaminophen and gabapentin
- Stopped seeing psychologist after 3 sessions but learned valuable relaxation skills
- Joined a monthly chronic pain support group at her church
- Completed a full course of physical therapy
- Individual PEG scores remained between 5-6/10
- Remained employed
- Remained adherent with treatment plan and monitoring
- Continued regularly scheduled follow-up visits

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Case Study – Michelle Jones – 54 yo female

Did well on regimen of ER/LA oxycodone 15 mg bid with gabapentin 300 mg 3x/day for 11 months...

Scenario 1a

- Worrisome opioid taking
- Potential loss of benefit
- Switching opioids

Scenario 2

- Patient requested opioid discontinuation

Scenario 3

- Worrisome opioid taking
- Diagnosing and managing OUD

Scenario 1b

- Continued lack of benefit after opioid switch
- Clinician initiated opioid discontinuation



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Case Study – Michelle Jones – 54 yo female

After switching
from oxycodone
to morphine...



Scenario 1b

- Pain remained out-of-control (PEG scores 9-10/10)
- On medical leave from work and spending most of the day in bed (according to her husband)
- Nonadherent with psychologist and physical therapy due to severe pain
- Duloxetine was added to pain regimen
- After one morphine dose increase, **she requested to be converted back to oxycodone**
- On multiple occasions she was confrontational to the office staff when she was unable to be seen by her PCP without an appointment
- She started smoking marijuana to treat her pain

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Cannabis and Pain

Cannabis

- >60 pharmacologically active cannabinoids including cannabidiol (CBD) and the psychoactive tetrahydrocannabinol (THC)
- Endocannabinoid receptors are found in high concentration in the brain and spinal cord



Efficacy

- Moderate-quality evidence can be effective for short-term (1-6 m) treatment of neuropathic and nociplastic pain but inconclusive for nociceptive pain
- **For 30% pain reduction** number needed to treat (NNT):
 - 24 for cannabinoids
 - 4-10 for TCAs, opioids, gabapentinoids, SNRIs

Risks/Harms

- Side effects are mild, can cause dizziness, sedation, and impaired coordination
- Long-term use in adolescents and young adults can result in cannabis use disorder and long-term cognitive impairment

Some states have community pharmacists dispense and report medicinal cannabis to the PDMP

Stockings E et al. *Pain* 2018
Noori A et al. *BMJ Open* 2021
Busse JW et al. *BMJ* 2021

McDonagh MS, et al. *Ann Intern Med.* 2022
Ang SP, et al. *Pain Ther.* 2023

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Pain Specialists & Continued Lack of Benefit



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Role of the Pain Specialists

Interventional Approaches



- When unsure of pain diagnosis and other treatments including interventional e.g., injections, ablation, nerve stimulation, vertebroplasty or kyphoplasty

- Evidence varies by procedure: strong short-term relief w/ epidural injections for radiculopathy, moderate evidence for radiofrequency ablation for facet-mediated spinal pain while others have mixed long-term data



- Set appropriate expectations e.g., don't send patient with expectations of a specific treatment as this sets up patients for disappointment and frustration

- Locate providers via the American Society of Interventional Pain Physicians or American Society of Regional Anesthesia and Pain Medicine



Lo Bianco G. et al. *J Pain Res.* 2023
Sayed D, et al. *J Pain Res.* 2022

40

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Continued Lack of Benefit

Remember:

- ☐ Not all chronic pain is opioid responsive
- ☐ More opioid is not always better
- ☐ More opioid may increase risk of adverse effects
- ☐ Some chronic pain improves after opioid taper

Baron MJ, McDonald PW. *J Opioid Manage.* 2006

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Discontinuing Opioids (Deprescribing)



- You **do not** have to prove addiction or diversion, only assess and reassess the risk-benefit ratio
- If patient is unable to take opioids safely or is non-adherent with monitoring, then discontinuing opioids is appropriate, even in the setting of benefits
- Need to determine how urgent the discontinuation should be based on the severity of the risks and harms
- Determine if the opioid needs to be tapered due to physical dependence
- Document rationale for discontinuing opioids

**You are NOT
abandoning
the patient,
you are
abandoning
the opioid**

Lin CW, Langford AV. *N Engl J Med.* 2025
Tobin DG et al. *J Gen Intern Med.* 2021

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Tapering Opioids

Clinician-Initiated



Potential Benefits (*Systematic Review: interpreted with caution due to poor quality of studies and high risk of bias)

- Statistically significant improvement after tapering for pain intensity, anxiety, depression, pain catastrophizing, and pain interference
- No statistically significant effect for physical functioning, mental health-related quality of life, and physical health-related quality of life

Potential Risks

- Observational studies identified harms (suicide & overdose) associated with opioid taper
- Comparative effectiveness study of individuals on long-term opioids with no evidence of OUD or opioid misuse, found tapering associated with small absolute increase in opioid overdose or suicide compared with maintaining stable opioid dosages

*Wuyts E et al. *Br J Anaesth.* 2024

James JR, et al. *J Gen Intern Med.* 2019
Mark TL, et al. *J Subst Abuse Treat.* 2019
Oliva EM, et al. *BMJ.* 2020

Jung M et al. *Pain.* 2024
Langford AV et al. *MJA.* 2023
Hopkins RE et al. *Pain.* 2026

Kennedy MC, et al. *Plos Med.* 2022
Laroche MR et al. *JAMA open.* 2022
Hallvik SE, et al. *Pain.* 2022

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Continued Lack of Benefit

Discussing Opioid Taper

- Stress how much you believe the patient's pain severity
- Show empathy for the patients suffering and frustration
- Focus on the patient's strengths and encourage therapies for coping with pain
- Show commitment to continue working to control pain and improve function
- If patient continues to request an increase in opioids, state "I cannot continue to prescribe a medication that is not helping (or is hurting you or both)"
- Schedule close follow-ups during and after the change in therapies

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Case Study – Michelle Jones – 54 yo female



Scenario 1b

- Despite the PCP's best efforts to explain the rationale for opioid taper due to lack of benefit and possible harm (e.g., opioid induced hyperalgesia), she continued to demand higher doses of oxycodone
- She was offered alternative pain treatments including increasing duloxetine and re-referral for cognitive behavioral therapy
- She became increasingly angry and stood up and stated that she was going to find a new doctor
- She left the office...

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Did well on regimen of ER/LA oxycodone 15 mg bid with gabapentin 300 mg 3x/day for 11 months...



Scenario 1a

- Worrisome opioid taking
- Potential loss of benefit
- Switching opioids

Scenario 1b

- Continued lack of benefit after opioid switch
- Clinician initiated opioid discontinuation

Scenario 2

- Patient requested opioid discontinuation

Scenario 3

- Worrisome opioid taking
- Diagnosing and managing OUD

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Case Study – Michelle Jones – 54 yo female



How will you help
her taper off
oxycodone?



Scenario 2

- Calls the PCP office after she was unable to get her oxycodone refilled due to her insurance's new prior authorization requirement
 - "My insurance keeps refusing to pay for my pain pills which leaves me without them for days."
- Very upset when describing how badly she is treated by her family, the primary care staff, and at the pharmacy:
 - "I am tired of being treated like a drug addict or criminal."
 - "I tried to stop but got sick."
 - "I want to get off these pills!"

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Stigma, Chronic Pain, and Opioids



- Stigma is being discredited, or undesirable, because of an attribute
- Stigma is common among people with chronic pain
- Individuals with pain with less clear pathophysiology report greater stigma
- Stigma can be internalized contributing to poorer pain-related outcomes
 - Positive correlation between stigma and pain intensity, disability, and depression
 - Patients might believe they deserve their pain, are being punished and do not deserve to be included in social activities
- Opioid-related stigma includes fears about anticipated negative attitudes and judgments from others

Hickling LM, et al. *Pain*. 2024
Bulls HW, et al. *Pain*. 2022

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Tapering Opioids

Patient-Initiated



- No validated protocols in patients on opioids for chronic pain
- Very low-quality evidence suggests several types of opioid tapers may be effective and that pain, function, and quality of life may improve for some patients with decrease opioid dose
- Study found 62% of patients in a pain clinic completed a **voluntary, patient-centered** opioid taper over 4 months with >50% dose reduction
 - Neither pain intensity nor pain interference increased with opioid reduction
 - Success was not predicted by starting dose, baseline pain intensity, years prescribed opioids or any psychosocial variable

Frank JW, et al. *Ann Intern Med.* 2017
Darnall BD, et al. *JAMA Intern Med.* 2018

Fenton JJ et al. *JAMA Network Open.* 2019
Lin CW, Langford AV. *N Engl J Med.* 2025

Darnall BD, et al. *Ann Intern Med.* 2026

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Opioid Tapering (Deprescribing)

General Approach

Speed and Goal
(decrease dose or discontinuation)
depends on reason for taper

- Lack of benefit taper over weeks to months
- Apparent harm/risk taper over days to weeks
- Build up alternative pain treatments as short-term withdrawal can lead to transitory increased pain flares

1st STEP
Reduce medication dose
to the smallest dosage unit

CDC Recommendation

- Decrease 10%/month if on opioids for years
- Decrease 10%/week if on opioids for weeks to months

Dowell D, et al. MMWR. 2022

2nd STEP
Increase amount of time
between doses

- IR opioid can be started when at lowest ER/LA opioid dose
- Can use α 2-adrenergic agonist (e.g., lofexidine, clonidine*, tizanidine*) to treat withdrawal symptoms

**Off-label*

Med Lett Drugs Ther. 2018

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Case Study – Michelle Jones – 54 yo female



Scenario 2

- Over 6 months she successfully tapered off oxycodone
- Her neuropathic pain was moderately well controlled on combination of APAP, gabapentin and duloxetine (*added during opioid taper*)
- She continue self-management skills taught by the psychologist including breathing, relaxation and mindfulness exercises and joined a monthly chronic pain support group
- PEG scores remained between 4-5/10 (*patient stated she was surprised her pain improved off oxycodone*)
- Remained employed
- Remained adherent with the treatment plan and monitoring
- Continued with regularly scheduled follow up visits

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Did well on regimen of ER/LA oxycodone 15 mg bid with gabapentin 300 mg 3x/day for 11 months...



Scenario 1a

- Worrisome opioid taking
- Potential loss of benefit
- Switching opioids

Scenario 1b

- Continued lack of benefit after opioid switch
- Clinician initiated opioid discontinuation

Scenario 2

- Patient requested opioid discontinuation

Scenario 3

- Worrisome opioid taking
- Diagnosing and managing OUD

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Case Study – Michelle Jones – 54 yo female



Scenario 3

- UDTs were consistently positive for oxycodone as expected except once her UDT was opiate positive (i.e., morphine and/or codeine) and oxycodone negative raising the concern for opioid misuse including diversion
 - She denied sharing or giving her oxycodone to others
 - Urine “quantity not sufficient” for confirmation testing
- Unexpected UDT resulted in increased monitoring frequency with no additional unexpected UDTs over the ensuing two months

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Discussing Possible Diversion



- Diversion is one form of opioid misuse and is defined as giving, selling, or trading prescription medications
 - Family and friends are common source of diverted opioids
- Discuss why you are concerned about diversion e.g., UDT negative for prescribed opioid, nonadherence with medication counts
- Discuss your inability to continue to prescribe opioids if the opioids are being diverted to others

SAMHSA. (2025). 2024 NSDUH

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Case Study – Michelle Jones – 54 yo female



2 months later... brought to
ED by ambulance after
suffering an opioid
overdose

How will you manage this
patient?



Scenario 3

- Husband found her unresponsive, administered intranasal naloxone with brisk response and called 911
- In the ED, husband reported that his wife has been running out of her oxycodone, and taking her father's morphine
- Husband had been in denial of how bad his wife's problem had gotten. He reported that she's been fired from her job for missing too many deadlines, and that she once fell asleep with a stove burner on, and melted a teapot
- He heard a staff person in the ED refer to his wife as a "drug abuser"

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Words Matter

 Stigmatizing Language	Non-Stigmatizing Language 
Addict, substance abuser, alcoholic	Person with a substance use disorder (SUD)
Substance abuse	Substance use
Clean urine	Expected test result
Patient is clean	Person with SUD in remission
Dirty urine	Unexpected test result
Patient is dirty	Active substance use

Botticelli MP, Koh HK. *JAMA*. 2016. Kelly JF, Wakeman SE, Saitz R. *Am J Med*. 2015

"Stigma surrounding SUD is perpetuated by the stigmatizing terminology used in healthcare settings, by the news and other media, and by society as a whole."

Zwick J, Appleseth H, Arndt S. *Subst Abuse Treat Prev Policy*. 2020

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Opioid Overdose Reversal & Future Risk



• Overdose Reversal

- **Naloxone:** short-acting (1-2h) opioid antagonist administered by IM, IV, IN, and SC
- **Nalmefene:** long-acting (9-11h), 5X higher binding affinity than naloxone administered IM, IV, IN and SC
- Potential benefits of nalmefene (greater affinity, longer duration action) carry risk of causing harm due to prolonged precipitated opioid withdrawal

• Future Risk

- Retrospective cohort study of adults who had nonfatal opioid overdose during long-term opioid therapy for chronic pain
 - Opioids were dispensed to 91% of patients after the overdose
 - **7%** had repeat opioid overdose and **17%** for patients on **high opioid dosages**

Stolbach AI, et al. *J Med Toxicol.* 2024

Med Lett Drugs Ther. 2026

Larochelle MR, et al. *Ann Intern Med.* 2016

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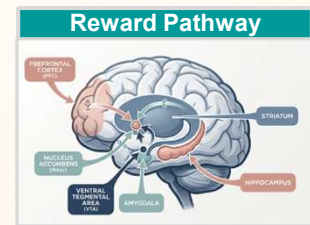
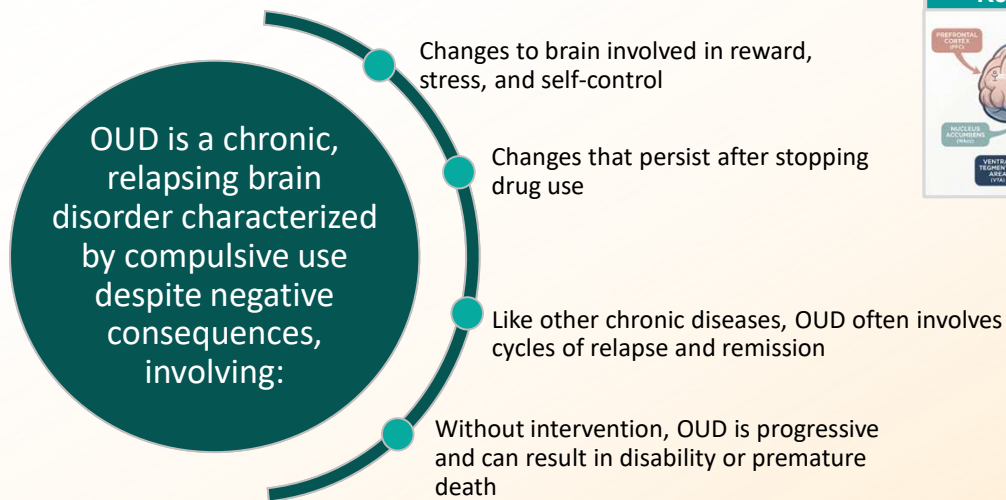
Opioid Use Disorder



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Opioid Use Disorder (OUD)



Harris MTH, et al. *JAMA*. 2026
Taylor JL, Samet JH. *Ann Intern Med*. 2022

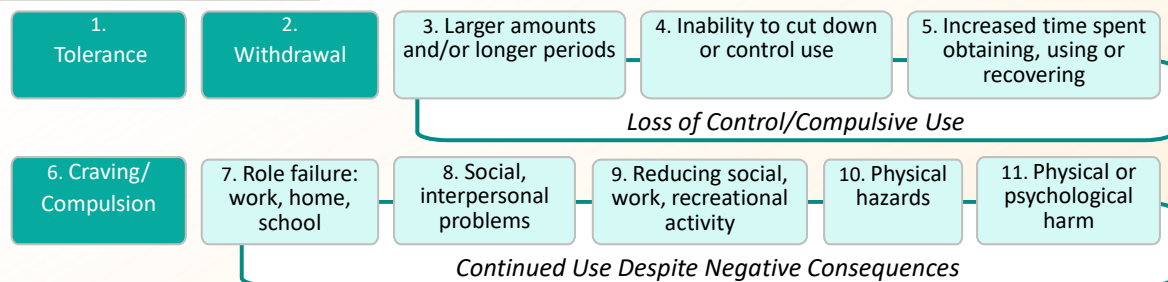
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Does Patient Have an OUD?

APA. 5th Edition, Text Revision (DSM-5-TR) . 2022

Mild: 2-3, **Moderate:** 4-5, **Severe:** 6+



Pain-Adjusted DSM-5 OUD

- Tolerance and withdrawal not counted if patient prescribed opioids
- Exclude symptoms driven solely by pain relief and/or therapeutic intent

FDA Anesthetic and Analgesic Drug Products Advisory Committee. May 5, 2025
Hasin DS et al. *Am J Psych*. 2022

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Discussing Possible OUD

Give specific, timely feedback about behaviors that raise your concerns for possible OUD (e.g., loss of control, compulsive use, continued use despite harm)

Remember patients may suffer from both chronic pain and OUD

May need to “agree to disagree” with the patient

Benefits no longer outweigh risks

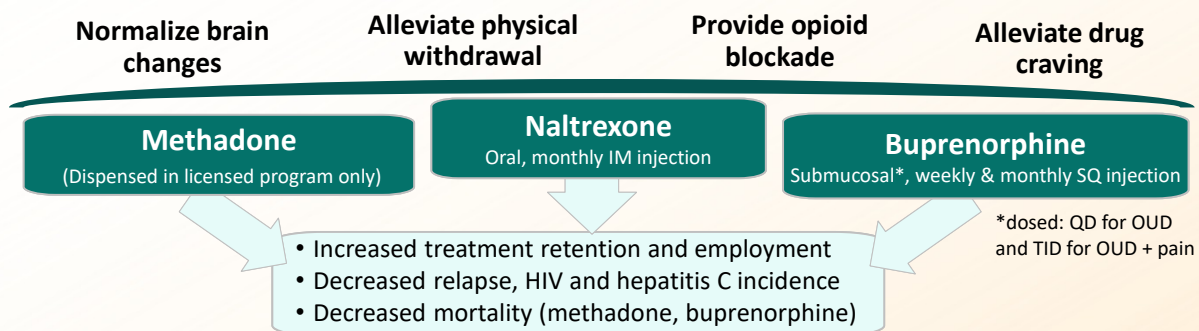
“I cannot responsibly continue prescribing opioids as I feel it would cause you more harm than good.”

Always support connection to and/or initiate OUD treatment

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Medications for OUD (MOUD)



MOUD is easy to use but not universally available even after overdose

Harris MTH, et al. *JAMA*. 2026
Crystal S et al. *Drug Alc Depend*. 2022,
Laroche MR, et al. *Ann Intern Med*. 2018



Recommendation 12

- Offer or arrange evidence-based medications for treating OUD

Dowell D, et al. MMWR. 2022

Treating OUD with Medications

www.SCOPEofpain.org

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Case Study – Michelle Jones – 54 yo female



Over the next 6 months...

How will you manage this patient perioperatively?



Scenario 3

- PCP continues buprenorphine 24 mg for the treatment of OUD and dosed it 8 mg TID to also treat her chronic pain
- Right hip pain from end-stage arthritis is affecting her quality of life despite trying nonoperative management
- She is schedule for a right hip arthroplasty

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Acute Pain in Patients on MOUD

Systematic Review



There is now consensus on perioperative management of patients on MOUD

Patients with OUD history are often more sensitive to painful stimuli

Continue methadone or buprenorphine throughout the perioperative period

Treat pain with analgesics on top of the patient's daily MOUD

Patients taking MOUD may need higher doses of opioid analgesics

Ineffective pain management can result in disengagement in care

Buonora MJ, et al. *Ann Intern Med.* 2025
Veazie S et al. *J Gen Intern Med.* 2020
Kohan L, et al. *Reg Anesth Pain Med.* 2021

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Case Study – Michelle Jones – 54 yo female



Scenario 3

- Did well postop with improved pain control
- Painful diabetic neuropathy well controlled on combination of buprenorphine 8 mg sublingual 3x/day, duloxetine and APAP (Note: gabapentin discontinued due to misuse risk)
- PEG scores remained between 5-6/10
- OUD in sustained remission with MOUD and counseling
- Remained employed
- Continued with regularly scheduled follow up visits

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Summary Part 2



- Match treatment plan to patient needs and functional goals
- Individualize universal precautions based on patient risk
- Document rationale and benefits, risks and harms
- Utilize interprofessional team for monitoring and support
- Identify and manage worrisome opioid-taking behaviors
- When indicated, taper opioids gradually and institute alternative pain therapies
- Diagnose and manage opioid use disorder (OUD) using highly effective medications
- Continue methadone or buprenorphine for OUD during perioperative period

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Post-test & Evaluation



- Complete the post-test with a score of >70%
- Complete the evaluation
- Download your certificate, worth:
 - 2.0 *AMA PRA Category 1 Credits™*
 - 2.0 nursing contact hours, or
 - 2.0 ACPE credits

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***SCOPE of Pain* Online Program Part 1**

Transcript

Ilana Hardesty: Welcome to Boston University Chobanian & Avedisian School of Medicine's Safer and Competent Opioid Prescribing Education: *SCOPE of Pain* program. I'm Ilana Hardesty, your moderator.

This web-based program consists of two parts that follow the case of Michelle Jones to discuss management of acute and chronic pain. Occasionally within the program, you'll be asked quick polling questions, which focus on the more challenging aspects of the case. After each one-hour part, you'll take a brief post-test accessible in the right-hand navigation bar. Further information about receiving credit is available on the information page and will be provided at the end of the second part.

You'll find a wealth of materials available at the *SCOPE of Pain* website, including a downloadable transcript, a PDF of the slides, and a comprehensive resource and reference document with complete bibliography. While you're there, you'll also find clinical resources available for your use, audio micro cases for quick study, a number of supplemental educational activities, and a trainer's toolkit for your use if you are training your colleagues.

Our faculty for this program include Dr. Daniel Alford, professor of medicine at the Boston University Chobanian & Avedisian School of Medicine, and Dr. Jane Liebschutz, professor of medicine at the University of Pittsburgh School of Medicine. Both are general internists with expertise in primary care, addiction and pain medicine, and medical education.

SCOPE of Pain was developed in collaboration with the Federation of State Medical Boards. This educational activity is supported by an independent educational grant from the Opioid Analgesic Risk Evaluation and Mitigation Strategy, or REMS, Program Companies.

Through the case presented in this program, learners will be able to quantify pain and functional impairment using validated tools, formulate individualized multimodal pain treatment plans using a risk-benefit framework, counsel patients on the therapeutic limitations of opioids and risk mitigation strategies, monitor opioid therapy continuously for efficacy, safety, and adverse outcomes, diagnose and manage opioid

use disorder in patients with or without concurrent pain, and use interprofessional team-based care for comprehensive pain management.

SCOPE of Pain covers strategies for the safer use of opioids for managing acute and chronic pain by reviewing best practices and sharing clinical pearls. As well, the content counts toward the eight-hour DEA pain and addiction education requirement as outlined in the MATE Act and aligns with the twenty twenty-two CDC Clinical Practice Guideline for Prescribing Opioids for Pain. Throughout the presentation, you'll see blue boxes with the CDC recommendations that address specific content on the slide. This training does not cover palliative care or end-of-life pain management due to the differences in overall treatment goals.

First, let's set the stage. Dan, could you review the big picture of acute and chronic pain? And could you talk about disparities and barriers in pain care and prescribing and overdose trends?

Dr. Daniel Alford: Let's start with a definition: pain as an unpleasant sensory and emotional experience. And let's look at acute pain. Acute pain is a life-sustaining symptom. It's adaptive, and it helps to minimize further harm and allows for healing.

Moving on to chronic pain, it's defined as pain that persists beyond the expected healing time, usually three or more months. And as far as I know, there's no evolutionary benefit. And for some, it can be a disease in and of itself. It's maladaptive, and it's influenced by genetics and epigenetics.

The classification can be helpful in influencing your workup, your treatment options, and prognosis. So let's start with nociceptive pain, which is actual or threatened tissue damage, which could be somatic, which involves bones, joints, and muscle, for example, or visceral, involving mucosal injury, obstruction, distension, or ischemia.

Next, neuropathic pain, a disease or injury of the somatosensory nervous system, which could be central (traumatic and vascular, for example), or peripheral, for example, a compression neuropathy.

Third, nociplastic pain. This is due to abnormal pain processing without evidence of tissue damage or discrete pathology. It includes diffuse sensitization, such as fibromyalgia; regional sensitization, such as complex regional pain syndrome; and visceral pain, for example, irritable bowel syndrome.

And then finally, mixed pain, which is a combination of different types of pain occurring simultaneously in the same area.

About 21% of US adults, that's about 50 million people, report pain on most days or every day. Up to 60% of emergency department visits are for pain-related complaints,

and I know in my primary care practice and in other primary care practices, pain is one of the most common reasons people show for visits.

Pain costs billions of dollars per year in medical costs, lost wages, and lost productivity. And we know that pain contributes to disparities by disproportionately impacting women, the elderly, racial and ethnic minorities, those with lower socioeconomic status, military veterans, and those that live in rural communities.

We also know that there are barriers to optimal pain care, and those include an overburdened primary care system with many competing priorities; inadequate training in managing patients with pain; lack of decision support to help with pain management; a very clear financial misalignment that favors the use of medications over other therapies; a lack of access to pain specialists and comprehensive multimodal pain care; negative attitudes and disparities in pain care; and patient access to misinformation online that can lead to unrealistic, misaligned, and often conflicting treatment expectations. When a clinician's evidence-based recommendations contradicts a popular online narrative, it can foster mistrust, leading patients to feel dismissed or undertreated.

Let's look at the state of opioids in two parts: opioid prescribing and opioid overdoses. In the United States, opioid analgesic prescribing increased dramatically in the 1990s and peaked in 2012. However, over the past decade, total national opioid prescriptions have fallen more than 44%.

What about overdoses? In 2025 opioid overdose deaths dropped to just over 44,500. That's down from over 55,000 in 2024. This is the third consecutive year that we've seen a national decline. Overdoses now are primarily due to illicitly manufactured fentanyl, along with polysubstances including cocaine, methamphetamine, or adulterants like xylazine.

Ilana Hardesty: Now we'll move to Part 1: Assessing and Managing Pain.

Meet Michelle Jones. At 36, she was in a motor vehicle crash resulting in a right hip fracture. After successful surgery, her pain was managed with nerve blocks and intravenous hydromorphone. Dan, can you discuss acute pain assessment, and what are the risk factors that would increase the likelihood that a patient's acute pain would progress to persistent or chronic pain?

Dr. Daniel Alford: Sure. So when I assess acute pain, I use the acronym SOCRATES, and that helps me think of all the various questions that I need to ask, such as S is site. Where does it hurt? O is for onset. When did it start? C is the character. What does it feel like? Is it burning? Is it sharp or stabbing? Does it radiate? Is it associated with any other symptoms? How long has it been going on? Are there any exacerbating or relieving factors? And finally, what's the severity?

And when I ask about severity, I use a pain intensity scale, and that could be a visual analog scale. There's even an emoji-based visual analog scale. But more often than not, I use a numeric rating scale, which is on a 10-point scale. Zero is no pain, one to three is considered mild pain, four to six moderate, and seven to 10 severe. I also like to consider the quote by Barry Oken, which says that many factors influence self-reported pain, including gender, social support, clinician characteristics, and most importantly, trust.

So you asked about risk factors in going from acute to chronic pain, and much of the literature looks at post-surgical pain. That is, which surgical pain becomes persistent, and what are the risk factors? Well, first, there's a lot that we don't understand about why this occurs, but we know that there are alterations in expression of neurotransmitters, receptors, and ion channels, and there are changes to actual neuron structure, connectivity, and survival.

So what's been some of the risk factors that have been identified for going from acute post-surgical pain to persistent pain? Well, there are patient-related factors like being younger, being female, and having history of anxiety, depression, someone who catastrophizes, pre-existing pain syndrome or preoperative opioid use puts you at higher risk for persistent pain.

But there are also intraoperative variables, including the surgical procedure, if there was nerve ligation or injury, or if there was ischemia. And then postoperatively, is the pain uncontrolled and severe, and is there a longer duration of postoperative pain?

In outpatient practice, I like to use the START MSK screening tool to assess the risk for developing chronic musculoskeletal pain after someone has an acute injury. And this tool helps to identify modifiable risk factors, biomedical, psychological, and social, for chronic musculoskeletal pain disability.

So this tool stratifies people into low, medium, and high risk for developing chronic pain. And you can see that the first four questions really deal with pain characteristics. That is, does it involve more parts of the body? Is it affecting the person's function? And is it causing other health problems?

But really the final questions really deal with catastrophizing. Does the person feel that it's unsafe to be active? Do they have worrying thoughts? Do they worry that it's going to last a long time? Have they stopped enjoying things that they usually enjoy? And then finally, how bothersome is the pain to them?

Ilana Hardesty: After her surgery, Michelle was discharged with orthopedic follow-up and physical therapy referral. She received prescriptions for ibuprofen, six hundred milligrams every eight hours, and oxycodone, five milligrams, one to two tablets every four to six hours as needed for pain. Her oxycodone prescription was for forty tablets.

Jane, I'd like to turn to you now. What is the correct amount of opioid to discharge this patient on?

Dr. Jane Liebschutz: Opioid over-prescribing for acute pain has been commonly known for a while. In studies of postoperative pain management, over 70% of patients took half or less of their opioids. After an emergency department visit, 93% of patients had leftover pills, and about half of the pills were unused.

When people talk about misusing opioids, about a third were obtained from family and friends, and three to five percent of opioid-naïve patients receiving an opioid become long-term opioid users, with the highest risk factors being males, age over fifty, having mental illness, and substance use disorders. Since 2012, new opioid prescription lasting more than seven days has gone down.

For treating acute pain, what are the most efficacious analgesics? Well, for acute dental pain and specifically molar extractions, nonsteroidals and acetaminophen are more effective compared to oxycodone alone or in combination with acetaminophen.

For acute musculoskeletal pain, there's no significant difference in pain reduction between opioids versus a combination nonsteroidal and acetaminophen or a different opioid and acetaminophen combinations. And in acute pain, multimodal approaches have been most efficacious. For minor surgeries, nonsteroidals and acetaminophen or very limited opioids are indicated, then a quick transition to nonsteroidals and acetaminophen. But for severe post-traumatic pain, opioids would be indicated and may be efficacious. Please note the CDC recommendations one and six, which refer to acute pain, use of nonpharmacological non-opioids, and only opioids if benefits are greater than the risks.

Ilana Hardesty: Dan, turning back to you, what's the role of ketamine and suzetrigine in treating acute pain?

Dr. Daniel Alford: These are two agents that you're hearing more about these days, and ketamine is being used for acute pain in multiple settings. It's important to remember that it's a dissociative anesthetic that was developed in the 1960s. It's an NMDA receptor antagonist that provides analgesia at sub-anesthetic doses, and it's an analgesic without the problems of respiratory depression.

Unfortunately, there's low oral bioavailability, which really limits its use currently to parenteral use as an analgesic in the emergency department or post-operative settings. Low doses reduce pain more rapidly but less sustained than morphine, and it decreases opioid requirements, oftentimes referred to as opioid sparing.

There are oral and sublingual and intranasal formulations that are now being studied, however, for efficacy and safety for refractory severe chronic pain. But there are dose-

dependent adverse effects, including hallucinations, agitation, anxiety, dysphoria, and euphoria, and there is misuse potential due to the psychoactive effects.

Suzetrigine is really the new kid on the block. It's the first non-opioid analgesic in over 25 years, and it's an oral systemic selective sodium channel blocker for short-term treatment of moderate to severe acute pain in adults. It's only been studied up to 14 days. For postoperative pain, it's more efficacious than placebo, but not more effective than hydrocodone with acetaminophen.

In clinical trials, it's well-tolerated, but in those trials, over 80% of participants still required rescue nonsteroidal anti-inflammatory drugs for their pain. But it is considered an alternative when NSAIDs or opioids are ineffective or the risk of adverse effects with their use is too high. The efficacy and safety for treatment of subacute or chronic pain is currently being investigated.

Ilana Hardesty: Michelle's postoperative course was uneventful. She ended up with 15 unused oxycodone tablets, which she threw away.

We next see Michelle Jones 18 years later when she presents for an initial appointment to establish primary care after her previous primary care physician retired. She's now 54 years old and has chronic foot and hip pain. Her past medical history includes type 2 diabetes with painful diabetic neuropathy and chronic right hip pain due to post-traumatic osteoarthritis.

She has hypertension, stage 3A chronic kidney disease, hyperlipidemia, and obesity. She complains to the new clinician that she has run out of her pain medication and needs a new prescription today. She says her feet and hip are killing her, and the pain is making her depressed. Jane, what will you do with that information?

Dr. Jane Liebschutz: Psychiatric comorbidities are a very important consideration in chronic pain. Almost every psychiatric diagnosis in the DSM-5 is also associated with increased rates of chronic pain, and this includes major depression, general anxiety, personality disorder, sleep disorder, post-traumatic stress disorder, substance use disorder.

And this is a bidirectional relationship where psychiatric conditions make pain worse and pain makes psychiatric conditions worse. In any patient like Michelle, we should assess for psychiatric conditions and attempt to co-manage.

So how might we do that? So there are a number of brief screeners for comorbidities. If they become positive, then we're obligated to do a more in-depth exploration of whether the individual has one of these disorders that can be treated. And these include the PHQ-2, which then can lead to the PHQ-9; the GAD-2, which can lead to the GAD-7; a five-item PTSD screener called the PC-PTSD-5; sleeping disorder; suicidality; and substance use.

And I want to mention the two items for substance use. One is the TAPS tool, which screens for tobacco, alcohol, prescription meds, and other substance use. And then the single item screening question. There's one for alcohol and one for drugs. If the alcohol test is positive, then it's important to use the AUDIT to identify serious or severe substance problems with alcohol.

And if the drugs are positive, it can be followed up with the DAST. It would also be important to characterize whether the individual patient meets criteria for DSM-5 substance use disorder.

Ilana Hardesty: Michelle screened positive for mild depression and anxiety, and negative for insomnia and substance use disorder. She is currently on metformin, empagliflozin, lisinopril, and atorvastatin. She's also taking gabapentin and short-acting oxycodone, ten milligrams four times a day. She had previously tried NSAIDs, acetaminophen, TCAs, tramadol, and acetaminophen with codeine. None of these offered adequate pain relief, and many caused intolerable side effects.

Michelle works part-time as a paralegal. She's married with no children. She does not smoke. She drinks a glass of wine one to two times per month. She does not use non-prescribed drugs, including cannabis. Her father is being treated for lung cancer. Her mother died from complications of alcohol-associated cirrhosis.

Michelle has been rationing her oxycodone prior to this visit, taking it every twelve hours rather than every six hours to avoid running out. She took her last pill this morning. She gets the best pain relief when she takes her ten-milligram tablet four times per day. Her current pain is more severe because she's spacing out her pills. She gives this new PCP her old medical records. Michelle reports mild to moderate right hip pain that is exacerbated by activity and relieved with rest. She has severe bilateral foot pain with burning, numbness, and tingling, which is worse at night.

On a ten-point scale, Michelle rates her pain as a twenty. Jane, what does it mean when a patient reports their pain beyond the scale, as Michelle did, and how would you assess a patient's chronic pain?

Dr. Jane Liebschutz: One of the reasons a patient may say their pain is a twenty when the top of the scale is a ten is they do not trust that the provider, the clinician, believes the severity of their complaints. And so they exaggerate their pain scores and also functional limitations.

So how to build trust when this happens? So a couple of things. First, the clinician needs to do a thorough pain history, a focused exam, and appropriate diagnostic testing. Throughout that process, it's very important for a clinician to show empathy to the patient because it's been proven that empathy is associated with better chronic pain outcomes.

Things like, “I can hear how much this pain is affecting your life. I can see how hard you’re trying to manage this pain.” It’s very important to validate that you believe the patient’s pain and suffering is real because it’s very real to them. “I hear how much pain you’re in, and I believe you. Your pain is real. We’ll figure this out together.” Believing the severity of the patient’s pain complaint does not mean that opioids are indicated.

So when a patient comes in with chronic pain of three months or longer, how do you assess? Well, in acute pain, we talked about the numerical rating 1 through 10 or those kind of things.

But in chronic pain, you don’t want just the pain, but you really also want function and how the pain is impacting their life. There are some very well-established multidimensional instruments, but these are really developed in a research setting, and they may be used in a specialty pain clinic, but generally not in a primary care, emergency medicine, or other urgent care type of settings.

What we like is something called the PEG scale, which asks about pain, enjoyment, general activity, and it’s pretty easy to administer. What number best describes your pain on average in the past week? Zero is no pain, 10 is bad as you can imagine. Similar question, how has pain interfered with your enjoyment of life? Zero does not interfere, 10 completely interferes. And what number best describes during the past week how pain has interfered with your general activity?

Ilana Hardesty: When asked the PEG questions, Michelle reported that over the past week, her pain on average was a ten, and her pain’s interference with enjoyment of life and general activity were both nine.

Michelle’s physical shows no acute distress and normal vitals with a BMI of thirty-two. She has normal cardiopulmonary function and normal musculoskeletal exam, except for her right hip, which has decreased range of motion and pain on internal rotation. Her neurologic exam is consistent with her diabetic neuropathy.

Turning back to you, Dan, what are the next steps as you think about managing a patient’s chronic pain?

Dr. Daniel Alford: So to start with, I think it’s important to establish the goals. And the goals should be obviously to reduce pain, but also to restore function, to cultivate well-being, to improve the patient’s quality of life, and to improve coping.

And there are lots of ways to try to achieve this. And I start in the middle with self-management. And what is self-management? It’s a patient-centered, multimodal approach that includes physical, emotional, and cognitive strategies, that reduces the impact of pain and improves function by transitioning patients from passive treatment to active partners in their care. So it’s very important that we educate our patients

about the importance of them being active partners and not just being a passive recipient.

So how do we do this? Well, there are behavioral strategies, integrative strategies, interventional strategies, medications, and physical and restorative strategies. We're going to talk about each one of these.

So let's start with behavioral interventions. And these include cognitive behavioral therapy, acceptance and commitment therapy, mindfulness-based stress reduction, pain reprocessing, biofeedback, and relaxation. And really, these target cognitive, emotional, and behavioral factors that contribute to the person's pain and suffering.

And the goal is to mitigate the psychological distress by reframing the maladaptive pain behaviors, reducing their catastrophizing and rumination, and correcting some somatic misinterpretation, which we'll talk more about, and to downregulate the central threat perception that patients feel when they feel any kind of pain.

Well, there are lots of different ways to get behavioral interventions, including in-person all the way to digital therapeutics. And I like this image from The Lancet, the reference is on the slide, that shows you that the most evidence supports in-person therapy, but it's not always available. Whereas the most available is digital therapeutics, which has less evidence base behind it. And you can see in between, there is remotely delivered therapy, that is virtual therapy, and self-management therapies.

So what's the evidence supporting behavioral interventions? Well, we have high-quality evidence that demonstrates reduced pain, reduced catastrophizing and emotional distress, and improvements in functioning and coping that match or even exceed the benefits of many medications that we prescribe.

So how can our patients access these interventions? Well, there are mobile health apps that include mindfulness, relaxation, reframing, pacing, and goal setting, many of which are free. And I put some examples here, like the Veterans Administration Pain Coach app or Manage My Pain app. Those are free. But there are some other apps that require a subscription or a paid version with more features.

But you can also find a health psychologist. Oftentimes, they're located in hospital-affiliated clinics. Patients can call their insurance plan to see if they have any referrals. But also going to *Psychology Today*, and I put the website here, which allows you to look for a therapist that specializes in pain in your part of the country. So it's a very unique and helpful resource to teach our patients about it, and also the Society of Behavioral Medicine.

Moving on to physical and restorative approaches, such as physiatrists, osteopathic physicians, physical therapists, occupational therapists, and chiropractors. And these

are mechanical interventions that are attempting to optimize the neuromuscular function, targeting physical forces, tissue manipulation, and biomechanical training.

And there is evidence supporting them for improving pain and function. The strongest evidence is with therapeutic structured exercise. There's moderate evidence for spinal manipulative therapies and weaker evidence for standalone passive treatments such as massage.

How do our patients find these or how do we find them for them? You can use professional medical directories and tools dedicated to each specific practice type. And I've put some examples here for chiropractors and physical therapists and PM&R physicians. And patients can also contact their insurance plans.

Moving on to integrative medicine approaches, and this includes things like acupuncture, mind-body practices, movement therapies like Tai Chi and Qigong and yoga. These are really whole-person approaches to address the biological, psychosocial, and environmental factors that contribute to the patient's pain experience. And there is evidence supporting them. There are systematic reviews and meta-analyses of randomized clinical trials that show moderate, clinically meaningful improvements in pain and function, and as you can imagine, a strong safety profile.

How do our patients access these? Well, certainly hospital departments of integrative medicine, local licensed acupuncturists, board-certified integrative physicians, and insurance plans again. And I put some examples here. The American Academy of Medical Acupuncture has a Find an Acupuncturist where you can search in your region of the country. But there are also great resources on the National Center for Complementary and Integrative Health at the NIH.

Ilana Hardesty: The PCP discusses the importance of self-management and the benefits of non-pharmacologic treatments. Michelle responds by saying, "You don't believe me. You think my pain is all in my head. I've tried these other things, and they didn't work, and some of them really made my pain worse. They were a waste of time." Dan, how do you respond to Michelle's concerns about non-pharmacologic approaches?

Dr. Daniel Alford: Well, I think first, we as the patient's primary care or clinician need to believe in these therapies ourselves. And saying things such as, "Seeing a psychologist doesn't mean that your pain isn't real. Pain changes the nervous system, making the brain's amplifier too sensitive, and this therapy will teach the brain how to quiet down those pain signals. Psychologists are experts in the brain." So that would be referring someone to a behavioral health specialist. For someone who's going to go to a physical therapist, you could say, you know, "Carefully guided movement actively repairs your body, and the soreness you feel during rehab is actually a safe sign that your body is adapting and getting stronger, not causing damage. You can use quick relief options like ice or heat to ease any discomfort and to help you get moving." And then finally, if you're referring to integrative treatments, you can say, you know, "Exploring integrative

treatments doesn't mean that your pain isn't serious, nor does it mean that conventional medicine is giving up on you. Instead, these therapies work hand in hand with your medications and other treatments to help your body heal and become stronger." So these are just some examples of ways that you can talk to your patients about these non-pharmacologic options.

Ilana Hardesty: Michelle is skeptical and reluctantly agrees to think about self-management strategies and see a psychologist for behavioral treatments of her pain. The PCP tells her that he'll review the medications she's taking and those she's tried in the past to determine if there are any improvements that can be made. Jane, what are the medication options for treating Michelle's chronic pain? And do the benefits of combining medications, as we discussed in the acute pain section, apply for chronic pain as well?

Dr. Jane Liebschutz: As we discussed earlier, nonsteroidals and acetaminophen are both evidence-based treatments for chronic pain. Nonsteroidals can include non-selective and selective COX-2 inhibitors, and they have anti-inflammatory, analgesic, and antipyretic features to them. However, they can cause adverse effects such as GI, renal, or cardiovascular, especially at high doses over long periods of time.

Acetaminophen is an analgesic and antipyretic. It's less effective than full-dose nonsteroidals in relieving chronic pain. However, it has fewer adverse effects than nonsteroidals.

So general considerations around non-opioid pharmacotherapies include that they have ceiling analgesic effects, so adding more may not improve the pain, that they have no analgesic tolerance, and as you asked, they may have a nice additive role. Some patients may respond better to one nonsteroidal than another.

So what about other kinds of pain medications? There are a number of analgesics who have a primary indication other than pain, and that includes antidepressants such as TCAs or SNRIs, or anticonvulsants such as gabapentinoids or carbamazepine. And these two categories are a mainstay of pharmacological treatments for neuropathic and nociplastic pain syndromes. And then for other types of pain, you can get muscle relaxants or antispasmodics or potentially local anesthetics such as topical lidocaine.

There is one caution. Some of these have been associated with misuse and have addiction potential, and these include gabapentinoids and some muscle relaxants. The other caution is there may be an additive burden of anticholinergic side effects, such as with tricyclic antidepressants or cyclobenzaprine.

What do we mean by opioid analgesics? Well, opiates are derived from the poppy seed plant and include medications such as morphine or codeine. Semisynthetic opioids are derived originally from the poppy seed plant, then are chemically modified. And examples of semisynthetic opioids include oxycodone, hydrocodone, and

buprenorphine. And then synthetic opioids such as fentanyl or methadone never came from the poppy seed plant. They were purely derived in a laboratory.

So how do opioid analgesics work? They turn on descending inhibitory systems such as the periaqueductal gray, and they prevent ascending transmission of pain signals. They inhibit activation of C fibers and the peripheral nociceptors. They activate the reward pathway, which can lead to euphoria. And of note, not all patients respond to the same opioid in the same way. There's variability driven by mu receptor polymorphisms and single nucleotide polymorphisms called SNPs, which influence metabolism, transport, and receptor kinetics. Individual patient pharmacogenetic profiles are not routinely used due to cost and lack of insurance coverage.

What about opioid tolerance and physical dependence? These are both adaptations, physiological adaptations to chronic opioid exposure. What is tolerance? It's an increased dosage needed to produce the specific effect. This develops readily for CNS and respiratory depression, less so for constipation, and it's really unclear whether it develops analgesia. Many folks who are on long-term opioids stay on the same dose with the same effect for a long time.

In terms of physical dependence, this is signs and symptoms of withdrawal by abrupt opioid cessation or a rapid dose reduction, or potentially exposure to an opioid antagonist, such as naloxone.

So we've presented opioids and non-opioid pharmacotherapies, and how do we best use them? Well, you really want to exploit synergism between them. And you could see on this diagram of a brain, spinal cord, peripheral nervous system, that the different medications work at different sites. And so exploring this opportunity for rational polypharmacy, you can see on the right, this was a study published in the early 2000s, but what they showed was that compared to baseline and placebo, gabapentin and morphine alone were neither as effective as the combination, and interestingly enough, the combination used lower doses of both. So you're likely to decrease the side effects and improve the safety profile and also improve the analgesia.

Ilana Hardesty: Dan, I think that this may be the elephant in the room. Do opioids really work for chronic pain? And what do you need to worry about when you decide to prescribe them?

Dr. Daniel Alford: So this slide summarizes what we know about the efficacy for chronic pain, and you can see that there have been meta-analyses that show that opioids had a statistically significant but small improvement in pain and physical functioning over placebo, and this was limiting it to high-quality studies. And then looking at opioids versus non-opioids, those were low to moderate quality studies, and they showed similar benefit. What's important to note is that these studies had three to six-month follow-up, so beyond six months, we really don't know about benefit.

There was a randomized controlled trial that found that opioids were not superior to non-opioids for improving musculoskeletal pain-related function over twelve months, so a longer-term study. And with any RCT, you need to look at who they included and who they excluded, and whether or not there are limits to generalizability or limits to how it generalizes to the patient sitting across from you. And you can see that in this study, they excluded any patient who was already on long-term opioids. So our patient, in our case, Michelle, would not have been enrolled in this study. But of those individuals who were not already on opioids, there was no superiority between opioids versus non-opioids.

There were two longer-term follow-up studies that found that 44.3% of subjects on chronic opioids for chronic pain had at least 50% pain relief. So it wasn't zero percent and it wasn't a hundred percent, but it was close to fifty percent.

Moving from efficacy to safety and risks, first of all, allergies to opioids are rare, but we do know that opioids can cause immunosuppression, and we've known this in animal models for some time. But there have been some observational studies that found that humans had an increased risk of invasive pneumococcal disease and an increased risk of community-acquired pneumonia when they were on opioids, and this seems to be a dose response. That is, higher opioid doses cause more immunosuppression.

What about organ toxicities? Well, we do know that there's suppression of the hypothalamic-pituitary-gonadal and adrenal axes causing menstrual irregularities, reduced fertility, erectile dysfunction, and hypogonadism, causing problems with bone health, osteoporosis, also fatigue, obesity, and metabolic syndrome.

What about adverse effects? Well, nausea, sedation, urinary retention, and sweating, but constipation is probably one of the most common due to a hypodynamic bowel and dry stool. Some people develop itching or pruritus, which is a histamine release, not a true allergy, but for some reason, we have mu-opioid receptors on our mast cells.

And then finally, the adverse effect that we worry about the most is respiratory depression. And respiratory depression, if it's severe enough, can lead to overdose and death.

So how do we manage these adverse effects? Well, nausea and vomiting usually resolve in a few days, but you certainly can use an antiemetic or switch to a different opioid. What about sedation? Well, this can happen during dose initiation or when you change your dose. And when sedation occurs, you really need to decrease the dose. Constipation: well, as I had mentioned, it's one of the most common and should be anticipated adverse effects. You can use stool softeners and osmotic stimulants, peripherally acting opioid antagonists, or switch to a different opioid. But you really need to avoid bulking agents because remember, you have a hypodynamic bowel and bulking agents can make that worse.

Pruritus, we mentioned, you could switch to a different opioid, or you can use a non-sedating antihistamine. And then finally, urinary retention, especially in our elderly male patients who have BPH, and oftentimes we need to switch to a different opioid.

There are also patient considerations. For instance, age. With age, there's a decline in therapeutic index and a predisposition to adverse drug effects. Risks such as falls, risks such as worsening cognitive function are important things to pay attention to.

What about medical comorbidities? Liver disease will decrease opioid clearance in many cases. Morphine, oxycodone, hydromorphone: you need to reduce the dose or prolong the dosing interval. What about kidney disease? Decrease in opioid excretion. The preferred opioids in somebody with kidney disease would be hydromorphone, fentanyl, buprenorphine, or methadone. Caution needs to be taken when you're prescribing oxycodone and morphine due to active metabolites.

And then finally, pregnancy. There's the risk of neonatal opioid withdrawal syndrome, and it's important for our patients to know that all opioids are transferred in the human milk to some degree.

What about drug-drug interactions? Well, significant interactions can occur between opioids and drugs that affect opioid metabolism, and these interactions often arise due to inhibition or induction of the cytochrome P450 system. There are opioids that are metabolized by cytochrome P450, and these interactions can reduce or increase the opioid effects. But there are also opioids that are not metabolized by cytochrome P450, and those have fewer interactions, such as morphine and hydromorphone.

We also need to worry about CNS depressants like benzodiazepines, alcohol, cannabis, or other sedatives. These may potentiate the opioid effect on sedation and respiratory depression. And alcohol. We need to worry about interactions with alcohol and opioids because when patients are taking extended-release long-acting opioids, alcohol can cause that opioid to rapidly release, the term is dose dumping, or increase the drug levels even without dose dumping.

This is noted in the CDC guideline about using caution when concurrently prescribing opioids and benzodiazepines or any other CNS depressant.

What do we know about problematic opioid use in patients with chronic pain? Well, this was the most recent systematic review and meta-analysis that looked at that question. It included a hundred and forty-eight studies with over four million participants, and the settings included pain clinics, primary care, and other specialty clinics. And what did they find? They found that almost 30% of individuals on opioids for chronic pain demonstrated some aberrant behavior. And the aberrant behavior was defined as worrisome behaviors including early refills, repeated dose escalation, lost prescriptions, seeking meds from multiple prescribers, or unexpected urine drug test results.

What about opioid use disorder? Just over 9%. And these were based on the DSM or ICD diagnostic criteria or codes.

Along with worrying about the risk to our patient, we also need to think about collateral risk. That is risk to young children who may ingest and overdose, adolescents who may experiment leading to overdose and addiction, and other household contacts.

How do we educate our patients about mitigating these risks? We should talk to them about safe storage, child-resistant packaging, using mail-back envelopes, safe disposal, and overdose education and co-prescribing naloxone. And this is consistent with the CDC guideline using strategies to mitigate risk, including naloxone co-prescribing.

When we talk about risk, we should also talk about concerns about higher dose opioids. And there's lack of high quality evidence supporting the use of high dose opioids for chronic pain. Higher dose opioids are associated with more immunosuppression, hyperalgesia, which is worsening pain, which we'll talk more about, reduced function, and overdose risk. We know that the overdose risk is increased by twofold when we're talking about twenty to forty-nine morphine milligram equivalents, and up to ninefold when patients are on greater than or equal to one hundred morphine milligram equivalents.

So what do we do with patients who are already on high dose opioids? We need to manage them as higher risk. That means increasing our monitoring and support. According to the CDC guideline, we should be starting and prescribing the lowest effective dose, trying to avoid higher dose opioids, use caution at any dose, carefully evaluate the benefits and risks when considering increasing dosages, and avoid increasing dosages above levels with diminishing benefit relative to risk.

Ilana Hardesty: Jane, Dan just provided a lot of information about opioids. So for any given patient on opioids like Michelle, or for a patient for whom you are considering prescribing opioids, is there a way to determine the risk for opioid related harm, including misuse, overdose, and addiction?

Dr. Jane Liebschutz: There's no way to predict in any individual patient their particular likelihood of having problems with opioids. However, there are a number of factors together which can point to higher risk for developing problems. So those include factors related to the medication. We just heard from Dan that the higher doses were associated with more side effects. We also know that long-term opioid use, meaning three months or longer, extended-release or long-acting opioids, particularly the initial two weeks after starting extended-release or long-acting opioids. And then, of course, we heard the combination of opioid and sedatives. Those are all medication factors that increase the risk for opioid-related harm.

In terms of patient factors, and again, we've talked about some of these already, but really mental health problems, other substance use problems, a family history of

substance use disorder, a personal history of opioid overdose, and then sleep-disordered breathing. These are all factors that increase the risk for harm.

So when we think about that question of sleep-disordered breathing, how would we assess that? And this is something that we often use preoperatively, the STOP-BANG questionnaire. Do you snore loudly? Do you often feel tired, fatigued, or sleepy? Has anyone observed you stop breathing? Do you have, are you being treated for high blood pressure? And then the BANG: is there a BMI over thirty-five? Is the age over fifty? What's the neck circumference? And is it a male gender? And then there's a point for each of those factors, and you could see on the right, five to eight gives you high risk for the likelihood of having obstructive sleep apnea, and the opioids combined with obstructive sleep apnea, opioids may give us some central sleep apnea and make them more at risk if they have obstructive sleep apnea.

So how do you assess for opioid misuse risk prior to prescribing? So first, and the easiest, is check for prior history of opioid misuse. So that involves checking the medical records, and if possible, speaking to prior PCPs or any other providers for any history of loss of control, compulsive use, continued use despite harm.

You want to verify the patient's substance use and medication history-taking by checking a urine drug screen, and we'll talk more about that later. And also checking your state and other states' prescription drug monitoring programs. And then there are a number of screening tools which essentially ask about some of these risk factors that I mentioned, which have been shown to predict higher risk of misuse. But there really is no gold standard, and there's really a lack of high-quality evidence supporting their use for predicting an individual's patient likelihood of having problems or harms or misuse from using opioids.

Ilana Hardesty: Michelle screened negative for sleep disordered breathing. She does have several opioid misuse risk factors, including being on long-term therapy, a personal history of depression and anxiety, and a family history of substance use disorder, as her mother had alcohol use disorder. So Jane, how would you manage patients like Michelle who are already taking opioids that were started by another clinician?

Dr. Jane Liebschutz: We heard that opioid prescribing peaked in 2012, and over the last many years since then, there are a lot of patients whose provider has retired or left practice, and they are legacy patients or sometimes called opioid orphans because their prior provider who was prescribing them these high dose or long-term opioids is no longer there.

So again, we use these safety concerns to see whether it's appropriate and safe to continue opioid therapy. You review the patient history from records and the former clinician, their prescription history in the PDMP, assess them for opioid use disorder with a urine drug screen, treat or refer to specialty care if opioid use disorder is identified, and consider a therapeutic bridge for the patient until a plan of care is

determined, given the risks associated with stopping opioid therapy abruptly. Document the rationale for your treatment in your medical record and also document what are the next steps. And this is part of the CDC recommendation to examine the benefits, the risks, and do not abruptly reduce opioids from higher dosage unless there are life-threatening issues.

Ilana Hardesty: Keep in mind that Michelle came in asking for an opioid prescription today. The state prescription drug monitoring program confirmed that she's been getting oxycodone from only one doctor and one pharmacy, and the prescription was last filled seven weeks ago. The PCP has Michelle leave a urine drug sample for a drug test. He arranges for a follow-up appointment in two weeks, prescribes a two-week course of oxycodone, ten milligrams four times per day, continues her gabapentin, and starts acetaminophen to be taken four times per day with the oxycodone.

Michelle was given a handout about self-management strategies and referred to a psychologist for behavioral therapy for her chronic pain, depression, and anxiety. Michelle's problem and medication lists are reconciled, and the PCP reviews her records from her previous PCP. There's inadequate documentation about benefits and an incomplete record of monitoring, including urine drug testing, but there's no evidence of misuse of her prescription opioid, such as early refills.

Before Michelle's next visit, the PCP is concerned about a number of things. Should Michelle be continued on opioids? Should her dose be changed? If so, should she be switched to an extended-release long-acting opioid? Remember, she's taking short-acting oxycodone to be taken every six hours. What other therapies should be considered? And what sort of treatment plan should be developed for Michelle Jones, including co-managing her depression and anxiety?

We'll discuss all of this in the next section. But first, as we conclude part one, Dan, could you please summarize what we've learned so far?

Dr. Daniel Alford: Sure. So we've covered a lot, including focus on reducing pain, improving coping, restoring function, and cultivate well-being, and really maximizing the patient's quality of life, building a strong therapeutic alliance to improve treatment adherence and clinical outcomes, utilizing validated multidimensional instruments to evaluate the full impact of chronic pain, using self-management strategies, including non-pharmacologic therapies, targeted and combined pharmacologic options, routinely assessing and actively co-managing co-occurring mental health conditions, and then finally, prescribe opioids judiciously while assessing all patients for opioid misuse risk.



***SCOPE of Pain* Online Program Part 2**

Transcript

Ilana Hardesty: Welcome back to part two of Scope of Pain.

Two weeks have gone by and Michelle Jones is at her second appointment. The new PCP was unable to contact Michelle's previous PCP as she'd retired and moved out of state. Michelle's drug test returned positive for oxycodone only, as expected. She's not yet made an appointment with the psychologist and has not had a chance to read the self-management information that she got at her first visit.

During this visit, Michelle reports a six out of 10 on each of the three PEG scales, but notes that her pain is sometimes a nine out of 10 immediately before her next oxycodone dose. She denies sedation, and she completed her two-week oxycodone prescription on schedule. So, Dan, how do you decide if opioids are indicated? And if they are indicated, how would you decide on which opioid to prescribe for a patient with chronic pain?

Dr. Daniel Alford: So, I think one important message is that opioids should not be the first choice, and I think we've made that clear. But when you consider opioids, pain should be severe and have a significant impact on the patient's function and quality of life, and that the expected benefits for pain and function outweigh the potential severe risks that we talked about, that the pain type is potentially opioid responsive. For example, nociceptive pain is more responsive than nociplastic pain. That the patient's agreeable to safety monitoring and risk mitigation practices. That non-pharmacologic and non-opioid therapies have proven insufficient. And if the patient's already taking opioids, like our patient, Michelle, I'd like to see some documented benefit and absence of harm.

And this is all consistent with the CDC guideline about maximizing non-pharmacologic and non-opioid therapies and only considering opioids if you think the benefits will outweigh the risks.

I then think about opioids in two buckets. One are the immediate release short-acting opioids, and the other extended release long-acting ones. And you can see when they're side by side that they're essentially the same molecules. It's just how they're formulated.

So when do I choose an immediate release short-acting opioid? Well, first, the patient needs to have no opioid tolerance. That is, they're opioid naive, and their pain is intermittent or occasional. And maybe I want to prescribe it PRN, depending on when they have their most pain. And this is consistent with the CDC guideline about when starting opioids, start with immediate release short-acting instead of extended-release opioids.

When do I consider extended release long-acting opioids? Well, if the patient has opioid tolerance, that is, they've already been taking an opioid, like our patient, Michelle; that the pain is constant, severe, around the clock, and I want to stabilize their pain relief when the patient's using multiple doses of short-acting opioids. It's important to educate and re-educate our patients that these long-acting opioids should not have their formulation disrupted. That is, they should not be broken, chewed, or crushed.

What do we know about the comparative effectiveness and safety of these two different types of opioids? Well- There are lots of uncertainties. So really, what we do clinically is to choose the option that best meets our patient's needs, is there tolerance, and what is their pain like during the day. However, we also want to remember, no matter whether we start short-acting or long-acting opioids, to always start low and go slow.

And now I'm going to talk about some specific opioids that have unique properties. First, let's start with transdermal fentanyl. Fentanyl is 100 times more potent than morphine, and it's dosed in micrograms. The patch has a slow peak onset, 12 to 24 hours, and a delayed offset, 12 to 24 hours. The sustained-release mechanism of the patch requires predictable blood flow and adequate subcutaneous fat. It needs to be applied to intact, clean, and healthy skin. The absorption will be increased if the person is febrile or has broken skin, and the absorption will be decreased if the person has edema or anasarca.

So the patch should be switched every 72 hours and put on a different location. It's important to note that even fully used patches, that is, a patch that's been used for 72 hours, still contains 20% to 60% of the original dose. Therefore, we need to talk to our patients about safe disposal, and the FDA suggests folding the sticky side together, and in this case, flushing them down a toilet if there's a high risk that that used patch will get into somebody's hands is totally appropriate. You may need to remove the patch before an MRI scan. Some have a metal foil backing, which can cause burns.

What about buprenorphine for pain? Well, the formulations approved for pain are dosed in micrograms, as opposed to those formulations approved for opioid use disorders, which we'll talk more about later, are dosed in milligrams. Buprenorphine is twenty-five to forty times more potent than morphine. So again, a very highly potent opioid. It has poor oral bioavailability due to hepatic first pass mechanism. It's a mu-opioid receptor agonist. It has high affinity and slow dissociation, and therefore it can precipitate opioid withdrawal if somebody has a full opioid agonist tightly bound to the receptors.

It is a partial agonist with a ceiling effect on respiratory and CNS depression, and it acts as a full agonist for analgesia. It also has properties at the kappa and delta opioid receptors as antagonists, which can prevent hyperalgesia and has an anxiolytic effect. Buprenorphine can prolong the QTC interval, and it has less effect on cognition and psychomotor function and less hypogonadism compared to other full opioid agonists.

And on the right, the little box shows you the different formulations for pain, the buccal film, and the transdermal patch.

What about methadone for pain? Well, methadone has complex pharmacology, which causes unique risks. Why? Because it has a long, variable, and very unpredictable half-life due to its extensive plasma protein binding. Its analgesia lasts six to eight hours, but its serum half-life can be 20 to up to 120 hours. It can also cause QTC prolongation and the risk of torsades.

Some possible advantages of using methadone for pain: It also is an NMDA receptor antagonist, which can result in reduced hyperalgesia and reduced analgesic tolerance. It inhibits serotonin and norepinephrine reuptake, making it maybe more efficacious for neuropathic type pain. Methadone doesn't have any active metabolites, and it's incredibly inexpensive and can be dosed at small dosage units.

What about dual mechanism opioids, which also involve norepinephrine and serotonin reuptake inhibition? And those include tramadol, which is a weak mu-opioid receptor agonist, and tapentadol, which is a stronger mu-opioid receptor agonist. These medications carry a seizure risk. They absolutely cause physical dependence and need to be tapered when they're being stopped. They can cause serotonin syndrome because of their inhibition of serotonin reuptake, and they're controlled substances with addiction potential.

Now, the pharmaceutical companies have been working hard to make safer opioids by creating formulations with abuse-deterrent properties. And these abuse-deterrent properties include creating physical barriers, that is, they can't be crushed; or combining them with sequestered antagonists; that is, if someone takes it in a different way than swallowing it, they'll get the antagonist; including aversive components, again, to try to prevent people from misusing the opioid; having prodrugs; routes of administration; and ways of reducing the drug reward.

It's important to note that when these medications are diverted, they have a lower street price because they're less desirable, but it doesn't prevent people from misusing these formulations by taking many intact tablets. They also tend to be very expensive, and some insurers don't cover them. I want to leave you with a very important note, and that is that currently there are no one hundred percent proven misuse-resistant opioids. If you want to learn more about abuse-deterrent opioids, I give you the FDA website here.

So the bottom line is you're going to individualize the opioid depending on your patient. You're going to consider the duration and onset of action, considering the pattern of pain, whether it's intermittent or constant. You want to consider the patient's prior experience, that is, with side effects or adverse effects or efficacy. Remember that mu-opioid receptor polymorphisms and differences in metabolism exist between patients. You also want to consider the patient's level of opioid tolerance. You always want to assess tolerance before starting an extended-release, long-acting formulation.

But you also want to consider the patient's age, other medications and diseases, the route of administration, and finally, the cost and whether their insurance company will cover that particular opioid.

Ilana Hardesty: The PCP changes Michelle's medication regimen. Since she tolerates short-acting oxycodone but experiences periodicity or on and off effects, her analgesia may improve with more stable blood levels, even at a lower overall daily dose.

He prescribes extended-release oxycodone fifteen milligrams two times a day. This is a lower overall opioid dose equal to forty-five morphine milligram equivalents, or MME, instead of the sixty MME she was on. He continues the acetaminophen and gabapentin. Note that the provider did not assume that Michelle would need medication for breakthrough pain when he switched her to long-acting opioids.

And before ending the appointment, they discuss strategies for weight loss and re-review the benefits and importance of self-management and behavioral approaches to improve her pain, and he refers Michelle to physical therapy for her hip. The PCP reviews a patient-prescriber agreement with Michelle, and they sign it. Over the ensuing months, Michelle reports improved pain control, allowing her to be more active.

Jane, could you give us some detail about the monitoring and documentation strategies that you put into place to monitor your patients on long-term opioid therapy?

Dr. Jane Liebschutz: As we talked about earlier, there is no true way of predicting or identifying when somebody has an opioid problem, so we really need to think about consistent application of precautions, and this reduces stigma and standardizes care.

What are the precautions? So first, we've already talked at length. You want to assess the patient, and you certainly need to document a pain diagnosis. And if they have particular strong risk factors, you want to make sure that you've noted them and documented them. And you want to present opioid prescribing as a test or a trial, and this would include both new and continued prescriptions. And the decision to continue or discontinue is really based on a risk-benefit profile, and we talk about that in a little bit. When you prescribe, you want to say on the prescription and to the patient, "This is the maximum number of tablets to be taken per day." Using patient-prescriber agreements, they should be written at a fifth-grade level without coercive language.

And of course, we need to monitor for misuse, adherence, and diversion, and we talk a little bit about the patient-provider agreements and monitoring in the next few slides. But this goes along with the CDC recommendations to evaluate benefits and risks within one to four weeks of starting opioids or after a change in dosage or change in medication, and regularly using risk mitigation strategies such as toxicology testing.

All right, so what do we mean by the patient-provider agreement? A lot of times people call this a pain contract. Well, it's not a contract. We're not in a legal relationship with our patients. It really is related to the clinical care that we're providing. Part of it is informed consent, and this includes discussing realistic goals. "You've had pain for 30 years. We're not going to eliminate it, but hopefully we can reduce it to improve your function."

You want to make specific, measurable, action-oriented, realistic, and time-sensitive goals with your patient, and this could include, "I want to be able to pick up my grandkids from school. I want to be able to sweep the kitchen. I want to be able to..." whatever it is that's really important to the patient to allow them to function and have enjoyment of life.

You also want to talk about potential risks. Those include the adverse effects that we've talked about earlier, and you want to look at the drug-drug interaction effects. One of the most severe problems could be oversedation or impairment, such as impaired driving or impaired use of equipment.

We also want to talk about misuse, taking the medication when it's not indicated or taking more than prescribed. Of course, overdose and death are the most worrisome risk for these medications. And then anyone who's pregnant can have their child develop neonatal opioid withdrawal syndrome. Hyperalgesia is something that we'll talk about, which is also a risk. And lastly, victimizations by others who hold their opioids hostage.

A plan of care can include engaging in other treatments, talking about safer opioid use, such as take as directed, don't double the dose, et cetera, no use of illicit drugs, and to avoid and minimize use of other sedatives, including alcohol. Reporting to the PCP or whoever's prescribing what other medications they're taking, what adverse effects they're having, and then the discussion about pregnancy plans is quite important.

So when we talk about monitoring, what are we talking about? We're talking about urine drug testing. So what is the goal of urine drug testing? It's getting objective data that informs us of therapeutic adherence. Are they taking the medications as prescribed? And it can also give us information on use of illicit drugs or potentially other prescribed drugs that weren't reported.

So when you're doing a urine drug test, you want to document their last medication use. Somebody who's taking a PRN medication and only takes it intermittently may not have taken it, and the urine drug test may be negative. But really, the most important part

about the urine drug test is facilitating an open conversation from the patient. “If I send your urine right now, what will I find in it?” And if there are unexpected findings, open-ended questions. “Your urine had cocaine in it. Can you tell me about that?”

One medical data point is the urine drug test, but it’s not the only one, and there can be false positives or false negatives. The urine drug screen is usually an immunoassay. These are quick, inexpensive, but again, risks false negatives and false positives.

Definitive testing with gas chromatography, liquid chromatography, or mass spectroscopy, and that will give the specific opioids, including the metabolites. So some of the metabolites may show up, such as hydrocodone that goes to hydromorphone. So it’s important to understand the chemistry of the medications, and really, your local lab toxicologist should be able to answer questions regarding unexpected results.

What about medication pill counts or prescription drug monitoring programs? So medication counts are really useful for adherence and possible diversion. And the prescription drug monitoring program can give you information on harmful polypharmacy, whether there are multiple prescribers that the patient has neglected to tell you about.

In terms of the medication counts, they are more time-consuming to do. The patient has to come in and bring their medications and look at. But these are really, really useful, particularly if patients are running out early, asking for early refills, or you’re concerned that they’re not taking the medication that’s been prescribed.

Some states require that a prescriber look at the PDMP prior to prescribing any controlled substance. Others allow delegating access to others. Some have interstate data sharing, and this is particularly useful if you have a new patient who’s moved from out of state, and you can look at the PDMP to see if they had been prescribed elsewhere. Or if, like me, you live near other states where patients go back and forth, it helps to see if they’ve had it in the next state.

Methadone that’s administered or dispensed at opioid treatment programs are not routinely included in the PDMP.

We don’t have sufficient evidence to know that PDMPs increase or decrease opioid overdoses. We do know that they’ve been associated with decrease in opioid prescribing overall. The CDC recommends that we use these strategies to mitigate risk, including reviewing the PDMP data.

All right, so how carefully should you monitor patients? Well, we need to have universal precautions when we think about monitoring and prescribing safely. However, individuals may have different levels of risk, and therefore we may have to monitor them differently. So again, when you’re talking with patients, you want to review their

personal and their community risk of opioids and discuss monitoring, that it's protecting them from harm, and also that this is what the practice does for everybody.

For patients with low to moderate risk, we recommend approximately four visits per year and urine drug and PDMP checks two to four times a year. Patients with high risk should probably be seen either every other month or every month, depending on your level of concern, and state laws may mandate certain levels of monitoring.

It should be noted that the DEA requires every three-month visit for patients on controlled substances.

We talked earlier about how to assess patients with acute pain, but we also want to think about how we evaluate and document patients with chronic pain. So of course, we want to understand the analgesia and the level of pain, but we also want to ask about their activities. How much are they doing? What are they doing compared to those smart goals that you set a little earlier? We want to talk about adverse effects, constipation or sedation. Evaluate any aberrant behaviors. Did the patient call a week early for their prescription? What is the patient affect? What's their mood? And what's their adherence to the recommended monitoring?

A study using the National Ambulatory Medical Care Survey data found that in visits when an opioid was prescribed, 30% had no pain diagnosis noted. And so you really need to note in any patient who's prescribed opioids, what they're getting them for.

You may include subjective reports from the patient or other providers who are also caring for the patient, their caregivers, their spouses, or reliable family members. Do be aware that sometimes when patients are having conflict with family members, that other people may call giving inaccurate information for secondary gain.

Obviously, objective information that we've already noted, such as the PEG scores, drug test results, pill counts, PDMP should be noted, and you want to do a 24-hour inventory. "Tell me in the last day how you're taking your medications," or, "Do you miss doses on some days? On average, how many doses do you take per day?"

[00:20:37] **Ilana Hardesty:** All of that sounds like a great deal of work. Can you tell us a little bit more about how you actually manage it, Jane, in your busy primary care practice?

Dr. Jane Liebschutz: Prescribing opioids can feel very difficult to some people because the patient is asking for the medication, and it's hard to know what to do because you don't want to cause harm, you don't want to cause addiction, and you do want to help the patient with their pain. So instead of being a policeman, a judge, a DEA law enforcement person, what you really want to be is the clinician that you are. You want to use a risk-benefit framework. You want to judge the treatment, not the patient.

So how might we set up a system to make that happen? So one concept to think about is opioid stewardship. We have antibiotic stewardship to prevent widespread antibiotic resistance, and we want to think about opioid stewardship in the same way. We want to prescribe opioids safely, correctly, and under the right circumstance.

It's really helpful to have established some sort of leadership or consensus for the practice or for you personally to think about ahead of time how you're going to do this. You want to develop, review, and improve any opioid prescribing policies and procedures in your practice. Use IT decision support to monitor for adherence. Maybe you have access to a patient registry. We want to educate and re-educate patients, prescribers, and our whole healthcare team. For your nurses or your front desk staff, teach them how to respond when patients ask for refills, ask for opioids, et cetera. And using the entire team may be really useful for you to have partners who you can do task sharing for some of the monitoring that we've just talked about. Importantly, it's very useful to have a referral and support resource list so you know when a patient has pain that's not responding to your current treatment, where you would send them for a referral for evaluation or potentially treatments, as Dan talked about earlier. You also want to know who are the local addiction specialists who can help you if you uncover opioid use or other addictions in the course of treating your patient. And then, of course, because mental health symptoms and diagnoses are so common in the case of chronic pain, you need to know who you can refer your patients to.

Another important resource is your community pharmacist. So these are retail pharmacists. They are required by their license to ensure that any prescriptions they dispense are for legitimate medical purposes. They can help you with medication choices, doses, and potential substitutions, particularly those that may be required because of insurance issues. They interact with patients, they educate patients on all the things that we've talked about: risks, storage, drug take-back programs, and use of naloxone as overdose prevention. They are also required to check the PDMP and monitor for worrisome behaviors. They may identify potential drug-drug interactions, and they may assist with formularies and prior authorizations.

Prescribers can help by including diagnoses or indications on the prescription, parameters for when scripts should be filled. When I write prescriptions, I'll write, "Please do not fill before thirty days from the last prescription." And it's very important to maintain open lines of communication, including getting direct phone lines to your office or for you to them.

Ilana Hardesty: Now, let's discuss four potential scenarios for this case, covering the following topics: assessing and managing worrisome behaviors, switching from one opioid to another, discontinuing opioids, and managing opioid use disorder.

Michelle did well on her pain treatment plan for her painful diabetic neuropathy and chronic hip pain for eleven months. Then her PCP was notified that Michelle was seen in the emergency room of a local hospital requesting an early refill of her oxycodone after running out early. The ED physician noted that she was in moderate opioid

withdrawal and gave her a prescription for enough oxycodone pills to last until her next PCP appointment.

At Michelle's follow-up appointment, she said that her foot pain had worsened in the last month and is a ten out of ten most days. She started taking an extra pill every day and ran out early. She is concerned that she's become used to the current dose, and she says her husband thinks she's addicted. She has trouble going to work and trouble sleeping and requests an increase in her dose. Her PCP re-educates her about the serious risks of self-escalating her dose.

She missed the first appointment with the pain psychologist due to her severe pain and is not convinced that it's going to help her. She's attended only one physical therapy session as she's having trouble finding the time to fit everything in. So Dan, what do you think is happening with Michelle here, and how would you respond to this recent worrisome behavior?

Dr. Daniel Alford: So I think the first thing to do is just take a deep breath and think broadly about what could possibly be going on, what's causing these worrisome medication-taking behaviors.

And it could be substance seeking. Maybe she has developed an opioid use disorder. Or maybe she's self-treating some other symptom like anxiety or insomnia. We know that opioids make people feel good. Or maybe there's some diversion. Maybe she's sharing or selling her prescription.

But there's also the possibility of pain relief-seeking. That is, maybe her disease, her neuropathy, has progressed. Maybe she has a new painful condition that she's treating. Maybe her pain is poorly opioid responsive, and we're really not going to get a handle on it with opioids. Maybe she has developed opioid analgesic tolerance or withdrawal-mediated pain, which we'll talk more about. Or she's developed something called opioid-induced hyperalgesia and/or allodynia, which we'll talk more about.

Unfortunately, sometimes it's a combination of multiple factors. Maybe there's worsening pain along with an opioid use disorder, and maybe she's diverting some of the opioid for income. But the important thing is to think broadly of all the possibilities.

So I mentioned opioid withdrawal-mediated pain. What is it? Well, in patients who are taking opioids around the clock, they have physical dependence, as Jane had described earlier. And maybe a drop in the blood opioid level causes some opioid withdrawal, which experienced as increased pain sensitivity. So maybe during the day she develops pain, but really it's opioid withdrawal. She takes her dose, feels better, but is she treating the pain or is she treating her physical dependence? And so these are important things to sort out, and part of it is the rationale for using extended-release long-acting opioids to prevent these up and down swings during the day.

We've also mentioned a few times this concept of opioid-induced hyperalgesia or allodynia. What is it? It's a paradoxical worsening pain despite an increase in opioid dose, and it has to do with hyperexcitability of the nervous system causing increased sensitivity to painful stimuli and even non-painful stimuli like allodynia, like touch. The underlying pathophysiology is unclear, but experiments have demonstrated NMDA receptor-mediated increased pain sensitivity after prolonged opioid exposure. The true incidence is unknown, but most studies that are reporting hyperalgesia are in patients on high-dose opioids. There's no validated diagnostic criteria, but clinically what we see is the pain is generalized, it's diffuse, it's ill-defined, and it really is beyond the site of the original pain, and it's refractory to opioid dose increases. When it's suspected, it could be managed with either a reduction or discontinuing the opioid or even switching to an alternative opioid.

But when someone has a lack or loss of benefits, what are the next steps? And the first thing is to reassess the factors affecting their pain, reattempt to treat or even diagnose any underlying disease or comorbidities, and then consider adding or increasing the non-opioid or non-pharmacologic treatments, potentially add breakthrough medications, switch to a different opioid, sometimes referred to as opioid rotation. And really, we want to try to avoid dose escalation to higher dose opioids because we now know about the increase in risks in doing so.

So when we consider breakthrough medication, the first choice, even though the person's on a long-acting opioid, is a non-opioid. So if they're having breakthrough pain, you could try treating them with an NSAID or acetaminophen. If that doesn't work, you certainly could use a short-acting opioid, either the same molecule as the long-acting opioid or a different molecule. Or you could try one of the dual mechanism opioids we talked about, tapentadol or tramadol.

If you're going to consider switching the opioid or an opioid rotation, the rationale for doing so is threefold. One, you want to try to restore analgesic efficacy by switching to a different opioid. You want to limit adverse effects if that's what the problem is. And ultimately, you'd like to decrease the overall morphine milligram equivalents, which I'll explain in a minute.

This switching opioids or opioid rotation is really based on large interindividual variation in response to different opioids, the different variants of the mu opioid receptors we talked about, and there's limited evidence as most of the trials were retrospective and studied with small numbers of patients. But it certainly is something to consider in a patient like Michelle, who seems to be losing the benefit of the opioid she's been on.

If you're going to switch to a different opioid, you're going to go to an opioid conversion table, and it's important to understand where these tables come from. They're derived from relative potency ratios using single-dose analgesic studies in opioid-naive patients. They're based on limited doses and limited ranges of doses, and you can see already that these tables don't necessarily reflect the clinical realities of our patients who are on chronic opioid therapy. There's problems with reliability due to the

individual pharmacogenetic differences between our patients, and most tables do not adjust for something called incomplete cross-tolerance.

What does that mean? Well, if you, for example, figure out the exact equal analgesic dose of opioid A to opioid B, and you give somebody opioid B at that same equal analgesic dose, it's possible that they will have some adverse effects like sedation that they didn't have with opioid A because of this incomplete cross-tolerance.

So let's actually use Michelle Jones as an example of opioid rotation. So remember, she's on extended-release long-acting oxycodone, 15 milligrams BID, or 45 morphine milligram equivalents. And I like to use the website globalrph.com, which is really a fancy calculator, which allows you to put in the person's current opioid, total daily dose. If she was on a short-acting opioid for breakthrough pain, you could put that in as well. And then it allows you to reduce the equal analgesic dose of the new opioid due to incomplete cross-tolerance. And there really is not an exact science. The recommendations are to decrease by 25 up to 50%.

So I'm going to pick something in the middle, 33% reduction, and I'm going to convert her to morphine. And I click Calculate, and it comes out to 30 milligrams. So I'm going to convert her to extended-release long-acting morphine, 15 milligrams BID or 30 MMEs. And you can see that I've achieved that third goal, and that is by decreasing the overall MME by making this rotation.

Ilana Hardesty: Over the next eighteen months, Michelle's pain improved on a stable morphine dose of 15 milligrams twice a day, and she had no recurrent worrisome medication-taking behavior. Along with the morphine, her acetaminophen and gabapentin were continued.

She stopped seeing the pain psychologist after three sessions but learned valuable relaxation skills that she continues to use. She joined a monthly chronic pain support group at her church. She completed physical therapy, which she thinks helped with her hip pain. Her individual PEG scores remained between five and six on the ten-point scale. She remained employed and remained adherent with treatment and monitoring. She continued with her regularly scheduled follow-up visits.

In an alternative ending, scenario 1B, after being switched to morphine and maintained on gabapentin and acetaminophen, Michelle's pain remained out of control with PEG scores between nine and ten out of ten. She's now on medical leave from her job, and according to her husband, spends most of the day in bed.

She was not able to see the psychologist or the physical therapist due to the severity of her pain. The PCP added duloxetine to her pain regimen to also address her apparent depression. Despite one dose increase of morphine, she demanded that she be changed back to oxycodone. After being converted back to oxycodone, her pain did not improve. Clinic staff reported on multiple occasions that she was rude and confrontational when she tried to be seen without an appointment. Michelle says she's

now smoking marijuana to help with her pain. Jane, what do we know about cannabis and pain?

Dr. Jane Liebschutz: Cannabis is now widely used across the US for pain. There are dispensaries in many states for medical cannabis, and many people report, like Michelle, that they've been using cannabis for pain.

So what do we know about it? So cannabis and the marijuana plant includes greater than 60 pharmacologically active cannabinoids, including cannabidiol and the psychoactive tetrahydrocannabinol, THC. Endocannabinoids receptors are found in high concentrations in the brain and spinal cord.

So what's the efficacy of cannabis? So there's moderate quality evidence that cannabis can be effective for short-term treatment of neuropathic and nociplastic pain, but inconclusive for nociceptive pain. And that short term is generally one to six months. To achieve a thirty percent pain reduction, the number needed to treat is twenty-four for cannabinoids and four to ten for TCAs, opioids, gabapentinoids, and SNRIs.

What are the risks or harms? Well, the side effects generally are mild, but it can cause dizziness, sedation, and impaired coordination. Long-term use in adolescents and young adults can result in cannabis use disorder and long-term cognitive impairment. Some states have community pharmacists dispense and report medicinal cannabis to the PDMP.

Ilana Hardesty: So at this point, would you consider referring Michelle to a pain specialist? And what do you do if there's continued lack of benefit?

Dr. Jane Liebschutz: So what is the role of pain specialists? There are a number of possibilities in the ways pain specialists can be helpful in this situation. So one is whether there's uncertainty about the pain diagnosis or whether there might be other treatments, including interventional ones that may be useful. Interventional treatments can include injections, nerve stimulations, nerve ablations, vertebroplasty or kyphoplasty. The evidence for those interventions varies by procedures, and there can be strong short-term relief with epidural injections for radiculopathy. There's moderate evidence for radiofrequency ablation for facet-mediated spinal pain, while others have more mixed long-term data.

It's important to set appropriate expectations to the patient. Don't send the patient with the expectations that they will get a specific treatment, as this sets them up for disappointment and frustration. If you want to locate a provider, the American Society of Interventional Pain Physicians or the American Society of Regional Anesthesia and Pain Medicine have directories that you can look for.

Unfortunately, sometimes the opioids may not be effective for chronic pain. And so we ourselves have to remember that not all chronic pain is opioid responsive and more

opioid is not always better, and that more opioid may increase risk of adverse effects, and some chronic pain improves after opioid tapering.

When to discontinue opioids or deprescribe: You really don't have to prove addiction or diversion. You just assess and reassess the risk-benefit ratio. If there is no benefit, it doesn't matter what the risk is. Even if there's no evidenced risk, there's no reason to continue the medication. If a patient is unable to take their opioids safely or is non-adherent with monitoring, then discontinuing opioids is appropriate even in the setting of benefits.

You're not abandoning the patient, you're abandoning the opioid. When you think about how to do this, you need to determine how urgent the discontinuation should be based on the severity of the risks and harms, and determine if the opioid needs to be tapered due to physical dependence or whether it can be stopped right away. And as we document when we prescribe, we also have to document when we discontinue, what the rationale is, and how we're going to help the patient manage their pain.

All right, so what are the benefits and risks to tapering? Unfortunately, we have very few high-quality studies that can give us an answer. There was a systematic review that reviewed 57 studies that investigated the effectiveness of tapering. I should note that the studies were all very, very different and most very low quality, and so the findings of this systematic review should be taken with a grain of salt. It did show that there were some statistically significant improvements after tapering for various outcomes, including pain intensity, headache, disability, anxiety, depression, pain catastrophizing, pain interference. But they did not find any difference between physical functioning, mental health-related quality of life, and physical health-related quality of life.

In contrast, there are some observational studies that have identified harms, most seriously suicide and overdose, that have been associated with opioid tapers. A comparative effectiveness study of individuals on long-term opioids with no evidence of opioid use disorder or opioid misuse found that tapering was associated with small absolute increase in opioid overdose or suicide compared with maintaining stable opioid dosages. So this is a caution when you want to taper that you may have risks and you may or may not have benefits.

It's really important to stress how much you believe the patient's pain severity, to show empathy for their suffering and frustration, focus on their strengths, and encourage therapy for coping with pain, and show the commitment to working to control the pain, improve functioning if you're planning an opioid taper or if you feel that there's a lack of benefit for the opioids.

And I know this was on a prior slide, but I want to reiterate, you're abandoning the opioid, not the patient, and it's highly important to emphasize that. If the patient continues to request an increase in opioids, state, "I cannot continue to prescribe a medication that is not helping you or is hurting you or both."

Highly important to schedule close follow-ups during and after any change in therapy.

Ilana Hardesty: Despite her PCP's best efforts to explain to Michelle why the treatment plan will include tapering off opioids due to lack of adequate benefit and focusing on non-opioid pain treatments, including increasing duloxetine and re-referral for cognitive behavioral therapy, Michelle keeps insisting that she needs a higher dose oxycodone.

Though she was offered alternative pain treatment, she became increasingly angry, stating that she was going to find a new doctor. Michelle stormed out of the office and said she would be calling patient advocacy.

In a new scenario, remember that Michelle was doing well on her pain treatment plan, including oxycodone for her painful diabetic neuropathy and chronic hip pain for 11 months. But then she started to struggle and became frustrated with the rules and the stigma of taking opioids. Michelle calls her PCP after being unable to refill her oxycodone because of new insurance requirements. She's angry, and she's crying with frustration, noting the stigma that she feels from her family, from the staff at the PCP office, and at the pharmacy. She says she's tired of being treated with suspicion like a drug addict and a criminal and just wants to get off the pills. Jane, what can you tell us about the stigma that Michelle is experiencing, and how do you taper someone who wants to discontinue opioids?

Dr. Jane Liebschutz: So stigma is being discredited or being made to feel undesirable because of a particular attribute. This is incredibly common among people with chronic pain and also people prescribed opioids, as well as people with substance use disorder. So individuals with pain who have less clear pathophysiology report greater stigma.

Stigma can be internalized, which can contribute to poorer pain-related outcomes. Studies have found a positive correlation between stigma and pain intensity, disability, and depression. Patients might believe they deserve their pain, they're being punished, or do not deserve to be included in social activities, and this can be a vicious cycle that can worsen the pain. Opioid-related stigma includes fears about anticipated negative attitudes and judgments from others.

So how do we taper opioids? There's no validated protocols in patients on opioids for chronic pain. There's very low-quality evidence which suggests several types of opioid tapers may be effective and that pain, function, and quality of life may improve for some patients who have a decreased opioid dose.

One study found 62% of patients in a pain clinic completed a voluntary patient-centered opioid taper over four months with more than 50% dose reduction. Neither pain intensity nor pain interference increased with this reduction, and success was not predicted by starting dose, baseline pain intensity, years prescribed opioids, or any psychological variable.

So what's a general approach to opioid tapering? So the CDC recommends that you decrease the opioid dose approximately 10% per month if the patient has been on the opioid for years. And if the patient has been on the opioids for weeks to months, you decrease by 10% per week, so a more rapid decrease.

So what we need to think about is the speed of the tapering and the goal. This will depend on the reason for the taper. The lack of benefit would be a taper over weeks to months. Apparent harm or high risk would be a taper over days to weeks. You want to build up alternative pain treatments as short-term withdrawal can lead to transitory increased pain flares. The first step is to reduce the medication dose to the smallest dosage unit. The second step is to increase the amount of time between doses. So for example, an immediate release opioid can be started when at the lowest extended-release long-acting opioid. You can also use alpha-2 adrenergic agonist for withdrawal symptoms. This includes lofexidine or clonidine or tizanidine, the last two of which are off-label for this use.

Ilana Hardesty: Over six months, Michelle successfully tapered off the oxycodone. Her neuropathic pain was moderately controlled on a combination of acetaminophen, gabapentin, and duloxetine. She continues to engage in self-management strategies that she learned from the psychologist, including breathing, relaxation, and mindfulness exercises.

Michelle joined a monthly chronic pain support group. Her individual PEG scores remained between four and five on the 10-point scale. She remained employed and remained adherent with treatment and monitoring. She continued with her regularly scheduled follow-up visits.

In the final scenario, we return to Michelle doing well on her pain treatment plan, including oxycodone for her painful diabetic neuropathy and chronic hip pain for 11 months. But then she started exhibiting some worrisome opioid-taking behavior. Her urine drug tests consistently returned expected results, except once when it was opiate positive but negative for oxycodone, raising concerns for opioid misuse, including possible diversion.

Michelle asserted that she has been taking her prescription on schedule and denied sharing it or giving her oxycodone to others. A confirmatory test could not be done due to the urine sample being too small. She has forgotten to bring in her pill bottles for medication counts on two occasions. The PCP shares his concern with Michelle and tells her that since these instances put her at greater risk for harm, he'll need to monitor her more closely, including more frequent urine drug tests and medication counts. There were no additional unexpected results over the next two months.

Jane, how do you talk to patients who you are worried may be diverting some of their opioid pain medications?

Dr. Jane Liebschutz: So when we talk about diversion, we're talking about one form of opioid misuse, which is defined as giving, selling, or trading prescription medications. And of note, family and friends are a common source of diverted opioids. When you want to have this conversation with a patient, you need to kind of calm yourself down because it's a painful conversation. You want to discuss what makes you concerned about diversion, things like, "Your urine drug test has been negative on three occasions for the opioid we prescribed but includes something that we didn't prescribe."

Also, when we've asked you to bring in your pills, you brought in a bottle that included Tylenol and not oxycodone." Discuss your inability to continue to prescribe opioids if the opioids are being diverted to others.

Ilana Hardesty: Two months later, Michelle is brought to the emergency department by ambulance after suffering an overdose.

Her husband explains that he found her on the bathroom floor and administered naloxone, to which she responded, and then called 911. Her husband reports that Michelle's pain has increased recently, resulting in her taking extra oxycodone pills and taking some of her father's morphine. She had been sleeping a lot and calling in sick to work.

Her husband acknowledges that he's been denying Michelle's problem to himself as he's immersed himself in his own work. He reports Michelle has now been fired from her job for missing too many deadlines, and that she once fell asleep with a stove burner on. He acknowledges that he's been rationalizing, telling himself the changes in Michelle were due to the pain, not the medications. He reports hearing a staff person in the ED refer to Michelle as an addict and drug abuser, and he's upset by this characterization.

Jane, is Michelle a quote, drug abuser, unquote? And how would your treatment plan change after this overdose and with the added history that she's been experiencing other negative consequences related to the opioids?

Dr. Jane Liebschutz: I think you bring up two really good points. The first one is that the words we use to describe our patients really matter. There's been a number of studies shown that when we use stigmatizing language, the clinical choices are not evidence-based and may withhold important treatment.

So what do we mean by stigmatizing language? Calling somebody an addict, a substance abuser, an alcoholic. What should we say? We should say a person with substance use disorder. Instead of saying substance abuse, substance use. Clean urine, expected test results. A patient is clean, a person with substance use disorder in remission. Dirty urine, unexpected test result. Patient is dirty, active substance use, or return to substance use when they had been sober for a period and now have been using again. Stigma surrounding substance use disorder is perpetuated by the

stigmatizing terminology used in healthcare settings, by the news and other media, and by society as a whole.

But the other question you bring up about Michelle is concern for overdose, and it's very important to think about this when we prescribe opioids to patients. First of all, there are two FDA-approved overdose reversal agents. Naloxone is short-acting, and it goes into effect and lasts for one to two hours, and it's an opioid antagonist administered either IM, IV, intranasal, or subcutaneous. Nalmefene is longer acting, and it has much higher binding affinity than naloxone and also is administered in those same routes. The potential benefits of nalmefene, greater affinity, longer duration action, carry a much higher risk of causing harm due to prolonged precipitated opioid withdrawal. In terms of future risk, a retrospective cohort of adults who had non-fatal opioid overdose during long-term opioid therapy for chronic pain found that opioids were subsequently dispensed to 91% of these patients after their overdose in the subsequent few years. 7% have repeated overdose and 17% for those on high opioid dosages. So when we see a patient who's experienced an overdose, we need to be very careful about whether we're going to continue to prescribe opioids, particularly high-dose opioids, because of this unacceptable risk.

Ilana Hardesty: Dan, let me turn back to you now. Does Michelle have an opioid use disorder? And how do you diagnose that? And finally, if she does, how will you treat that OUD?

Dr. Daniel Alford: Yeah, these are very important questions. Let's start with describing opioid use disorder. It's a chronic relapsing brain condition that's characterized by compulsive use despite negative consequences. It involves changes to the brain pathways that are involved in reward, stress, and self-control. These changes can persist even after stopping the opioid. Like other chronic diseases, opioid use disorder often involves cycles of relapse and remission. And we know that without intervention, opioid use disorder is progressive and could result in disability and/or premature death.

So how do we diagnose it? Does this patient, does Michelle, have an opioid use disorder? And some would say, "Oh, she had an overdose, therefore she has an opioid use disorder." But not necessarily. It could have been an unintentional overdose. So we go to the gold standard, the DSM-5, and we look at the eleven criteria or eleven symptoms, including tolerance, withdrawal, and then three that involve loss of control or compulsive use, and five that indicate continued use despite negative consequences, and then craving and compulsion. And if you have two to three of these, you have mild OUD, four to five moderate, and six or more gives you a severe opioid use disorder.

But in someone who's been doing this work for a while, I understand that some of these symptoms, like using large amounts for longer periods of time or inability to cut down or control use or increased time spending obtaining or using or recovering, or even some of these reducing social, work and recreational activities, could be related to their pain and not necessarily the opioid in and of itself.

And so there is now described a pain-adjusted DSM-5 for opioid use disorder. Tolerance and withdrawal, as you heard from Jane earlier, are expected outcomes in someone who's on chronic opioids. So you can't count them in someone who's being prescribed opioids by a clinician.

So let's get rid of those two, and that leaves us with nine. And then we need to look at the symptoms that the patient has and exclude any that are driven solely by pain relief and/or therapeutic intent to make that distinction. So you can already see that it's complicated. It's doable, but we really need to think about is some of these symptoms related to uncontrolled pain or is it due to the opioid exposure?

But if we diagnose somebody or we think they have an opioid use disorder, we want to talk to the patient about why we think so. So we give specific, timely feedback about which behaviors raise our concern about possible OUD. That is loss of control, compulsive use, and continued use despite harm. And remember that patients may suffer from both chronic pain and OUD.

Sometimes we need to agree to disagree if the patient isn't open to the possibility that they have this new diagnosis. And we need to understand that the benefits can no longer outweigh the risks. And we would say something like, "I cannot responsibly continue to prescribe opioids as I feel they would cause you more harm than good." We always want to support connecting our patients to and/or initiating opioid use disorder treatment

So what is the treatment? Well, the good news is we have options, and those options are medications. And these medications normalize brain changes that I described earlier. They alleviate physical withdrawal, they provide opioid blockade, and they alleviate drug craving. And just a word about opioid blockade. That is when the patient is on these medications on the right dose, if they relapse, they do not get the euphoria that they would normally get from the opioid. So it's causing blockade.

And the options include methadone, which can only be dispensed in a licensed opioid treatment program. Remember earlier we talked about methadone for pain? Well, now when we talk about methadone for opioid use disorder, we cannot legally prescribe methadone for treating OUD. It can only be dispensed in a licensed program.

Then there's naltrexone, a full opioid antagonist, which can be given orally or a monthly intramuscular injection. And then finally, buprenorphine, which can be given submucosally or a weekly or monthly subcutaneous injection. And for buprenorphine, which we can prescribe now without any additional training, you can start prescribing it today, we dose it once a day to treat OUD. But if the person has OUD and pain, we would dose it three times a day because the analgesic properties of buprenorphine only lasts six to eight hours.

These medications, through multiple studies, have shown positive outcomes, including increased retention in treatment and improved employment, decreased relapse,

decreased HIV and hepatitis C seroconversion, and probably most importantly, decreased mortality. These medications decrease mortality, and I'm talking specifically about methadone and buprenorphine.

Medications for OUD or MOUD is easy to use. Unfortunately, however, it's not universally available even after a patient has had an overdose. The CDC last recommendation in their guideline is to offer and arrange evidence-based medications for treating OUD in those patients who you've diagnosed. If you want to learn more about treating OUD with medications, you can go to [scopeofpain.org](https://www.scopeofpain.org) and look at the supplemental trainings.

Ilana Hardesty: Michelle's PCP continues the buprenorphine started in the ED to treat both her pain and OUD. Months later, because Michelle's hip pain from her end-stage osteoarthritis is affecting her quality of life, she is scheduled for a right hip arthroplasty.

Now that Michelle is taking buprenorphine, how should her surgical pain and OUD be managed perioperatively?

Dr. Daniel Alford: Yeah. This is one of the more common questions that I get asked as an addiction medicine specialist. And the good news is there's now consensus on how we should manage these patients. First, we need to realize that patients with OUD often are more sensitive to painful stimuli, whether they were born that way or whether their OUD history made them that way, but they tend to be more sensitive to pain.

The next thing is to continue their methadone or buprenorphine throughout the perioperative period because if you stop it, they will go through withdrawal, and it'll become very difficult to manage their pain. So continue the methadone or buprenorphine. Then treat their pain with analgesics on top of their MOUD similar to how you would treat someone else's acute pain. Patients taking MOUD may need higher doses of their opioid analgesics due to cross-tolerance. We do know that ineffective pain management in these patients can result in disengagement in care.

Ilana Hardesty: Michelle did well following the surgery with improved pain control of her right hip. Her painful diabetic neuropathy is well controlled on a combination of buprenorphine taken three times per day, duloxetine, and acetaminophen. Her gabapentin was discontinued due to the misuse risk.

Her PEG scores remained between five and six on the 10-point scale. Her OUD is in sustained remission with MOUD and outpatient addiction counseling. She regains employment and continues with regularly scheduled follow-up visits.

Dan, can you please summarize what we've learned in part two of this program?

Dr. Daniel Alford: Sure. So we talked about matching treatment plans to the patient's needs and functional goals, that we individualize universal precautions based on the

patient's risk. We clearly document the rationale and the benefits and risks and harms when patients are prescribed opioids. We utilize interprofessional teams for monitoring and support. We identify and manage worrisome opioid taken behaviors and, when indicated, taper opioids gradually and institute alternative pain therapies. We talked about diagnosing and managing opioid use disorders using highly effective medications and to continue methadone or buprenorphine for their OUD during the perioperative period.

Ilana Hardesty: Thank you for participating in the *SCOPE of Pain* online activity. Please complete the part two post-test and the evaluation. Then you'll be able to download your certificate. If you haven't already done so, please download the transcript, slides, and large reference document so that you have it for your information.

Also, be sure to visit our resources pages where you'll find additional educational modules, tools to help you implement what you've learned into your practice, and videos that model challenging clinical interactions.