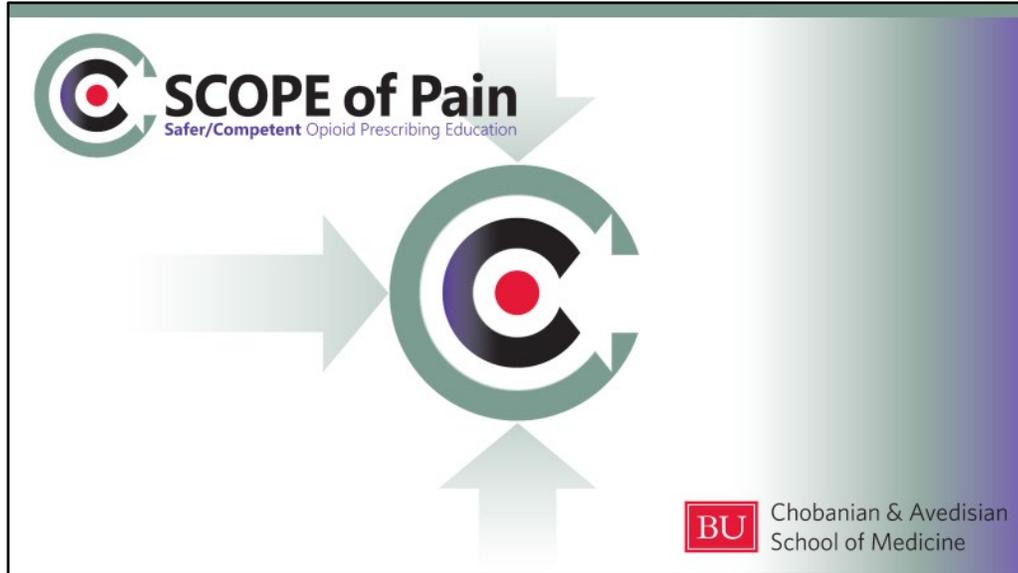


Slide 1



John Emery: Thank you for participating in Boston University's Safer and Competent Opioid Prescribing Education – *SCOPE of Pain* – Program. I'm John Emery, your moderator.

How the Program Works



Description

- Web-based program, with CME, CNE, and CPE credit available
- Two parts, with a post-test after each part (note: stars in upper right-hand corner of slides indicate post-test content)
- Certificate available upon completion of post-tests and evaluation, at the end of both parts
- Additional resources, tools, and supplemental educational activities available here at this website: www.scopeofpain.org



This web-based program consists of two parts that follow the case of Michelle Jones to discuss management of acute and chronic pain. After each part, you'll be directed to a post-test. Further information about receiving credit is available on the information page and will be provided at the end of the second part.

In addition, you'll find a wealth of materials available at the SCOPE of Pain website, including detailed information on content we'll be discussing today, 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're training your colleagues.

Faculty



Melissa Weimer is a consultant for CVS Health. Other faculty members have no relevant financial relationships to disclose.

These presentations include discussion of the off-label use of sublingual buprenorphine to treat pain. Sublingual buprenorphine has been FDA approved for addiction treatment but not pain treatment. 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. This presentation does include discussion of the off-label use of gabapentin for chronic pain (other than post-herpetic neuralgia).

Daniel P. Alford, MD, MPH (Course Director)
Professor of Medicine
Associate Dean, Continuing Medical Education
Director, Clinical Addiction Research and Education (CARE) Unit
Boston University Chobanian & Avedisian School of Medicine
Boston Medical Center

Content Development/Planning Committee
Erica Bial, MD, MS, Private Practice
Patrick Kelly, PharmD, University of Rhode Island College of Pharmacy
Kristin Wason, NP, Boston University Chobanian & Avedisian School of Medicine | Boston Medical Center
Melissa Weimer, DO, Yale University School of Medicine

Ilana Hardesty, MA, Assistant Director, Boston University Chobanian & Avedisian School of Medicine
Carmela Townsend, DNP, MS/MBA, RN, Boston University Chobanian & Avedisian School of Medicine



We'll be discussing this case with Dr. Daniel Alford, Professor of Medicine, Associate Dean of Continuing Medical Education, and Director of the Clinical Addiction Research and Education Unit at Boston University. Dr. Alford is a general internist, practicing primary care at Boston Medical Center.

Partners and Supporters



- National Partner**
 - Federation of State Medical Boards
- Grant Support**

This activity is supported by an independent educational grant from the Opioid Analgesic REMS Program Companies. See https://ce.opioidanalgesicrems.com/RpcCEUI/rems/pdf/resources/List_of_RPC_Companies.pdf for listing of REMS Program Companies. This activity is intended to be fully compliant with the Opioid Analgesic REMS education requirements issued by the US FDA.
- Opioid REMS**
 - Content dictated by FDA *"Blueprint for Prescriber Education"*
 - FDA requires opioid analgesic manufacturers to fund CME certified education by approved providers



SCOPE of Pain was developed in collaboration with our national partner, 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.

About the Program



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

- Assess pain, function and for opioid misuse risk
- Educate patients about opioid risks and limitations
- Develop patient-centered treatment goals
- Monitor patients prescribed opioids for benefits and harms
- Use a risk-benefit framework when initiating, maintaining, modifying, or tapering opioid analgesics
- Diagnose and manage patients with opioid use disorder with or without concurrent pain



Through the case presented in this program, learners will be able to assess pain function, and opioid misuse risk, educate patients about opioid risks and limitations, develop patient-centered treatment goals, monitor patients prescribed opioids for benefits and harms, use a risk benefit framework when initiating, maintaining, modifying, or tapering opioid analgesics, and diagnose and manage patients with opioid use disorder with or without concurrent pain.

Purpose of the Training



SCOPE of Pain
Safer/Competent Opioid Prescribing Education
www.scopeofpain.org

- Covers strategies for safer use of opioids for managing acute and chronic pain by reviewing **best practices** and sharing **clinical pearls**
- Does NOT cover palliative care or end of life pain management

Alford DP, et al. Pain Med. 2016



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. This training does not cover palliative care, or end of life management, due to the differences in overall treatment goals.

Slide 7



SCOPE of Pain
Safer/Competent Opioid Prescribing Education
www.scopeofpain.org

Introduction:
Setting the Stage

First, let's set the stage. Dr. Alford, could you review the big picture of acute and chronic pain, including disparities and barriers in pain care, and prescribing in overdose trends?

Acute Pain <i>Life sustaining symptom</i>	Chronic Pain Pain persisting beyond expected healing <i>Can be a disease in and of itself</i>
Adaptive by eliciting motivation to minimize harm and allow healing	Maladaptive disorder influenced by genetic and epigenetic factors <ul style="list-style-type: none"> • Nociceptive: tissue or potential tissue damage including somatic (e.g., bones, joints, muscle) and visceral (e.g., mucosal injury, distention, ischemia) • Neuropathic: disease or injury affecting the nervous system including central (e.g., trauma, stroke, neurodegenerative) and peripheral (e.g., compression, trauma, ischemia) • Nociplastic: amplified processing of, or decreased inhibition of pain stimuli at multiple levels in the nervous system including diffuse sensitization (fibromyalgia), functional visceral pain (IBS), regional somatic sensitization (complex regional pain syndrome)

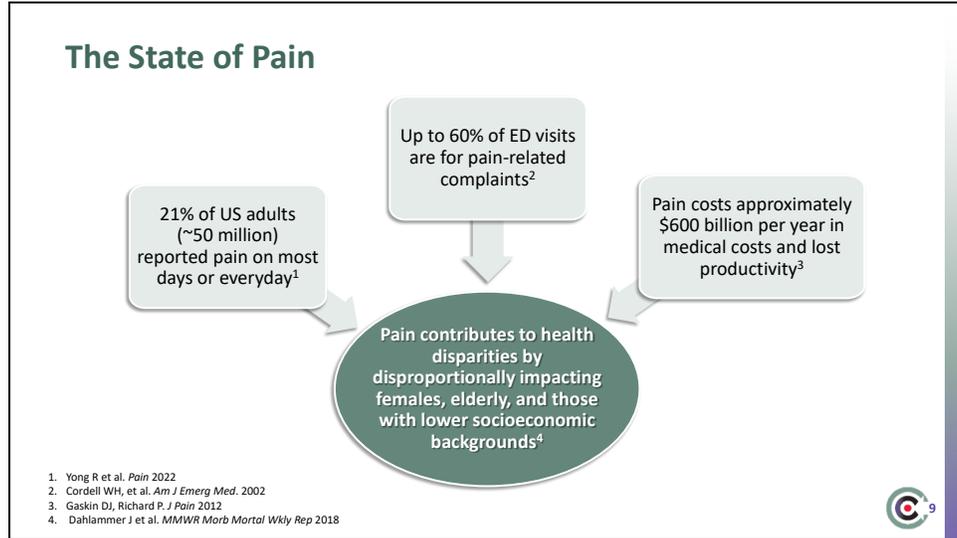
Cohen SP, et al. *Lancet*. 2021



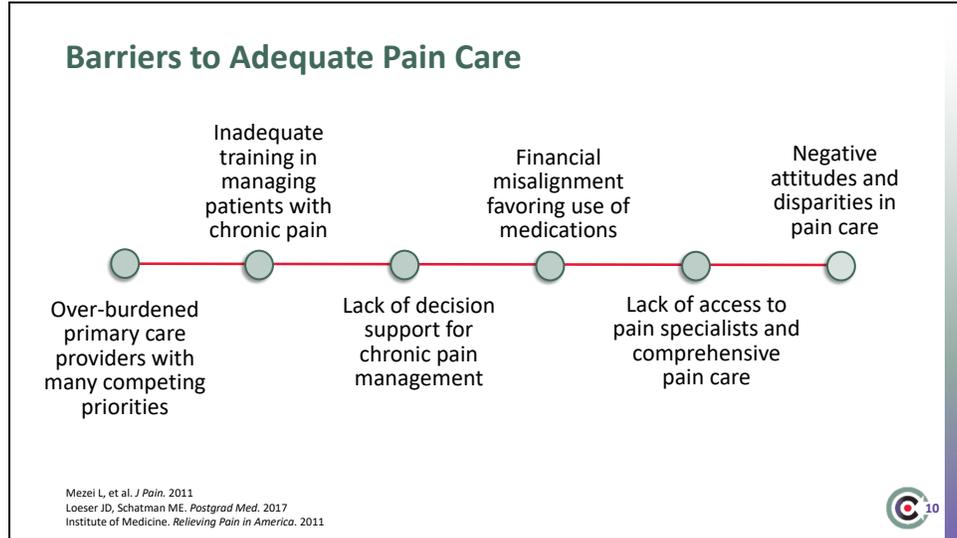
Daniel Alford, MD: Sure. So, when we think about acute pain, we think about it as a life-sustaining symptom, which is adaptive, by eliciting motivation to minimize further harm, but also to allow healing. When we talk about chronic pain, it's pain that persists beyond the expected healing time, and really it can be a disease in and of itself. It's maladaptive, and we don't completely understand it, but we believe it's influenced by both genetic and epigenetic factors.

So, there are three main categories:

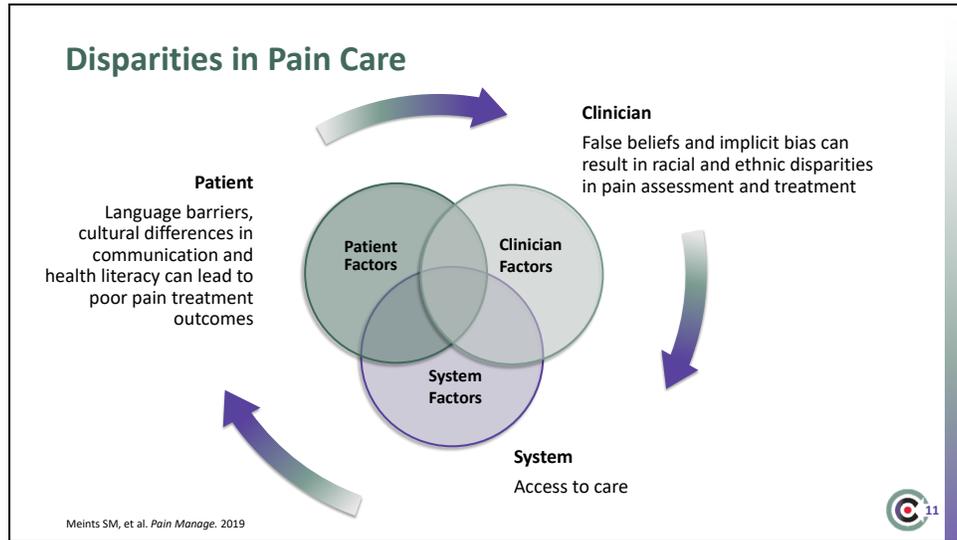
- Nociceptive pain, which involves tissue, or potential tissue damage, including somatic, which includes bones, joints, and muscle, and visceral, or mucosal injury, distention, ischemia, and these are the causes.
- Neuropathic pain, disease or injury affecting the nervous system, which could be the central system, or the peripheral nervous system.
- And then, a new category called nociplastic. Nociplastic is an amplified processing of, or decrease inhibition of pain stimuli at multiple levels of the nervous system, and it includes diffuse sensitization, like fibromyalgia, functional visceral pain, like irritable bowel syndrome, and regional somatic sensitization, like complex regional pain syndrome.



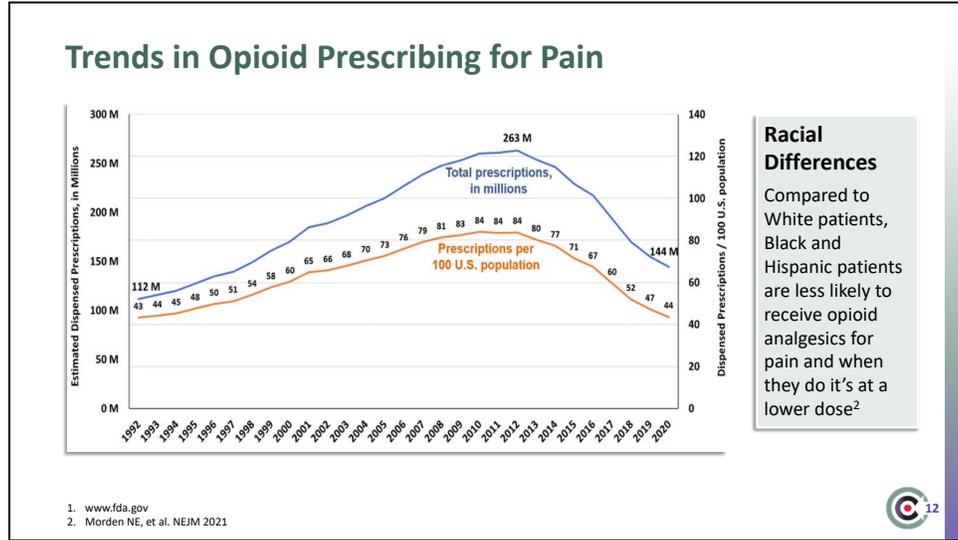
The state of pain? Well, we know that approximately 50 million, or 21 percent of US adults report pain on most days, or every day. Up to 60 percent of emergency department visits are for pain-related complaints. Pain is costly. Chronic pain costs approximately \$600 billion per year in both medical costs, and lost productivity, and we know that chronic pain contributes to health disparities by disproportionately impacting females, the elderly, and those with lower socioeconomic backgrounds.



There are barriers to adequate pain care, including an overburdened primary care system with many competing priorities, inadequate training in managing patients with pain, lack of decision support for pain management, and one that I think is really important is financial misalignment that favors the use of medications. It's a whole lot easier to write a prescription for a medication, than it is to send somebody to comprehensive pain management, lack of access to comprehensive pain management, and negative attitudes and disparities in pain care.

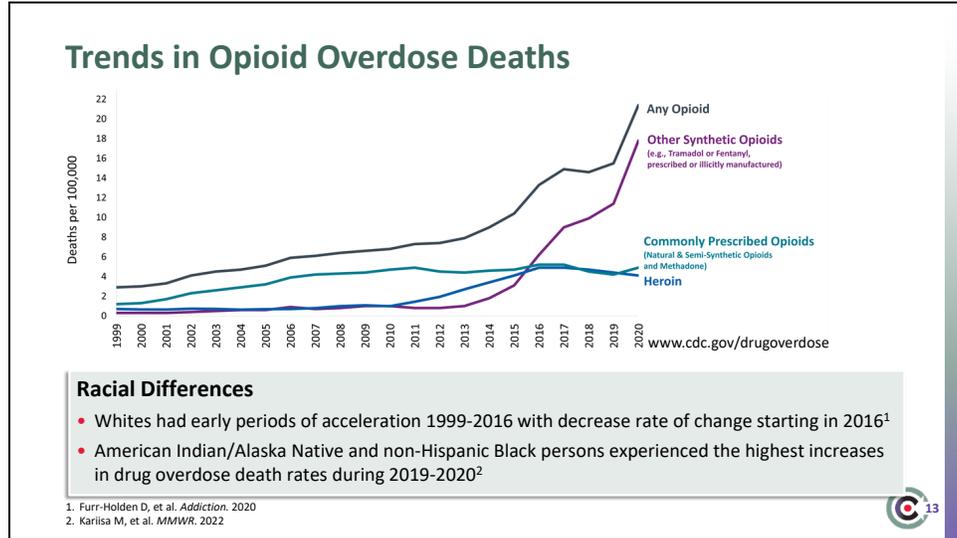


Disparities in pain care can be patient-related, that is perceived bias, and discrimination may lead to increased pain, feelings of pain and suffering. Language barriers, cultural differences in communication and health literacy can lead to poor treatment outcomes, and clinicians can have false beliefs and implicit bias, which can result in racial and ethnic disparities in pain assessment, and treatment, and the lack of access to care.



There have been trends in opioid prescribing over the years. As many of you are aware, there was an increase in opioid prescribing in the 1990s, peaking in around 2011-2012. We became very opioid-centric in our management of both acute, and chronic pain, but since that time there's been a decrease in opioid prescribing, and whether that's related to more judicious opioid prescribing, which I hope, or more fearful prescribing, it's probably a combination of both.

And we know that there are racial differences and disparities in the use of opioids for pain. Compared to white individuals, black and Hispanic patients are less likely to receive opioid analgesics for pain, and when they do, it's at a lower dose.



So, over the years, there have been trends in opioid overdose deaths. Coinciding with the increase in opioid prescribing in the 1990s, we started to see an increase that was related to prescription opioids.

But around 2011 or so, that became heroin-related, that is heroin became the most common opioid, resulting in overdose deaths, and most recently this third trend is related to synthetic opioids, namely illicit fentanyl analogs that are now responsible for most opioid-related overdose deaths.

There are also racial differences in overdose deaths. White populations had an accelerated overdose rate between 1999 and 2016, which was followed by a decrease in annual rates, starting in 2016. Around that time, American Indian, Alaskan Native, and non-Hispanic black populations experienced the highest increase in drug overdose deaths, starting in 2019.

Slide 14



John Emery: Thank you. Now, we'll move to Part One: Understanding Pain and Opioids.

Case Study
Michelle Jones



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



Meet Michelle Jones. At 36, she was in a motor vehicle crash, resulting in a right hip fracture. On imaging, she had a displaced femoral neck fracture. After successful surgery, her pain was managed with nerve blocks, and intravenous hydromorphone. Dr. Alford, can you discuss acute pain assessment, and are there risk factors that might increase the likelihood that a patient's acute pain will turn into persistent or chronic pain?

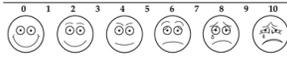
Assessing Acute Pain

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

“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**

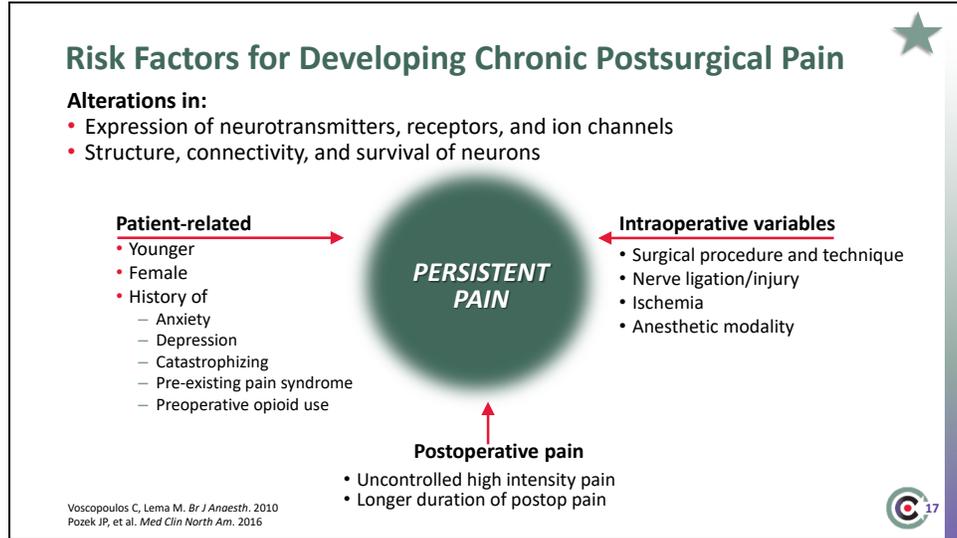


He S, et al. *JAMA*. 2022
 Oken BS. *Brain*. 2008
 Breivik H, et al. *Br J Anaesth*. 2008
 Mason ST, et al. *Handbook of Pain Assessment*. 2011

Daniel Alford, MD: Sure. When assessing acute pain, there are many factors that influence self-reported pain, including gender, social support, and clinician characteristics and trust. One mnemonic to think about is SOCRATES, which stands for:

- The **site**: where is the pain?
- The **onset**.
- The **character** of the pain.
- Does it **radiate**?
- Are there any **associations** related to the pain?
- The **time** course.
- Anything that **exacerbates** it, or relieves it.
- And how **severe** is it?

And oftentimes we use pain intensity scales, including the visual analog scale, but there’s also been developed an emoji-based visual analog scale, and then, numeric rating scales on a 10-point scale where mild would be 1 to 3, moderate would be 4 to 6, severe is 7 to 10.



There are risk factors for developing chronic postsurgical pain, or persistent pain, and then due to alterations in the expression of neurotransmitters, receptors, and ion channels, and changes in structure, connectivity, and survival of neurons.

What are some of those risk factors? Well, there are some patient-related risk factors, like being younger, being female, and having a history of anxiety, depression, catastrophizing, preexisting pain syndrome, and preoperative opioid use. There were interoperative variables, including the surgical procedure and technique, whether there's any nerves that have been ligated or injured, and ischemia, and the anesthetic modality. And finally, there are some postoperative risk factors, including uncontrolled high-intensity pain in the postoperative setting, or longer duration of postoperative pain.

Risk of Progression from Acute to Chronic Musculoskeletal Pain: STarT MSK Screening Tool

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

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

Pain Characteristics	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?
Catastrophizing	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... <i>(not at all, slightly, moderately, very much, extremely)</i>

Campbell P, et al. *J Pain Res.* 2016

There is a way to predict the progression of acute to chronic musculoskeletal pain, using something called the STarT MSK Screening Tool, which helps to identify modifiable risk factors for chronic musculoskeletal pain disability, and it scores people into low, medium, and high risk.

And there are nine questions, and they all start with, “In the last two weeks, do you agree, or disagree with...”, are there characteristics, like troublesome joint, or muscle pain in more than one part of your body? Only being able to walk short distances, dressing more slowly, and other important health problems?”

And then there are questions around catastrophizing. “Does it feel unsafe to be active? Do you have worrying thoughts about your pain? Your pain condition will last a long time? Have you stopped enjoying all the things you usually enjoy, and how bothersome has your pain been?”

Case Study
Michelle Jones
36 yo female



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



Discharge

- Discharged home with visiting nurse and physical therapy services and orthopedic follow-up in 1 week
- Received prescriptions for
 - Oxycodone (5 mg) 1-2 tablets every 4-6 h prn pain (#40 tablets)
 - Ibuprofen 600 mg every 8 h



John Emery: After her surgery, Michelle was discharged with home-based physical therapy and orthopedic follow-up. She received prescriptions for ibuprofen 600 mg every eight hours, and oxycodone 5 mg, one to two tablets every four to six hours, as needed for pain. Her oxycodone prescription was for 40 tablets. Dr. Alford, what are the correct amounts of opioids to prescribe after surgery, or for any acute, severe pain? What is the role of non-opioids, including ketamine for treating acute pain?

Opioid Overprescribing for Acute Pain

Overprescribing	Overprescribing Risk
<ul style="list-style-type: none">• Postoperatively over 70% of patients took half or less of their opioids ^{1,2,3}• After ED visit (e.g., renal colic, fracture/dislocation) 93% of patients had leftover pills, 52% of pills were unused⁴	<ul style="list-style-type: none">• 3-5% of opioid-naïve patients receiving an opioid became long-term opioid users (risk factors: male, over 50 yo, mental illness, substance use disorder) ^{5,6}• Source of prescription opioids misused 47% family, friend, 42% single prescriber⁷

Since 2012 there has been a decrease in new opioid prescriptions for more than 7-day supply⁸

1. Bartels et al. *Plos One*. 2016
2. Bartels et al. *Plos One*. 2016
3. Rodgers et al. *J Hand Surg*. 2012
4. McCarthy DM, et al. *Pain Med*. 2021
5. Deyo RA, et al. *J Gen Intern Med*. 2017
6. Sun EC, et al. *JAMA Intern Med*. 2016
7. SAMHSA. (2021). 2020 National Survey on Drug Use and Health
8. Zhu W et al. *N Engl J Med*. 2019



Daniel Alford, MD: Yeah, these are important questions, because we know that there has been a history of over-prescribing for acute pain. We know from the postoperative literature that over 70 percent of patients take half or less of their opioids. We also know in the emergency department setting, that 93 percent of patients had leftover pills, and 52 percent of the pills were unused. Why is this a problem? Because of diversion.

Approximately 50 percent of prescription opioids that are misused in the community were obtained from family members or friends, usually from leftover pills. It also can result in long-term opioid use. We know that about 3 to 5 percent of patients who are opioid-naïve, who receive an opioid develop long-term, that is defined as over three months, opioid use.

And some of the risk factors for long-term opioid use include being male, being over 50, having mental illness, and a substance use disorder. Looking at population-based data, since 2012 there has actually been a decrease in new opioid prescriptions for more than a seven-day supply.

Treating Acute Pain

Acute Dental Pain

Molar extractions:
NSAID + APAP more effective compared to oxycodone alone or in combination with APAP¹

Acute Musculoskeletal Pain

No significant difference in pain reduction at 2 hours among single-dose treatment with NSAID + APAP or 3 different opioid + APAP combinations²

Acute Pain Guidelines^{3,4}

Multimodal, individualized approach

Some minor surgeries, appropriate to d/c patients w/ NSAIDs +/- APAP or limited opioids before 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

1. Moore RA, et al. *Cochrane Library*. 2015
2. Chang AK, et al. *JAMA*. 2017
3. Chou R, et al. *J Pain*. 2016
4. U of Michigan - Opioid Prescribing Engagement Network (OPEN) <https://michigan-open.org/prescribing-recommendations/>

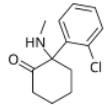


What about treating acute pain? Are opioids always indicated? Well, when we look at the literature for acute dental pain, mostly molar extractions, it turns out that non-steroidal anti-inflammatory drugs with acetaminophen, were actually more effective compared to oxycodone alone, or in combination with acetaminophen.

We also know from a study looking at the emergency room, an acute musculoskeletal pain study, that there was no statistically- or clinically-significant difference in pain reduction among single-dose treatment with an NSAID and acetaminophen, or three different opioid and acetaminophen combinations. Acute pain management guidelines talk about offering multimodal analgesia, but individualizing your approach, based on the patient, and based on what pain they're suffering from.

For some minor surgeries, treating with NSAIDs, and/or acetaminophen, or limited opioids before transitioning to NSAIDs and acetaminophen is completely appropriate. I want to direct you to a wonderful website from the University of Michigan that outlines postsurgical opioid prescribing guidelines that's tailored for specific procedures. The website is on this slide.

Ketamine for Acute Pain



- Developed in the 1960s as a dissociative anesthetic
- Subanesthetic doses studied for treatment of perioperative pain, neuropathic and nociceptive pain, depression and substance use disorders
- Analgesic without respiratory depression
- Increased use (IV, IM, intranasal [off-label]) as analgesic in ED and perioperative settings
- Decreases opioid requirements (“opioid-sparing”)
- Low oral bioavailability and very limited evidence for use in chronic pain
- Dose-dependent adverse effects including hallucinations, agitation, anxiety, dysphoria, euphoria
- Misuse potential due to psychoactive effects

Bell RF, Kalso EA. *Pain Rep.* 2018
Schwenk ES et al. *Curr Pain Headache Rep.* 2021



You asked about ketamine for acute pain. Well, ketamine is actually an analgesic, anti-inflammatory, and an antidepressant, and it doesn't have respiratory-depressant, or blood pressure depressing effects. There's been an increase in use, mainly IV and subcutaneous, as an analgesic in emergency medicine, and perioperative settings, and it's been shown to decrease postoperative pain scores, and opioid requirements, or having an opioid-sparing effect.

But there's a lack of consensus on what the optimal dose is. There's low oral bioavailability, and very little evidence for its use in chronic pain. There are dose-dependent adverse effects, including hallucinations, agitation, anxiety, dysphoria, and euphoria, and there absolutely is a misuse potential, due to the psychoactive effects.

Case Study
Michelle Jones
54 yo female



AGE 36:
Postoperative course was uneventful with patient only requiring opioids for 4 days – (15 unused oxycodone tablets which she eventually threw away)

18 Years Later...

- Presents for primary care 18 years later, at age 54, after her previous PCP retired
- Chief complaint: **“I need my pain med refilled today. My feet and hip are killing me!”**
- Past medical history:
 - Type 2 diabetes mellitus (A1C 7 %)
 - Painful diabetic neuropathy
 - Diabetic nephropathy (Cr 1.44, GFR 40)
 - Hypertension
 - Hyperlipidemia
 - Obesity (BMI 32)
 - Post-traumatic osteoarthritis of right hip



John Emery: Michelle’s postoperative course was uneventful. She ended up with 15 unused oxycodone tablets, which she eventually threw away. We next see Michelle Jones 18 years later, when she presents for an initial appointment with a new primary care provider.

+++++

Daniel Alford, MD: Good morning, Ms. Jones. I’m Dr. Alford. It’s great to meet you. Let’s see... What brings you here today?

Michelle Jones: Hi, Dr. Alford. It took forever to get an appointment with you. You must be a really busy doctor. I made an appointment with you, because Dr. Robertson, my old doctor retired. Basically, I’m here because of my blood pressure, diabetes, and the pain in my feet and hip. Here, I brought you my medical records.

Daniel Alford, MD: Okay, thanks. Let’s see... So, it looks like you’ve had diabetes for a few years, and that’s likely the cause of your foot pain. And your hip pain, it looks like – oh, it started after your accident, and you had surgery.

Case Study
Michelle Jones
54 yo female



Current Medications		Current Pain Medications	
Metformin, Empagliflozin, Lisinopril, Atorvastatin		Oxycodone 10 mg 4x/day (60 MME*) Gabapentin 300 mg 3x/day	
Previous Pain Medications			
NSAIDs (ibuprofen, naproxen)		<i>Diabetic nephropathy and GI upset</i>	
Acetaminophen		<i>Inadequate pain relief</i>	
Tricyclic antidepressants (TCA) (amitriptyline)		<i>Inadequate pain relief and dry mouth</i>	
Serotonin-norepinephrine reuptake inhibitor (SNRI) (venlafaxine)		<i>Unable to tolerate due to nausea and dizziness</i>	
Tramadol		<i>Inadequate pain relief</i>	
Acetaminophen with codeine		<i>Inadequate pain relief and nausea</i>	



Daniel Alford, MD: Your diabetes, blood pressure, and cholesterol seem under good control with the medications you're on, and your kidney functions seem stable. Oh, I see you're also on a couple of different pain medications, too?

Michelle Jones: Yeah. And I've tried everything else. All the other things either didn't work, or they made me sick.

Case Study
Michelle Jones
54 yo female

Social History
Paralegal law office 20 hours/week
Married, no children

Substance Use History
Alcohol use 1 glass of wine on special occasions
No illicit drug or cannabis use
No tobacco use

Family History
Mother died from complications of alcoholic cirrhosis

Daniel Alford, MD: Well, tell me about yourself. Tell me about your home. Are you working?

Michelle Jones: Yeah. I'm married, no kids. I work as a paralegal downtown, but these days it's just part-time.

Daniel Alford, MD: Well, I also have some health behavior questions that I ask all my patients. Do you smoke?

Michelle Jones: No, never have. And I know the drill. I drink socially. I don't do drugs. Honestly, my biggest vice is food. I know I should be losing some weight.

Daniel Alford, MD: Any medical problems run in your family?

Michelle Jones: Yeah. My dad has lung cancer. He smoked his whole life. My mom was an alcoholic, died of it, in fact, and I saw what that can do to you, and your family.

Daniel Alford, MD: That must have been difficult.

Case Study

Michelle Jones
54 yo female



Pain Medications

- Has been spacing out oxycodone to avoid running out
 - Past 2 weeks taking oxycodone 10 mg every 12 hours
 - 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 12 hours. I’m suffering. It’s almost impossible to go to work.”**
- Presents with some medical records from previous PCP



Daniel Alford, MD: So, tell me what’s going on with your pain medications at this point?

Michelle Jones: Well, honestly, because it took so long to get an appointment with you, for the past couple of weeks I’ve been trying to ration out my pills. I’m taking it just twice a day, instead of four times, but man, I’m in awful pain. I’m taking half my dose, and I’m in more than twice as much pain. I took my very last pill this morning, so I definitely need a refill today.

Daniel Alford, MD: Yeah. Now, it sounds like you’re pretty uncomfortable. Can you tell me a bit about your pain right now?

Michelle Jones: So, even now, 18 years after my car crash, my hip still hurts, especially when I try to move a lot. Also, it’s really bad when I stand up after sitting. Dr. Robertson told me I now have bad arthritis in that hip. And my feet are terrible. I always have burning and tingling, and they get numb sometimes. There are days when I can’t put on my shoes, because of the pain. It’s almost impossible to get to work.

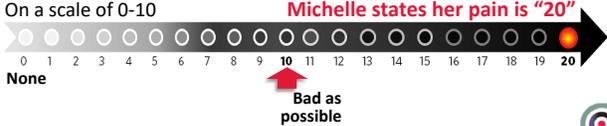
Case Study
Michelle Jones
54 yo female



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"

None

Bad as possible



Daniel Alford, MD: Wow. That sounds like a lot. Can you tell me on a scale of zero to 10, zero being no pain at all, and 10 being the worst pain imaginable, where would you rate your overall pain right now?

Michelle Jones: Oh, jeez. Right now, it's a 20.

+++++

John Emery: Dr. Alford, what does it mean when a patient reports their pain beyond the scale, like in this case?

Building Trust: Patient Issues

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



Demonstrated by
exaggerating pain scores
and
exaggerating functional limitations



Daniel Alford, MD: Yeah. I think unfortunately it's common, and the first thing I think about is trust. The patients may assume that you do not believe the severity of their pain complaints, and that leads to an exaggeration of their pain score and can also lead to an exaggerated functional limitation report, that is, "I can't do anything," even though you know that they are able to.

Building Trust: Clinician Issues

After you complete a thorough pain history, focused physical exam, and appropriate diagnostic testing...

Show **empathy** for patient experience...

"It must be difficult to enjoy life with such severe pain."

Validate that you believe pain and suffering is real...

"I believe you and want to help."

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



And as a clinician, once you've completed a thorough pain history, and you've done a focused physical exam, and you've ordered appropriate diagnostic testing, we should be empathic for the patient's experience and suffering.

And also, we should validate 100 percent of the time that we believe their pain is real, and I say that because there's zero percent risk in validating someone's pain as real every single time. Why? Because just because you believe the severity of someone's pain complaint, it does not mean opioids are indicated. That's where a risk and benefit framework fits in, and we'll talk much more about that later in this program.

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 routine use in most primary care settings

Brief Multidimensional Tool
Pain, Enjoyment, General Activity (PEG) Scale

1. What number best describes your pain on average 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 enjoyment of life?
0 1 2 3 4 5 6 7 8 9 10
Does not interfere Completely interferes

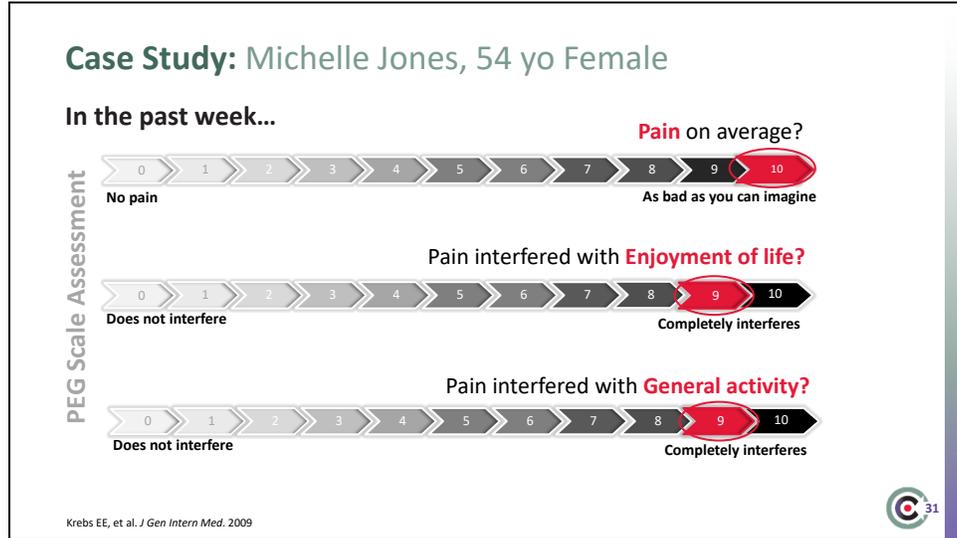
3. What number best describes how, during the past week, pain has interfered with your general activity?
0 1 2 3 4 5 6 7 8 9 10
Does not interfere Completely interferes

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



So, how do we assess chronic pain? We talked about unidimensional scales for acute pain, like the numeric rating scale, but it really has limited value in assessing chronic pain. In chronic pain, we're really much more interested in a multidimensional instrument, and there are many out there, including the McGill Pain Questionnaire, the Graded Chronic Pain Scale, and the Brief Pain Inventory. If you can use these in your practice, that's great, but I find them to be impractical for routine use in most primary care settings.

What would I recommend? I'd recommend something called the Pain, Enjoyment, General Activity Scale, which has been validated in primary care settings. We're asking people about their pain on average in the past week, how much their pain has interfered with their enjoyment of life, and how much it's interfered with their general activity.



John Emery: Dr. Alford now addresses Michelle’s report of pain beyond the 10-point scale and assesses her pain using the PEG Scale.

+++++

Daniel Alford, MD: Ms. Jones, I absolutely believe you that you have terrible pain, and that you’re suffering a great deal, but it would be really helpful if you could tell me what your pain level is within the scale, so that I can follow it over time. Remember, that 10 is really the most severe pain possible, so what number best describes your pain on average in the past week, where zero is no pain, and 10 pain as bad as you can imagine?

Michelle Jones: It is terrible. I’d have to say it’s the worst. It’s a 10.

Daniel Alford, MD: Well, what number best describes how, during the past week, pain has interfered with your enjoyment of life? Zero, it doesn’t interfere at all, 10 it completely interferes with your enjoyment of life.

Michelle Jones: Well, it’s really ruining my life right now. I’d have to say not quite a 10. It’s a 9.

Daniel Alford, MD: And how about interfering with your general activities? Zero, it doesn’t interfere at all; 10 it completely interferes with your general activity?

Michelle Jones: Well, that’s also a 9. I really can’t do anything now.

Case Study
Michelle Jones
54 yo female



How will you manage this patient's chronic pain?

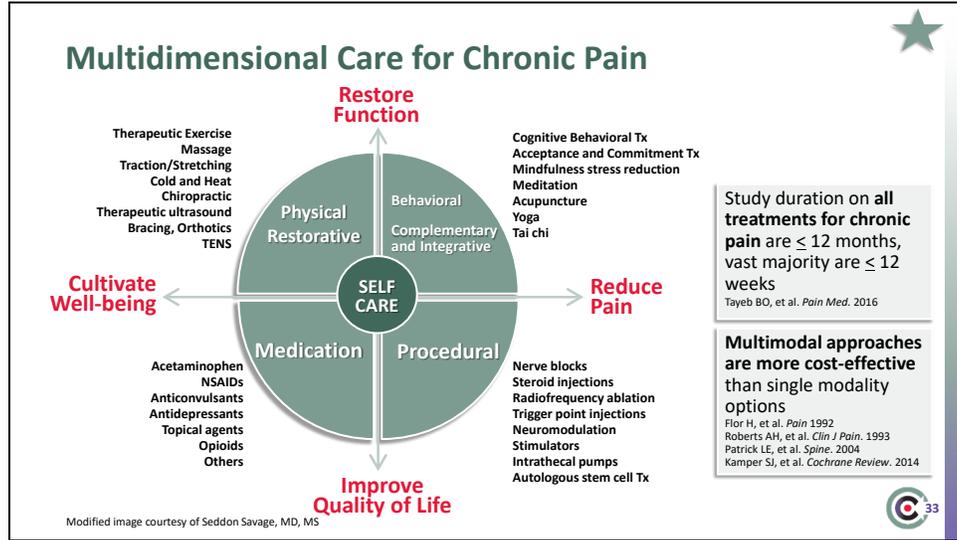


Physical

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



John Emery: Michelle's physical shows no acute distress, and normal vitals with a BMI of 32, normal cardiopulmonary function, and 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, as is her foot exam, including loss of protective sensation by vibration and monofilament testing. Dr. Alford, what are the next steps, as you think about managing a patient's chronic pain?



Daniel Alford, MD: Yes. So, for chronic pain, you really want to think about a multidimensional care plan, and it really starts with self-care, that is that the patient can't come in, and say, "Can you fix my pain?" It really is a joint effort. They need to participate. And that the goals are not only to reduce pain, but to improve quality of life, cultivate wellbeing, and to restore the patient's function as much as possible.

And how do we do that? There are certainly behavioral approaches, and there are complementary and integrative approaches that are listed here. There are also procedural approaches, a variety of medications that we can choose from, and physical and restorative approaches. Now, I completely understand that not all of these approaches are available to all of our patients all the time, but it's important to help our patients access them, as much as possible.

It's important to know that the study duration on all these treatments listed here for chronic pain have follow-ups that are less than 12 months, and the vast majority are less than 12 weeks. We don't really know how well these work in the long-term. What we do know is that multimodal approaches are not only more effective, but they're more cost-effective than single modality options. So, again, we really need to take a multidimensional care approach, and try to get our patients active in many of these different modalities.

Getting Help from a Pain Specialist

When to refer to a pain specialist:

```
graph LR; A[Unsure of pain diagnosis] --> B[Unsure of other treatment options]; B --> C[Want second opinion on opioids for individual patient]
```

- Know what services your pain specialist offers
- Get second opinion from your colleagues
- Remain up to date with local or state requirements requiring pain specialist referrals



Sometimes we need to get help from a pain specialist, and when do I refer to a pain specialist? One, if I'm unsure of the pain diagnosis. Two, if I'm unsure of the other treatment options that are available to me, and if I want a second opinion on whether opioids for this individual patient are helping, or hurting, or too risky. You need to know what services your pain specialist offers, and sometimes I just get a second opinion from one of my colleagues to look over the chart, or even meet the patient to help me kind of sort through what the different treatment modalities might be.

It's important to remain up to date with your local or state requirements, because sometimes it's required that you have a pain specialist weigh in on your treatment plan for patients, especially those that are on long-term opioids.

Non-Opioid Pharmacotherapies

<p>Salicylates, Nonacetylated Salicylates</p> <p>Non-steroidal Anti-inflammatory Drugs (NSAIDs)</p> <ul style="list-style-type: none">• Nonselective and selective COX-2 inhibitor (celecoxib)• Anti-inflammatory, analgesic, antipyretic	<p>Acetaminophen (APAP)</p> <ul style="list-style-type: none">• Analgesic, antipyretic• Less effective than full dose NSAIDs in relieving chronic pain but fewer adverse effects	<p>General Considerations</p> <ul style="list-style-type: none">• Ceiling analgesic effects• No known analgesic tolerance• Additive role (NSAID+APAP)• Some patients may respond better to one NSAID than another• Side effects (GI, renal, CV) especially at high NSAID doses
--	--	---

Finnerup NB. *N Eng J Med*. 2019



There are some non-opioid pharmacotherapies that we'll talk about, the most common being nonsteroidal anti-inflammatory drugs that can be nonselective, or selective COX-2 inhibitors; they're anti-inflammatory, analgesic, and antipyretic.

There's acetaminophen, which has analgesic and antipyretic effects. They tend to be less effective for chronic pain, than full-dose NSAIDs, but have fewer adverse effects. Some general considerations include this is a ceiling analgesic effect for both NSAIDs and acetaminophen. There's no analgesic tolerance. That is, if someone is benefitting from one of these medications, they shouldn't need an increase in their dose.

There's an additive role in combining NSAIDs and acetaminophen, and some patients may respond better to one NSAID than another, but as you're well aware, there are many side effects for NSAIDs, including GI, renal, and cardiovascular, especially at high NSAID doses.

Non-Opioid Pharmacotherapies

- Analgesics with primary indication other than pain
 - Antidepressants (TCAs, SNRIs)
 - Anticonvulsants (gabapentinoids, carbamazepine)
 - Antispasmodics/muscle relaxants
 - Local anesthetics (lidocaine)

} **Mainstay of treatment for neuropathic pain syndromes**

- **Caution:** misuse and addiction potential with:
 - Gabapentinoids^{1,2} (gabapentin, pregabalin)
 - Muscle relaxants² (carisoprodol metabolizes into meprobamate (barbiturate-like drug))

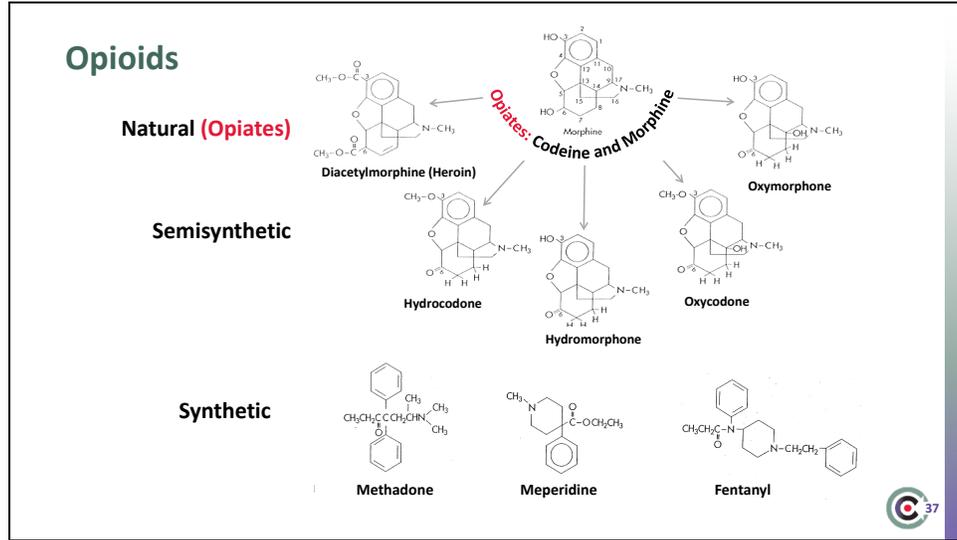
Finnerup NB. *N Eng J Med*. 2019
1. Evoy KE et al. *Drugs*. 2021
2. Hill J, Alford DP. *Semin Neurol*. 2018



There are other non-opioid pharmacotherapies to consider. These are analgesics that have a primary indication for something other than pain. They include the antidepressants, and anticonvulsants.

And these two categories are really the mainstay of treatment for neuropathic pain syndromes, and the antidepressants include the tricyclic antidepressants, and the SNRIs. You'll note that I do not have SSRIs here, because they've not been shown to be beneficial. In terms of anticonvulsants, we're talking about the gabapentinoids and carbamazepine. They're antispasmodics and muscle relaxants, and local anesthetics, like lidocaine.

A word of caution: Some of these medications have misuse and addiction potential, mainly the gabapentinoids. Both gabapentin and pregabalin have been shown to have an addiction potential for some patients, as well as some muscle relaxants, namely, carisoprodol, which is metabolized into a barbiturate-like drug, so beware.

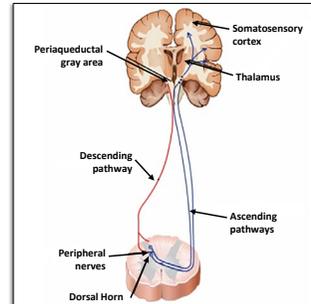


Now, let's talk about opioids. We'll start with the natural opiates, which include codeine and morphine, and if you take them to the lab and create a semisynthetic opioid, you can create heroin, which is diacetylmorphine, hydrocodone, hydromorphone, oxycodone, and oxymorphone. What's important to note is that these medications originated from codeine, and/or morphine, and many of them will metabolize back to codeine, and/or morphine, and will turn your urine positive for an opiate. We'll talk more about urine drug testing later.

This is in distinction to the synthetic opioids, like methadone, meperidine, and fentanyl, which never came from an opiate, will never convert back to an opiate, and should never turn your urine positive for an opiate. But again, we'll talk more about these in relation to urine drug testing later in the program.

Opioid Analgesics

- Turn on descending inhibitory systems
- Prevent ascending transmission of pain signal
- Inhibit terminals of C-fibers in spinal cord
- Inhibit activation of peripheral nociceptors
- Variable response (not all patients respond to the same opioid the same way)
 - >3,000 polymorphisms in human MOR gene
 - Single nucleotide polymorphisms (SNPs) affect opioid metabolism, transport across the blood brain barrier, and activity at receptors and ion channels
- **Activate the reward pathway**



(ScienceMedia.com), Acute versus Chronic pain and Pain Pathways, Nov 2019.

McCleane G, Smith HS. Med Clin N Am. 2007. Smith HS. Pain Physician. 2008. Ren Z et al. Pain Physician. 2015



So, what do opiate analgesics do? They turn on the descending inhibitory system in the periaqueductal gray, which is a norepinephrine, serotonin system. They prevent the ascending transmission of the pain signal, and they inhibit terminals of the C-fibers in the spinal cord in the dorsal horn of the spinal cord. They also inhibit activation of the peripheral nociceptors, or pain receptors.

Now, we know that not all patients respond to the same opioid in the same way, and so, why is there variability in response? One, because there are greater than 3,000 polymorphisms in the human mu opioid receptor gene, so each one of us has a slightly different mu opioid receptor system. Also, there single nucleotide polymorphisms, or SNPs, which affect opioid metabolism, transport across the blood-brain barrier, and activation at receptors, and ion channels.

We also know that opioids can activate the reward pathway, which is a dopaminergic system, which is incredibly rewarding and reinforcing, which is where a lot of substances act that result in patients losing control or becoming addicted.

Opioid Tolerance and 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 (naloxone)



We need to consider opioid tolerance and physical dependence. Both tolerance, and physical dependence are physiologic adaptations to being on chronic opioids.

Remember what tolerance is. It means you need an increased dose to produce a specific effect over time. It develops readily for CNS and respiratory depression, less so for constipation. If someone has constipation with a specific dose, they usually don't develop tolerance over time. And then, what about tolerance for analgesia? Well, it's unclear. It seems that some patients may develop tolerance, and some don't. So, it's not something that's guaranteed either way.

What about physical dependence? Well, that includes signs and symptoms of withdrawal, if you abruptly stop the opioid, if you decrease it too fast, or you expose the patient to an opioid antagonist, like naloxone.

John Emery: Do opioids really work for chronic pain? And what do you need to worry about when you prescribe them?

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

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

*Study limitations:*⁴

- Excluded patients already on long-term opioids
- 89% of eligible patients declined to be enrolled

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

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

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

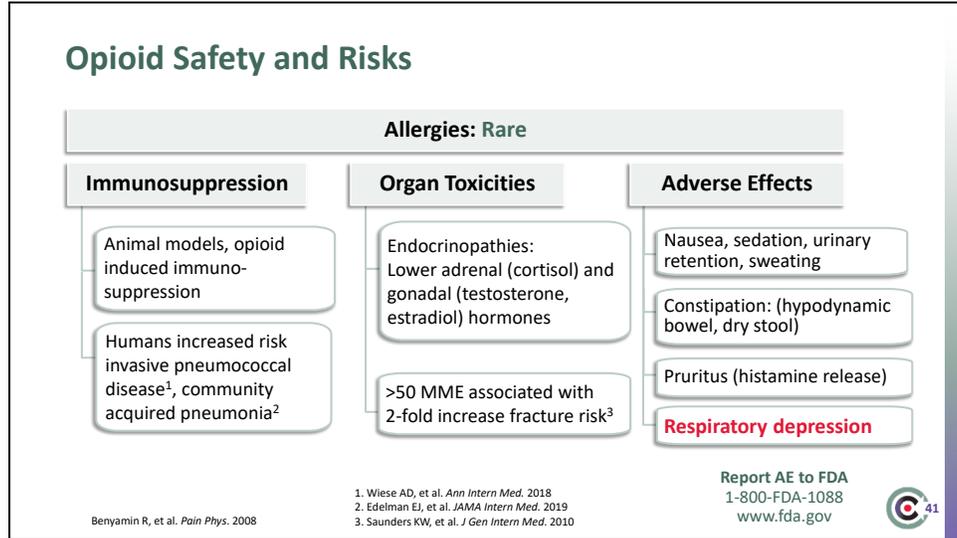
5. Noble M, et al. *Cochrane Syst Rev.* 2010

Daniel Alford, MD: Yeah. It's an important question, and there's a lot of misinformation out there. So, let's talk about opioid efficacy for chronic pain. Well, on this slide you'll see that there are some meta-analyses that looked at opioids versus placebo, and they were high-quality studies, and they show that show that opioids had a small improvement in pain, and physical functioning.

What about opioids versus non-opioids? Well, these were low- to moderate-quality studies, and they found that they both had similar benefits. One thing you'll notice that's very important is that these meta-analyses found studies that only had follow-up up to six months, so anything beyond six months is really a black box. We really don't know how effective opioids are versus placebo, or non-opioids beyond six months.

There was an important randomized control trial that found that opioids were not superior to non-opioids for improving musculoskeletal pain-related function over 12 months, so a longer-term trial. But there are some limitations to generalizability, that is, does this study apply to the patient sitting across from me? Well, when you look at the methods, they excluded any patient who was already on long-term opioids, so if you have a patient who's already currently taking long-term opioids, they would not have been included in this study. So, we're already talking about a different population, and of those that were eligible 89 percent said, "No, I'd rather not be in this study, where you're going to randomize me to opioids or non-opioids." So, of the 11 percent that said, "Sure, I'll join the study," there was no difference between opioids and non-opioids.

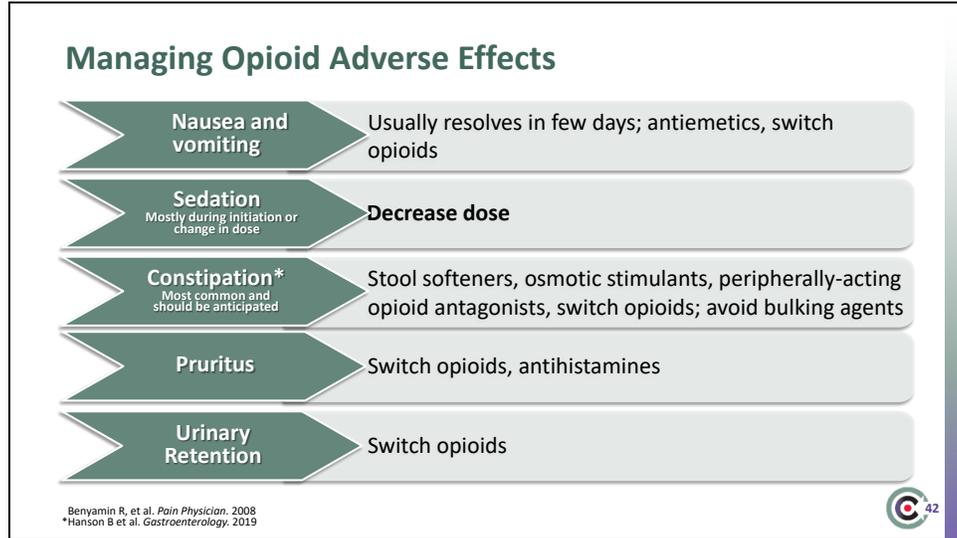
Now, there were two longer-term observational studies that found that 44.3 percent of patients prescribed long-term opioids for chronic pain, had at least 50 percent pain relief. So, it wasn't zero percent, and it wasn't 100 percent. It was about half of patients prescribed long-term opioids had at least 50 percent pain relief.



Now, what about safety and risks? Well, the good news is that allergies are rare, and we know that there is some opioid-induced immunosuppression. We've known this for a while in animal models, but more recently there have been some studies that have shown that humans have an increased risk of invasive pneumococcal disease, and community-acquired pneumonia, when they're on opioids.

In terms of organ toxicities, we're very familiar with the organ toxicities of NSAIDs and acetaminophen, but what about opioids? Well, there are some endocrinopathies, including lower adrenal, and gonadal hormones. The lower gonadal hormones resulted in poor bone health, and we know from one observational study that individuals who are on greater than 50 morphine mg equivalents had a twofold increase in fracture risk.

What about adverse effects? Well, they can be quite common, including nausea, sedation, urinary retention, sweating, and constipation, which is a hypodynamic bowel problem, along with dry stool. Pruritus? Pruritus is not an allergy. In most cases it has to do with a histamine release, related to how opioids act on our mast cells, and the adverse effect we worry about the most is respiratory depression, especially in our patients with sleep apnea, whether it be obstructive, or central sleep apnea.



So, how do we manage these adverse effects? Well, nausea and vomiting usually resolve within a few days. We can certainly use an antiemetic, but sometimes you just have to switch to a different opioid. What about sedation? You need to decrease the dose. What about constipation? Well, we can use stool softeners, osmotic stimulants, peripherally acting mu opioid antagonists. We can switch to a different opioid, but we need to avoid bulking agents, because we have a hypodynamic bowel.

What about pruritus? Well, you can switch to a different opioid, or you can use a non-sedating antihistamine. And what about urinary retention? Oftentimes, we need to switch to a different opioid.

Opioids and Patient Considerations

- **Age**
 - Decline in therapeutic index
 - Predisposition to adverse drug effects
 - Fall risk, worsening cognitive function
- **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
 - Oxycodone 2nd line, due to active metabolites
 - Morphine, codeine not recommended due to active metabolites



There are some patient considerations when prescribing opioids. When our patients are getting up there in age, we need to remember that there's a decline in therapeutic index with a predisposition to adverse trait effects, including fall risk, and worsening cognitive function.

What about our patients with comorbidities, like liver disease? Well, we know liver disease is going to result in a decrease in opioid clearance, and we know that morphine, oxycodone, and hydromorphone require a reduction in dose, and a spacing out of their dosing intervals, because of the liver disease.

What about kidney disease? Well, we know that there will be a decrease in opioid excretion, and the preferred opioids in patients with kidney disease are hydromorphone, fentanyl, buprenorphine, and methadone. Oxycodone is really a second line agent, due to the accumulation of active metabolites, and we know that morphine and codeine are generally not recommended, due to the accumulation of active metabolites.

Opioids: Drug-Drug Interactions (DDI)

- Most common mechanisms are changes in opioid metabolism by **inhibition or induction of cytochrome P450 (CYP450)**
 - Opioids metabolized by CYP450 (codeine, oxycodone, hydrocodone, fentanyl, tramadol, methadone) have numerous DDIs that can reduce or increase opioid effects
 - Opioids not metabolized by CYP450 (morphine, hydromorphone) have fewer DDIs
 - Helpful resource: <http://dailymed.nlm.nih.gov/dailymed>
- CNS depressants (benzodiazepines, alcohol, cannabis, other sedatives, hypnotics, TCAs, MAOI) may potentiate opioid effect on sedation and respiratory depression
- Alcohol may rapidly release opioid (dose dump) or increase drug levels w/out dose dumping
- Opioids can reduce efficacy of diuretics by inducing release of antidiuretic hormone



Recommendation 11

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

Dowell D, et al. MMWR. 2022

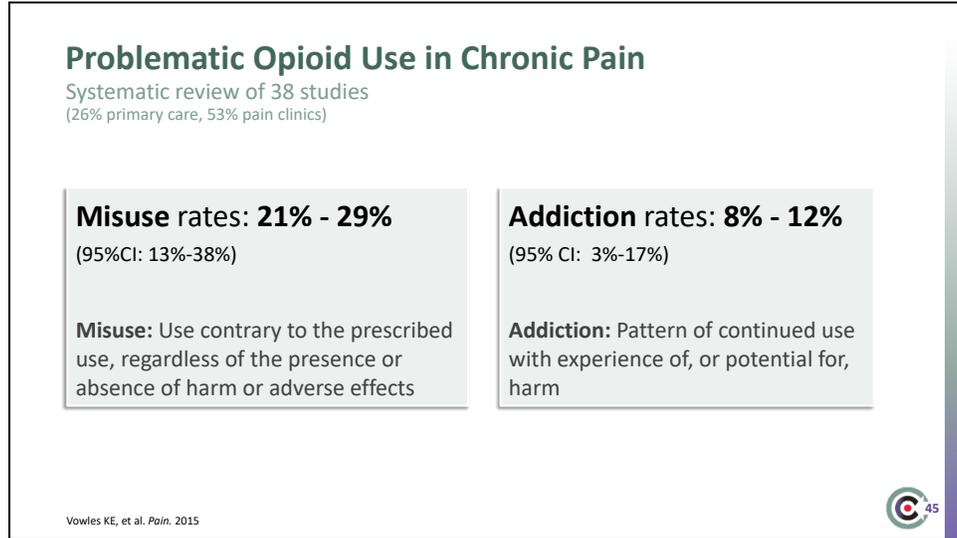


What about drug-drug interactions? Well, the most common mechanism causing drug-drug interactions with opioids are changes in opioid metabolism by inhibition, or induction of the cytochrome P450 system. We know that opioids that are metabolized by cytochrome P450, including codeine, oxycodone, hydrocodone, fentanyl, tramadol, and methadone have numerous drug-drug interactions that can reduce or increase opioid effects.

There are some opioids that are not metabolized by this cytochrome system, including morphine, oxymorphone, and hydromorphone, and they have fewer drug-drug interactions. If you have a patient on an opioid that you're not familiar with, or you're not sure whether it's metabolized by the cytochrome P450 system, you can go to DailyMed, the DailyMed website, which is a National Library of Medicine NIH website that takes the package insert and reformulates it in a clinically helpful way.

We also need to worry, in general, about CNS depressants when we're prescribing opioids, that is benzodiazepines, alcohol, cannabis, and other sedative-hypnotics. They may potentiate the opioid effect on sedation and respiratory depression. Alcohol, which is not only a sedative, but also has another potential risk, that is in patients on long-acting formulations of opioids, alcohol can rapidly release the opioid called "dose dump." You can also increase some drug levels, even without dose dumping.

And then, finally, opioids can reduce the efficacy of diuretics by inducing the release of ADH, or antidiuretic hormone.

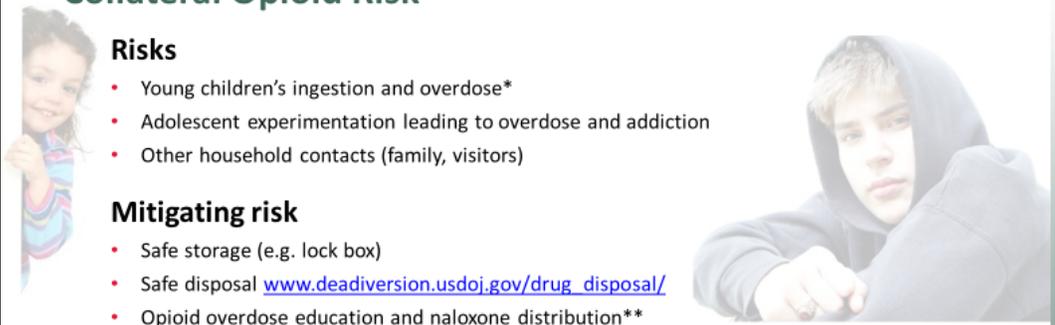


How common is problematic opioid use in chronic pain? Well, I'll refer you to the systematic review of 38 studies about a quarter on primary care settings, and about half in pain clinic settings. The rest were in other subspecialty settings.

And they found that the misuse rates were somewhere between 21 and 29 percent, and misuse was defined as using the opioid contrary to the way it was prescribed, whether or not there was harm or not. So, for instance, if you're prescribing an opioid for someone's back pain, but they took it for their headache, that would be considered misuse.

What about addiction? The addiction rates in these studies were somewhere between 8 and 12 percent, and addiction was defined as a "pattern of continued use with experience of, or potential for harm."

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)
- Safe disposal www.deadiversion.usdoj.gov/drug_disposal/
- Opioid overdose education and naloxone distribution**

– More information: www.prescribetoprevent.org

CDC **Recommendation 8**

Use strategies to mitigate risk including naloxone co-prescribing

Dowell D, et al. MMWR. 2022

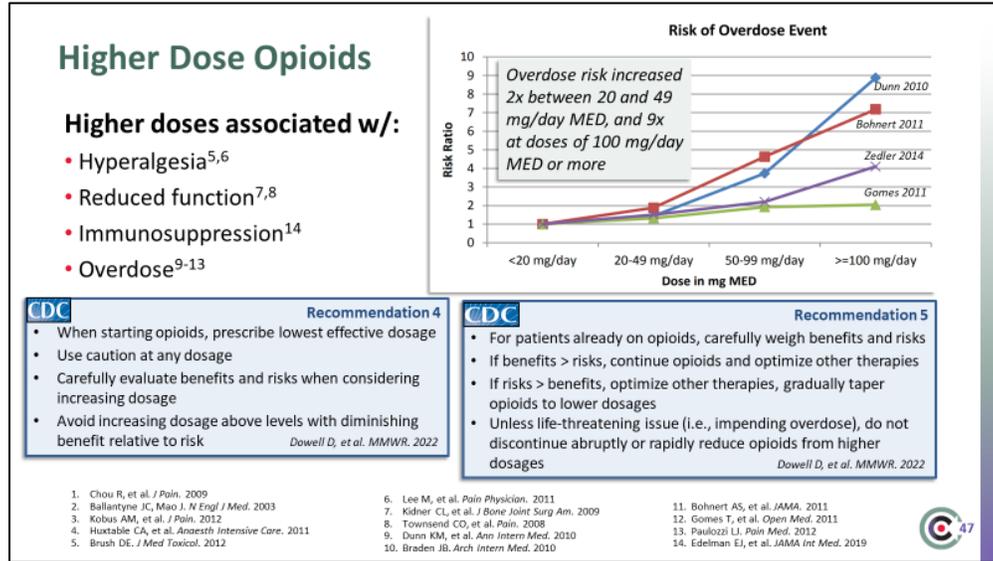
* Gaither JR, et al. *JAMA Pediatr.* 2016
** Beletsky L, Rich JD, Walley AY. *JAMA* 2012
** SAMHSA *Opioid Overdose Prevention Toolkit* 2018



But it's not just worrying about our individual patients, there's also collateral risk. For instance, young children can ingest and have an unintentional overdose. Adolescents can experiment, leading to unintentional overdose and addiction, and certainly other household contacts.

So, how do we mitigate these risks? We talk to our patients about safe storage, including using a lockbox, safe disposal, and here I give you the DEA Diversion website, which talks about the instructions we should talk to our patients about around drug disposal, and we should talk to our patients about opioid overdose, and naloxone use, that is co-prescribing naloxone.

And if you're interested in learning more about co-prescribing naloxone, I would encourage you to go to prescribetoprevent.org, which allows you to go to your specific state, and look at what are some of the regulations, and procedures for prescribing naloxone to your patients.



And there's a lot of talk about the risk of higher-dose opioids, and how higher-dose is defined depends on what study you're reading, but here you can see that there were four population-based studies that looked at the risk ratio around overdose, and the opioid dose.

And you can see that once you start to get around 50 mg of morphine equivalents, you start to see a dramatic increase in risk of overdose. And then when you start getting over 100 mg per day, the risk has gone way up. Higher opioid doses are associated with not only unintentional overdoses, but hyperalgesia, or worsening pain, a reduction in function, and worsening immunosuppression that I had talked about earlier.

Now, if you have a patient who's already on high-dose opioids, you should manage them as higher-risk, that is increasing the level of monitoring, and support for them. Ultimately, we'd like to prevent people from getting on these higher doses, but many of our patients are already on them, so we need to manage them as high-risk.

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)
ER/LA opioid formulation	Family history of SUD
Initial 2 weeks after starting ER/LA opioid	Sleep-disordered breathing
Combination opioids and sedatives (e.g., benzodiazepines)	History of opioid overdose

Akbik H, et al. *J Pain Symptom Manage.* 2006
Ives J, et al. *BMC Health Serv Res.* 2006
Liebschutz JM, et al. *J Pain.* 2010

Michna E, et al. *J Pain Symptom Manage.* 2004
Reid MC, et al. *J Gen Intern Med.* 2002
Volkow ND, et al. *N Engl J Med.* 2016



John Emery: For any given patient on opioids, like Ms. Jones, or for a patient for whom you are considering prescribing opioids, is there a way to determine the risk for opioid misuse and harm?

Daniel Alford, MD: Sure. So, I like to think of the risks as medication factors and patient factors. So, what are some of the medication factors? Well, as we talked about, being on higher dose, but also being on long-term opioids, as defined as greater than three months, being on an extended-release long-acting opioid formulation puts you at higher risk, the initial two weeks after starting the long-acting opioid, and certainly, whenever an opioid is combined with a sedative, like a benzodiazepine.

But what about patient-related risk factors that put people at higher risk for opioid-related harm? Well, having a history of mental health disorder, depression, anxiety, having a substance use disorder, including alcohol, including nicotine, or tobacco, illicit and prescription drugs, having a family history of a substance use disorder, having a history of sleep disorder breathing, like sleep apnea, and a history of an opioid overdose. So, having a prior opioid overdose puts you at very high risk for a subsequent overdose.



Psychiatric Co-Morbidities

Condition	Prevalence with Chronic Pain	References
Depressive Disorders	33 - 54%	Cheatle M, Gallagher R. 2006. Dersh J, et al. 2002.
Generalized Anxiety Disorders	17 - 50%	Knaster P, et al. 2012. Cheatle M, Gallagher R. 2006.
Personality Disorders	31 - 81%	Polatin PB, et al. 1992. Fischer-Kern M, et al. 2011.
PTSD	49% veterans 2% civilians	Otis, J, et al. 2010. Knaster P, et al. 2012.
Substance Use Disorders	15 - 28%	Polatin PB, et al. 1992. Cheatle M, Gallagher R. 2006.



Now, there are lots of psychiatric comorbidities in patients with chronic pain, including depression, anxiety, personality disorders, PTSD, and substance use disorders. And not only are they prevalent, but they make chronic pain worse, and chronic pain makes them worse. So, it behooves us to be looking for these comorbidities whenever we have a patient presenting with chronic pain, because oftentimes we can co-manage them.

The question is how do we identify these comorbidities?

Screening for Depression: PHQ2

Over the *last 2 weeks*, how often have you been bothered by any of the following problems?

1. Little interest or pleasure in doing things			
0	1	2	3
Not at all	Several days	More than half the days	Nearly every day

2. Feeling down, depressed, or hopeless			
0	1	2	3
Not at all	Several days	More than half the days	Nearly every day

Positive if ≥ 3 points
 Test Sensitivity: 83%
 Test Specificity: 92%

If positive, administer PHQ9

Kroenke K, et al. *Med Care*. 2003



So, to screen for depression, I would encourage you to use the PHQ-2. Many of you may use the PHQ-9. Well, the PHQ-2 asks, “Over the last two weeks, how often have you been bothered by any of the following problems: Little interest or pleasure in doing things? Feeling down, depressed, or hopeless?” And the responses are, “Not at all, several days, more than half the days, nearly every day.”

If a patient responds, “Nearly every day” to either one of these questions, they’ll get three points, and a positive PHQ-2 is three or more points. If it’s positive, you then need to ask the additional seven questions of the PHQ-9 to fully assess their depression. The good news is the majority of your patients are going to screen negative, and therefore, you’re done.

Screening for Anxiety: GAD-2¹

Over the *last 2 weeks*, how often have you been bothered by any of the following problems?

0	1	2	3
Not at all	Several days	More than half the days	Nearly every day

0	1	2	3
Not at all	Several days	More than half the days	Nearly every day

Positive if ≥ 3 points
Test Sensitivity: 83%
Test Specificity: 92%

If positive, administer PHQ9

Assess for other Mental Illness

- **PTSD**² Primary Care PTSD Screen for DSM-5, 5-items
- **Suicidality**³ Ask Suicide-Screening Questions, 4-items

1. Kroenke K, et al. *Ann Intern Med*. 2007
2. www.ptsd.va.gov
3. www.nimh.nih.gov/labs-at-nimh/asq-toolkit-materials



What about anxiety? Well, you could use the GAD-2. “Over the last two weeks, how often have you been bothered by any of the following problems? Feeling nervous, anxious, or on edge? Not being able to stop or control worrying.” The responses are the same, “Not at all, several days, more than half the days, nearly every day.” And a positive GAD-2 is also anything three or more, that is if they score “nearly every day on either one of these, it’s positive.

If it’s positive, you then need to ask the additional five questions of the GAD-7 to fully assess their anxiety. The good news is, again, the majority of patients are going to screen negative, and you’re done. There are also quick screening assessments for PTSD, a five-item screener, and suicidality, a four-item screener, that are listed here.

Screening for Substance Use
TAPS (Tobacco, Alcohol, Prescription Medication, and Other Substance Use) Tool

In the PAST 12 MONTHS, how often have you...

- ...used tobacco or any other nicotine product (i.e., e-cigarette, vaping or chewing tobacco)?
- ...had **5 or more** drinks (men)/**4 or more** drinks (women) containing alcohol in one day?
- ...used any prescription medications just for the feeling, more than prescribed or that were not prescribed for you?
- ...used any drugs including marijuana, cocaine or crack, heroin, methamphetamine (crystal meth), hallucinogens, ecstasy/MDMA?

McNeely J, et al. *Ann Intern Med.* 2016; Available at: <https://nida.nih.gov/taps2>



What about screening for substance use? Well, I would encourage you to use something called the TAPS, which stands for tobacco, alcohol, prescription medication, and another substance use tool.

And it's the following: "In the past 12 months how often have you used tobacco, or any other nicotine delivery product, had five or more drinks, if you're a man, four or more drinks, if you're a woman containing alcohol in one day, used any prescription medication just for the feeling, more than prescribed, or that were not prescribed to you, and then, finally, used any drugs, including marijuana, cocaine, or crack, heroin, methamphetamine, hallucinogens, Ecstasy, or MDMA?"

You'll note that the stem is, "How often have you." It's asking you in a very normative way. It's not saying, "Do you smoke tobacco? Do you drink five or more drinks?" It's how often, so even if somebody underestimates anything other than "never" for these questions would be considered positive.

<p>Case Study Michelle Jones 54 yo female</p>  <p>Will you prescribe opioids???</p> 	<p>Screening Results</p> <ul style="list-style-type: none">• Negative for unhealthy substance use• Negative for depression and anxiety 
--	--

John Emery: As we know, Michelle doesn't smoke. She screened negative for other unhealthy substance use, depression, and anxiety. Dr. Alford, how do you decide whether to prescribe opioids for patients like Michelle?

When Are Opioids Indicated?

- Pain is severe
- Pain has significant impact on function and quality of life
- Pain type potentially opioid-responsive
(e.g., musculoskeletal or neuropathic but NOT fibromyalgia, migraines)
- Inadequate benefit from non-opioid modalities
- If already on opioids, is there documented benefit?



Daniel Alford, MD: Great question. So, when are opioids indicated? Well, first of all, I want to make sure the pain is severe, but that it also has a significant impact on their function and quality of life, and also that their pain type is one that is potentially opioid-responsive, such as musculoskeletal or neuropathic pain. We know that fibromyalgia and migraines are less responsive to opioids.

I also want to make sure that they've had inadequate benefit from non-opioid modalities, and also, like in our case, with our patient Michelle, if she's already on opioids, is there documented benefit?

Opioids and Chronic Pain in Perspective

The efficacy of **long-term opioid therapy** for chronic pain has been **inadequately studied**

- Opioid prescribing should be more judicious
- Opioid misuse can be fatal (overdose, opioid use disorder)
- Opioids for chronic pain...
 - Are indicated after alternative safer options are inadequate
 - Are only one tool of a multimodal approach for managing severe chronic pain

CDC Recommendation 2

- Maximize non-pharm and non-opioids
- 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

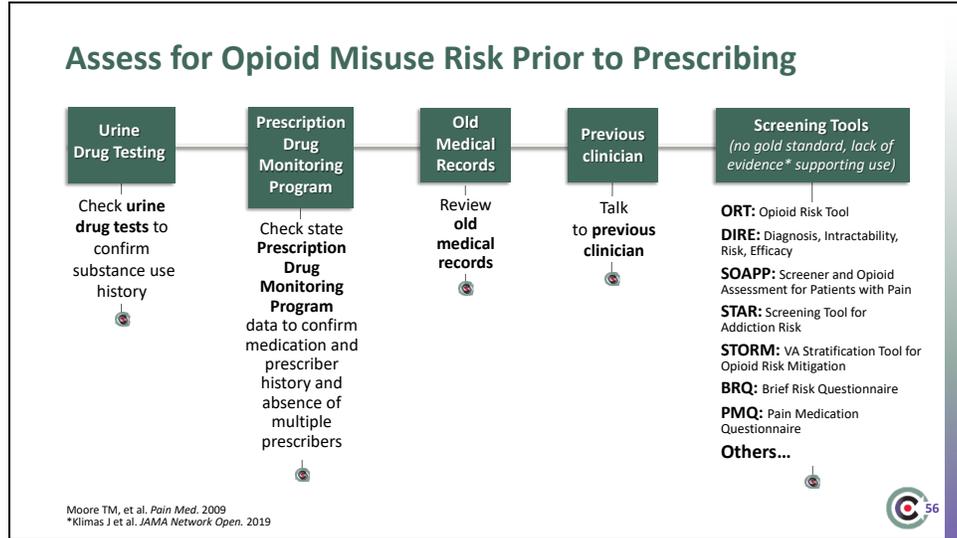
Chou R, et al. *Ann Intern Med.* 2015
Dowell D, et al. *JAMA.* 2016
Manchikanti L, et al. *Pain Physician.* 2011
Reuben DB, et al. *Ann Intern Med.* 2015
Volkow ND, McLellan T. *N Engl J Med.* 2016

Dowell D, et al. *MMWR.* 2022



So, let's put opioids and chronic pain in perspective. As I've discussed, the efficacy of long-term opioid therapy for chronic pain has been inadequately studied. Opioid prescribing should be more judicious.

Opioid misuse can be fatal, including overdose, and opioid use disorder, and that opioids for chronic pain are indicated after alternative, safer options have been found to be inadequate, and remember that they're only one tool of a multimodal approach for managing severe, chronic pain.



So, how do we assess for opioid misuse risk prior to prescribing? We're going to do urine drug testing. We'll talk more about that, really to confirm the substance use history that we obtained from the patient.

We're also going to check the Prescription Drug Monitoring Program, that includes checking your own state, but also, if your state allows interstate sharing of data, you want to confirm the medication history, and the prescriber history, and any absence of multiple prescribers. You want to check out the old medical records, if it's available. You want to talk to the previous clinician, if you can. And then there' are some screening tools.

There's no gold standard, and they all lack robust evidence supporting their use, but they're listed here as various screening tools, that basically incorporate some of the risk factors we talked about earlier, and score people in low-, moderate-, and high-risk.

<p>Case Study Michelle Jones 54 yo female</p>  <p>PDMP showed oxycodone 10 mg #120 tablets per month with one prescriber and one pharmacy, last filled 7 weeks ago</p>	<p>Next Steps</p> <ul style="list-style-type: none">• Prescribed oxycodone 10 mg every 6 hours x 2 weeks (#56)• Continued gabapentin• Added acetaminophen 500 mg every 6 hours• Sent urine drug test (UDT)• Obtained release to contact previous PCP <p>Reviewed Previous Medical Records</p> <ul style="list-style-type: none">• 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) 
---	---

John Emery: As we return to our clinical case, keep in mind that Ms. Jones came in asking for an opioid prescription today.

+++++

Daniel Alford, MD: So, before you came in, I checked, as I do with all my patients, the state website of your prescriptions. They were written and filled, and I verified that you've been getting the same medication over the last year from Dr. Robertson, and while I wouldn't normally prescribe an opioid to a new patient on the first visit, I'm going to give you a prescription for enough pills for the next two weeks, which will give me a chance to review your medical records and come up with a longer treatment plan.

So, I'm going to give you a prescription for oxycodone, and also, one for acetaminophen to try to improve your pain control. And since, as you know, there's lots of concerns about the risks of opioid pain medications, we require all patients on opioids to agree to urine drug testing to confirm that you're taking the medication safely. My medical assistant will help you with that. And then, before you come back, I'll look over these medical records.

Michelle Jones: It sounds like you really don't trust me.

Daniel Alford, MD: Oh, please don't think I don't trust you. It's just that these types of medications, as you probably know, can cause problems for people, and I absolutely want to make sure that you're safe.

Michelle Jones: Oh, I get it. I keep reading about people overdosing, and people with pain being shut off from their meds. It's really a terrible situation. I'll see you in a couple of weeks.

+++++

John Emery: Michelle's problem, and the medication lists are reconciled, and Dr. Alford reviews the radiology reports. He also thoroughly reviews her records from her previous PCP. There is inadequate documentation about benefits, and an incomplete record of monitoring, including urine drug testing, but there is no evidence of misuse of her prescription opioid.

Questions for Next Visit

Clinician Concerns:

- 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?



Before Michelle's next visit, Dr. Alford is concerned about a number of things. Should Michelle's dose be changed? If so, should she be switched to an extended release long-acting opioid? Remember, he continued her short-acting oxycodone and acetaminophen to be taken every six hours. What other adjuvant medications, or therapies, or both should be considered? What sort of treatment plan should be developed for Michelle Jones? As we begin the next section, keep those questions in mind. And as we conclude part one, Dr. Alford could you please summarize what we've learned so far?



SCOPE of Pain
Safer/Competent Opioid Prescribing Education

SUMMARY Part 1

Opioids:

- Should not be first line treatment option
- Are just one tool in a multimodal approach
- Side effects are common but can be managed
- Carry significant risk including addiction, overdose, death
- Misuse risk can be assessed using systematic approach which includes screening for co-morbidities and use of validated risk assessment questionnaires

Daniel Alford, MD: Sure. So, opioids should never be first line treatment, that they're just one tool in a multimodal approach, that there are adverse effects that are common, but they can be managed, and that opioids can carry significant risk, including addiction, overdose, and death, and that risk can be assessed using a systematic approach, which includes screening for opioid misuse risk factors.

Slide 60



John Emery: Welcome back to Part Two of SCOPE of Pain: Safer Opioid Prescribing. Now, let's return to Michelle Jones, and her second appointment with Dr. Alford.

<p>Case Study Michelle Jones 54 yo female</p>  <p>Should opioids be continued? If so, should the opioid be changed?</p> 	<p>In the interim...</p> <ul style="list-style-type: none">• Unable to contact previous PCP who retired• UDT positive for oxycodone only (as expected) <p>Office Visit 2</p> <ul style="list-style-type: none">• PEG scores:<ul style="list-style-type: none">– “6 out of 10” after oxycodone– “9 out of 10” right before next oxycodone dose• Denied sedation• Completed 2-week oxycodone prescription on schedule
--	---



+++++

Daniel Alford, MD: Good to see you again, Ms. Jones. I tried to speak to Dr. Robertson, but he wasn't available, but your old records, and the urine result from last visit were completely helpful, so thanks for that, and good to see you again.

Michelle Jones: Yeah. Good to see you, too. I think Dr. Robertson moved away when he retired.

Daniel Alford, MD: Well, let's review how you've been doing. Remember those questions that I asked last time. Can you tell me over the last week, what was your pain on average? Zero, no pain; 10 as bad as you can imagine?

Michelle Jones: Well, I'd say it's pretty much a 6 out of 10, most of the time, except right before I'm scheduled to take my next pill, when it's definitely a 9 out of 10. But I've been taking them just as you told me to, and they haven't made me tired or anything.

Daniel Alford, MD: What about its interference with your enjoyment of life? Doesn't interfere at all; 10 completely interferes?

Michelle Jones: I'd say on the medication it's probably a 6.

Daniel Alford, MD: And what about interfering with your general activity? Again, zero no interference; 10 completely interfering?

Michelle Jones: That's also a 6. My pain is always there. It really never goes away.

+++++

John Emery: Dr. Alford, would you make any changes to Michelle's opioid prescription?

Opioids

Immediate Release/ Short-acting (IR/SA)	Extended Release/ Long-acting (ER/LA)
<ul style="list-style-type: none">• Morphine• Hydrocodone• Hydromorphone• Oxycodone• Oxymorphone• Tramadol• Tapentadol• Buprenorphine (buccal)• Fentanyl (transmucosal)	<ul style="list-style-type: none">• Morphine• Hydrocodone• Hydromorphone• Oxycodone• Oxymorphone• Tramadol• Tapentadol• Buprenorphine (transdermal)• Fentanyl (transdermal)
<ul style="list-style-type: none">• Codeine	<ul style="list-style-type: none">• Methadone

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



Daniel Alford, MD: Yes, when I think about different opioids, I think about the immediate release, short-acting, and the extended release, long-acting opioids. And if you look on this slide, you'll see that they're listed side by side, because they're essentially the same molecule. It's just how they're packaged. So, we're going to talk more about that.

★

Choosing IR/SA vs ER/LA Opioids

IR/SA Opioids

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

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**

**Always
start low
and
go slow**



CDC Recommendation 3
When starting opioids, use IR instead of ER/LA opioids
Dowell D, et al. MMWR. 2022

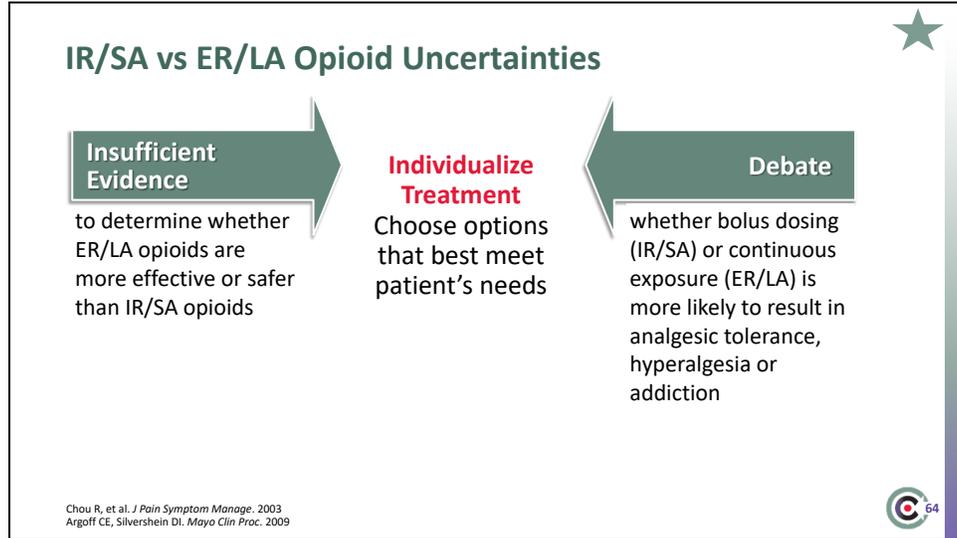
Note: No adequate studies of ER/LA opioids in pregnant women; use only if benefit significantly outweighs risk.



How do I choose between short-acting, and long-acting opioids? Well, if somebody has no opioid tolerance, and they're completely opioid naïve, I'm going to start with a short-acting opioid.

Or if they have intermittent or occasional pain, then I'm only going to dose it as need, then I'd use a short-acting opioid. But a long-acting opioid could certainly be considered in someone who's already tolerate, like our patient here, or if they have constant, severe, around the clock pain, and it's going to require just scheduled dosing each day, or to stabilize pain relief when a patient is using multiple doses of short-acting opioids.

It's important, though, to remember to remind our patients that these medications should never be broken, chewed, or crushed, because they're long acting, because of their formulation. We also want to remember to always start low and go really slow. Remember, chronic pain has been going on for months, if not years, and so, there shouldn't be a hurry to escalate any dose, and we really need to follow patients over time.

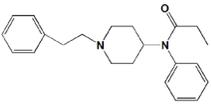


Now, there are uncertainties about when to use a short-acting versus long-acting. For instance, there's insufficient evidence to determine whether long-acting opioids are more effective or safer than short-acting opioids. There's also debate whether the bolus dosing of short-acting, or the continuous exposure of long-acting is more likely to result in analgesic tolerance, hyperalgesia, or even addiction.

So, really what we're left with is we need to individualize our treatment. We should choose the option that best meets our patients' need, based on their pain history.

Transdermal Fentanyl

- Dosed in micrograms
- Slow peak onset (>24-72h)
- Delayed offset (serum t_{1/2} life >17-26h)
- Sustained release requires predictable blood flow and adequate subcutaneous fat
- Absorption increased with fever or broken skin
- Absorption decreased with edema
- Some with metal foil backing not compatible with MRI



Fentanyl

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

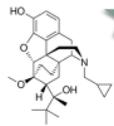


So, now I'm going to talk about a few specific opioids and formulations that are unique.

Transdermal fentanyl: It's dosed every 72 hours. It's dosed in micrograms.

Remember that the peak onset can take up to 24 hours, and if you overshoot, that's a problem, because of the delayed offset, whereas the serum half-life can be 24 hours. The sustained release mechanism requires a predictable blood flow, and adequate subcutaneous fat, and that the absorption will be increased if the person has a fever, or has broken skin, where the patch is. It will be decreased if the patient has edema, or anasarca. Remember that some of the patches have a metal foil backing that's not compatible with MRIs.

Buprenorphine



Partial opioid agonist with formulations approved for treatment of pain or opioid use disorder (OUD)

- Pain (dosed in mcg)**
 - Can precipitate opioid withdrawal if initiated while full opioid agonist highly bound
 - Taper prior opioid to ≤ 30 MME before starting buprenorphine
- OUD (dosed in mg)**
 - Some formulations contain naloxone
 - Induction procedure to avoid precipitating opioid withdrawal
 - OUD** dosed 1x/day
 - OUD + Pain** dosed 3x/day

Buccal 75-900 mcg q12-24

- Film shouldn't be cut, chewed or swallowed

Transdermal 5-20 mcg/hr q 7 days

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

Sublingual tablets and film } Maintenance ~12-24 mg/d
Buccal tablets and film }
SQ monthly injection

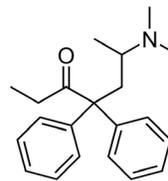


What about buprenorphine? Well, buprenorphine is a partial agonist at the mu opioid receptor with formulations that are approved for pain, and formulations that are approved for treating opioid use disorder. Those that are approved for pain are preparations that are dosed in micrograms. They can precipitate opioid withdrawal, if they're initiated while a full opioid agonist is highly bound to the mu opioid receptor.

So, the recommendation is to taper prior opioid to less than, or equal to 30 morphine mg equivalents before starting the buprenorphine. The formulations that are approved for opioid use disorder are dosed in milligrams. There's a longer wash out period from the previous full agonist opioid, before initiating buprenorphine, and we're going to talk more about buprenorphine for treating opioid use disorders later in the program.

Methadone is Complex

- The problem...potentially the most dangerous opioid
- Long, variable, unpredictable half-life
 - Analgesia 6-8 hours
 - Serum $t_{1/2}$ 20-120 hours
- QTc prolongation, risk of torsades de pointes



Some possible advantages:

- NMDA receptor antagonist
 - Potentially less analgesic tolerance, better efficacy in neuropathic pain
- No active metabolites
- Inexpensive, small dosage units (5mg tablets)

Fredheim OM, et al. *Acta Anaesthesiol Scand.* 2008
Chou R, et al. *J Pain.* 2014



Methadone is really complex. The problem is that it's potentially the most dangerous opioid, because of the long, variable, and unpredictable half-life. The analgesic properties last six to eight hours, whereas, the serum half-life can last for days, and there's a risk for QTc prolongation, putting someone at risk for Torsades, a fatal arrhythmia.

But there are some possible advantages to methadone. It also has activity at the NMDA receptor as an antagonist, resulting in potentially less analgesic tolerance, better efficacy in neuropathic pain. There are no active metabolites, and it's inexpensive, and it comes in small dosage units, for instance, 5 mg tablets, which in this case can be split, because methadone's long-acting properties are not related to the formulation, but to the medication, itself.

Dual Mechanism Opioids
Norepinephrine and Serotonin reuptake inhibition

Tramadol	Tapentadol
Weak μ-opioid receptor agonist	Stronger μ-opioid receptor agonist
Minimal norepinephrine effect	Prominent norepinephrine effect
Prominent serotonin effect	Minimal serotonin effect

- Seizure risk
- Physical dependence
- Serotonin syndrome
- Controlled substances with addiction potential

Medical Letter, April 2010



What about the dual mechanism opioids? Well, these are medications that also act as norepinephrine, and serotonin reuptake inhibitors, and include tramadol, and tapentadol. Tramadol is a weak mu opioid receptor agonist with minimal norepinephrine effect, and prominent serotonin effect, whereas tapentadol is a stronger mu opioid receptor agonist with prominent norepinephrine effect, and minimal serotonin effect.

But they can cause seizures. They absolutely result in physical dependence. There's also the risk of serotonin syndrome, and they are controlled substances with addiction potential.

John Emery: Can you talk about types of opioids that are supposed to be safer?

Abuse Deterrent/Resistant Formulations

Physical Barriers
(crush resistant, gelling agents)

Reducing Drug Rewards

Routes of Administration

Prodrugs

Agonist with sequestered antagonist

Aversive Components

- Post-marketing studies show decrease diversion and street price
- Does not prevent taking large numbers of intact tablets or prevent the inherent risks or negative ADRs of the substance
- Are expensive and some insurers do not cover them

Warning: Currently, there are **no 100% proven misuse resistant opioids**

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

Passik SD. *Mayo Clin Proc.* 2009
Stanos SP, et al. *Mayo Clin Proc.* 2012
Nichna E, et al. *Curr Med Res Opin.* 2014
Cassidy TA, et al. *Pain Med.* 2014
Medical Letter. June 5, 2017

Daniel Alford, MD: Yeah. So, in response to the misuse of opioids, the pharmaceutical companies created abuse deterrent, resistant formulations, and there are a variety of ways of doing this. For instance, creating physical barriers, so that they cannot be crushed, or combining it with an antagonist, that is, if they take it incorrectly, the antagonist has more of an effect, resulting in withdrawal, and certainly adding aversive components, different routes of administration, and so forth.

Now, the post-marketing studies of these formulations did show a decrease in diversion, and a decrease in what they were being sold for on the street but remember that they don't prevent taking large numbers of intact pills or prevent the inherent risks of negative adverse drug reactions of the substance. They tend to be more expensive, and some insurers do not cover them, and please keep in mind that currently there are no 100 percent proven misuse-resistant opioids. So, even if we're using these formulations, we should use them cautiously.

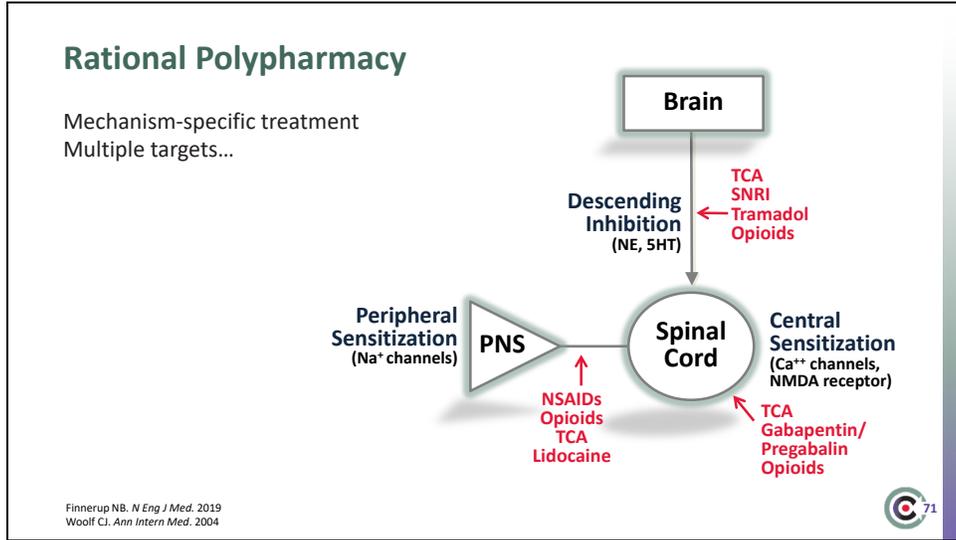
Opioid Choice Summary

- Duration and onset of action
 - Consider pattern of pain – intermittent vs. constant
- Patient's prior experience (differing effects and side effects)
 - Mu-opioid receptor polymorphisms
 - Differences in opioid metabolism
- Patient's level of opioid tolerance
(always assess before starting ER/LA opioid formulations)
- Other drugs, age, other diseases
- Route of administration
- Cost and insurance issues

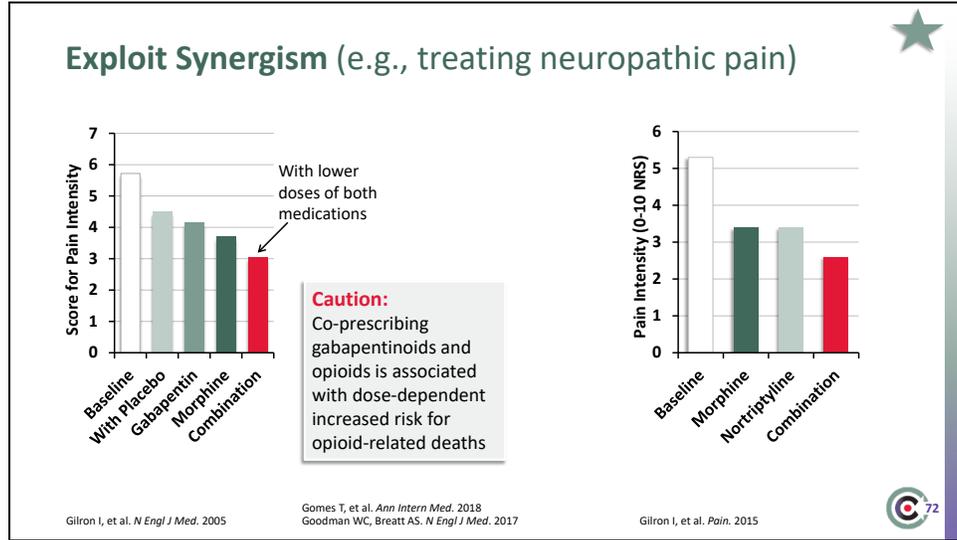


Now, let me just summarize what we just talked about around opioid choice. First, we want to consider the duration, and onset of action, and we should consider the patient's pain pattern. Is it intermittent or constant? But also, the patient's prior experience, remembering different effects, and different side effects. Remember the mu opioid receptor polymorphisms, and the differences in opioid metabolism.

So, when a patient tells you that they responded to one opioid better than another, that can be very helpful information. We also want to keep in mind the patient's level of opioid tolerance. We always assess tolerance before starting a long-acting opioid formulation, which we would never do in an opioid-naïve patient. We also want to consider other drugs, their age, and other diseases, the route of administration, but also the cost and insurance issues. There are certainly some issues with some formulations not being covered by someone's insurance.



We also want to think about something called “rational polypharmacy,” and I was taught in medical school that polypharmacy is always bad, but when we’re thinking about pain management, polypharmacy can actually be helpful. Why? Because various medications work on different pathways within the pain system. We have certain medications that turn on the descending inhibitory pathway, others that act centrally around central sensitization, and others that work peripherally.



And so, we want to consider the various targets, and we want to exploit synergism, especially when treating things like neuropathic pain, and I'm showing here some studies that demonstrate this. The first study on the left for individuals with neuropathic pain, had a baseline pain score on a scale of 10 of around 5.5 to 6, and then they were randomized to placebo, gabapentin, morphine, or the combination gabapentin and morphine.

And you can see here that the group that did the best was the combination group that got both gabapentin and morphine. But that's not even the most interesting part of the story. The most interesting part of the story is they got better pain relief with lower doses of either medication, because of the synergy.

The study on the right is just a similar study. Again, neuropathic pain, but this time they randomized people to morphine, or nortriptyline, or the combination, and again, the combination group did the best. Now, in the first study, I talked about gabapentin. Remember that co-prescribing gabapentinoids, whether it be gabapentin, or pregabalin, and opioids are associated with harm, dose-dependent increased risk of opioid-related deaths, and misuse.

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)
- Referred to PT for chronic right hip pain
- Counseled on weight loss



+++++

Daniel Alford, MD: Okay, Ms. Jones. Here’s what I suggest that we do moving forward. Since you have severe pain all day, and you tolerate the oxycodone four times a day, but you told me that your pain gets worse right before your next dose, I’m going to switch you to a long-acting version of the same medication, which you’ll take twice a day, instead of multiple times, and that, I hope, will stabilize your blood levels, and should prevent you from having these severe pain episodes right before your next dose.

And with the long-acting medication, and more stable blood levels, I’m going to decrease your overall daily dose, and see how that works. Please, please, please, don’t break or crush these tablets, because that could be really dangerous. I’m also going to continue the acetaminophen you’re on, and increase your gabapentin a little bit, because that will help the oxycodone work better. I’m also going to refer you to a physical therapist to help work on that hip pain of yours.

Michelle Jones: I don’t understand how getting a lower amount of pain med is going to help my pain. Dr. Robertson never recommended these changes.

Daniel Alford, MD: I get it, and listen, I hope you trust that I’m really trying to make these changes to improve your pain control. Because we know that opioids carry serious risks, I’m going to walk you through our office policy around how we’ll monitor you for safety. This is our operative standard for all patients on opioids, so I’m not singling you out. It’s what we do for everybody to keep everyone safe. So, let’s go over an agreement, which outlines my responsibilities, your responsibilities, and if we both agree on it, we can sign it, and then, I’ll have the nurse out front get you that appointment with physical therapy.

Michelle Jones: Wow, all right. That’s a lot of stuff to do, but I do trust that you are trying to help me.



Universal Precautions when Prescribing Opioids

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 d/c based on risks/benefits (e.g., every 1-3 months)
- State maximum number of tablets to be taken per day
- Patient Prescriber Agreements (PPA) including informed consent and plan of care
- Monitor for adherence, misuse, and diversion

 **Recommendation 7**

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

Dowell D, et al. MMWR. 2022

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

Franklin GM. *Neurology.* 2014
Federation of State Medical Boards *Model Policy* April 2017.



John Emery: Note here that Dr. Alford 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 Michelle's weight loss. Dr. Alford can you give us some detail about the monitoring and documentations strategies you put into place in order to try to keep your patients on chronic opioid therapy safe?

Daniel Alford, MD: The standard of care now is to use universal precautions when prescribing opioids, because we believe that there is no patient with zero percent risk, and so if you assume everyone has some risk, but also that predicting opioid risk and misuse is imprecise, by using universal precautions it protects all patients, the public, and community health, as well.

It also allows for consistent application to precautions, and reduces patients from feeling stigmatized, and it standardizes systems of care. So, what do I mean by universal precautions? Well, it includes regular assessment, and documentation of the pain diagnoses, and opioid misuse risk that when we prescribe opioids, we're doing it as a test, or a trial, and that we're continuing it, modifying, or discontinuing it, based on the patient's risks and benefits, and this should be done every one to three months, that we prescribe naloxone, and that we use the Patient Prescriber Agreement, or a PPA, that includes an informed consent, and outlines the plan of care, and we're going to monitor our patients for adherence, misuse, and diversion.



Patient Provider Agreement (PPA)

Informed Consent	Plan of Care
<p>Realistic Goals <i>Reduce (not eliminate) pain</i></p> <p>Increase function (SMART goals):</p> <ul style="list-style-type: none"> Specific Measurable Action-oriented Realistic Time-sensitive 	<p>Potential Risks</p> <ul style="list-style-type: none"> • Adverse effects and drug interactions • Over-sedation and impairment (<i>esp. during dose adjustments</i>) • Misuse • Overdose • Death • Risk of neonatal withdrawal • Hyperalgesia • Victimization by others seeking opioids
<p><small>Nicolaidis C. <i>Pain Med.</i> 2011 Paterick TJ, et al. <i>Mayo Clin Proc.</i> 2008 Cheatle MD, Savage SR. <i>J Pain Symptom Manage.</i> 2012 Tolia VN, et al. <i>N Engl J Med.</i> 2015</small></p>	<p><small>Mailis-Gagnon A, et al. <i>Clin J Pain.</i> 2012 Schumacher MB, et al. <i>Psychopharm.</i> 2017 Fishman SM, Kreis PG. <i>Clin J Pain.</i> 2002 Arnold RM, et al. <i>Am J Med.</i> 2006</small></p>



So, now let me just talk a little bit about the agreement, and the agreement, remember, includes informed consent, and plan of care. So, informed consent, it starts with creating realistic goals for your patient, that is to reduce, not eliminate pain, but also to increase function, and the best way to follow function, and functional changes over time is to use SMART goals, and SMART stands for specific, measurable, action-oriented, realistic, and time-sensitive.

We're also going to talk about potential risks, like the adverse drug effects that we talked about, drug-drug interactions, the risk of over-sedation, and potential for impairment, especially during dose adjustments, the risk of misuse, overdose, and death, and the risk for our patients who are of reproductive age, the risk of neonatal opioid withdrawal syndrome, but also the risk of hyperalgesia, and the risk of being victimized by others who may be seeking opioids.

Plan of care? So, the plan of care is going to talk about engagement, and other recommended treatments, medication management, including clear instructions on the maximum number of pills to be take in a day, and to use the medications exactly as directed, but also refill policies, and what should be expected, safe storage, safe disposal, and no sharing, no illegal drug use, and avoid or minimize sedative use.

And to notify me of all of the medications, and drugs that the person is being prescribed by others, and permission to communicate with key others, but also to discuss birth control, and periodic monitoring for pregnancy, again, in those who may be pregnant, while taking opioids.

Monitoring: Urine Drug Testing



Objective data that can provide:

- **Information on therapeutic adherence**
- **Information on use or non-use of illicit drugs**

- Discuss urine drug testing openly with patient
 - “If I send your urine right now, what will I find in it?”
- Document time of last medication use
- One medical data point to integrate with others
 - Cannot discriminate elective substance use from substance use disorder and diversion
 - Concentrations cannot determine how much opioid is being taken
- Dedicated deceivers can beat the system

CDC Recommendations 10
Use strategies to mitigate risk including using toxicology testing

Argoff CE, Alford DP, Fudin J et al. *Pain Med.* 2018
Nagpal G et al. *JAMA.* 2017
Christo PJ, et al. *Pain Physician.* 2011

Dowell D, et al. *MMWR.* 2022



And now, I'm going to talk about monitoring strategies, including urine drug testing, which is objective data that can provide us with information on therapeutic adherence, that is the patient taking the medication that we're prescribing? But also, information on use, or nonuse of illicit drugs. I always discuss urine drug testing openly with my patient, like I do with any test that I'm sending them for, and sometimes I'll even start by saying, "If I send your urine right now, what will I find in it?"

And sometimes they'll tell me about stuff that I'm not even testing for, and really the goal here is not to catch someone doing something wrong, but it's to adjust the risk/benefit ratio, that is if they're using other drugs that may interact, or be problematic with the opioid, and that's going to change how you think about continuing to prescribe.

You want to document the last time they took their medication. You don't want to find that the urine is negative for the medication you're prescribing only to find out that they haven't been taking it every day, but remember, also, that the results are just one medical data point to integrate with others. It can't discriminate elective substance use from a substance use disorder, or diversion.

And just a word of caution that opioid concentrations can not determine how much opioid is being taken. Sometimes labs will tell you that, that they can, but it really has not been shown to be that helpful, that is looking at concentrations, and trying to determine adherence with the actual dosing. Also, keep in mind that dedicated deceivers can beat the system if they really want.

Monitoring: Urine Drug Testing



Urine drug screens are usually immunoassays	Unexpected findings can be verified with definitive testing*
<ul style="list-style-type: none">• Quick, inexpensive and can be done at point of care• Know what is included in your testing panel• Risk of false negatives due to cut offs and false positives due to cross reactions	<ul style="list-style-type: none">• Very specific (identifies specific molecules) but more expensive• Know opioid metabolism to interpret GC-MS or LC-MS results<ul style="list-style-type: none">– e.g., hydrocodone → hydromorphone;oxycodone → oxymorphone

*Using 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
Reisfield GM, et al. *Bioanalysis.* 2009



So, if you have an unexpected finding on an immunoassay, it can be verified with definitive testing, using gas chromatography, or liquid chromatography, and mass spectroscopy. These tests are very specific. They identify specific molecules, and they're more expensive. You also need to understand the opioid metabolism for the medication that you're prescribing in order to interpret the GCMS.

For instance, if a patient's on hydrocodone, it can get metabolized into hydromorphone, or if they're on oxycodone, it can be metabolized oxymorphone, so you really need to understand that, because you're going to see these molecules show up in their urine.

Now, it can be complex, and not everyone is going to become an expert in interpreting your drug testing, so what you do need to know is who is the lab toxicologist that you can call, or e-mail for questions regarding the unexpected results.

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

Medication Count

- Information on medication adherence
- Information concerning for diversion

28-day (rather than 30-day) prevents running out on weekends and medication hoarding

PDMP

- Information on harmful polypharmacy
- Information on multiple provider use

Some states allow delegating access to allied health professionals and have interstate data sharing

Insufficient evidence that implementation either increases or decreases nonfatal or fatal overdoses

CDC Recommendation 9
Use strategies to mitigate risk including reviewing PDMP data
Dowell D, et al. MMWR. 2022

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

Some other monitoring strategies include medication counts, and this gives you information on medication adherence, and also give you information about concerning behaviors that may make you worried about diversion. Now, we prescribe a 28-day supply, rather than 30-day supply, which will prevent patients from running out on weekends, and from holding onto extra medication.

So, what do I mean? If I prescribe on a Tuesday a 28-day supply, you will be due for a refill in exactly four weeks on a Tuesday. If I give a 30-day supply, and I'm filling it every Tuesday, they're going to start collecting pills, or if they wait until the 30 days is up, eventually it's going to start running out on weekends. What about the Prescription Drug Monitoring Program? Well, that helps you with finding information on harmful polypharmacy, but also, information on multiple providers.

Some states allow delegating access to the PDMP, to allied health professionals, and also, have the capacity to have interstate data sharing, especially in states or communities that are bordering other states. There was a study that showed insufficient evidence that implementation of PDMPs, either increases or decreases nonfatal, or fatal overdoses, but it's still a useful, monitoring tool to make sure your patients are safe.

MINIMUM Level of Monitoring Based on Risk

TOPCARE (Transforming Opioid Prescribing in Primary Care) <http://mytopcare.org/>

One example from TOPCARE program:

Risk Level	Visits (per year)	• UDT • Pill Counts • PDMP (per year)
Low	4	2
Moderate	4	4
High	6	6

- States laws may mandate level of monitoring
- Monitoring more intensive during first 6 months of opioid therapy

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



Oftentimes, I'm asked, "How often should we be doing these monitoring tests? What's the minimal level?" And I would suggest that it's based on the patient's risk. This table comes from a study that was funded by the NIH, looking at safer opioid prescribing practices, and what they did is they risk stratified the individuals as low-, moderate-, and high-risk, based on their risk profile, and based on that, they determined how often the patient should be seen, and how often they should have urine drug testing, pill counts, and PDMP checks.

And you can see from this table that low-risk patients were seen four times a year, and had the monitoring strategies done twice a year, as opposed to high-risk patients, where they were seen six times a year, and had these strategies implemented six times a year, as well.

So, this is just kind of a guideline. However, remember that some state laws mandate the level of monitoring. For instance, in the state that I practice in, Massachusetts, it requires that I check the PDMP before every single prescription. Also, keep in mind that monitoring can be more intensive during the first six months of opioid therapy until you assure yourself that the patient is able to take these medications, as prescribed, and safely.

Monitoring and Documentation: Office Visits

Six A's

- A**nalgesia
- A**ctivities
- A**dverse effects
- A**berrant behaviors
- A**ffect
- A**dherence

Subjective reports from patient, co-care providers, caregivers and “reliable” family members
(beware of family members with secondary gain for giving inaccurate information)

Objective information (observations, drug tests, pill counts, PDMP)

Also review...Opioid use using a **24-hour inventory**
“Tell me how you are taking your medications.”

Know federal and state guidelines and regulations:
www.deadiversion.usdoj.gov/pubs/manuals/index.html

Templates in Resources at:
www.scopeofpain.org and mytopcare.org

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



Monitoring and documentation with office visits, you could use the 6As, which includes looking at analgesia, pain relief activities, function, adverse effects, aberrant behaviors, affect, and adherence. And you want to document subjective reports from the patient from co-care providers, from caregivers, and “reliable” family members.

And I put “reliable” in quotations, because beware that some family members may have secondary gain for giving inaccurate information, either they want their family member to continue getting the prescription, or maybe they’re angry at them, and they want them to not get it anymore. So, you just have to know who you’re getting the information from.

You also want to document objective information, that is your clinical observations, the results of drug tests, pill counts, and the PDMP. You could also review, and I find this incredibly helpful, their opioid use over a 24-hour inventory. And I ask the question, “So, tell me how you’re taking your medications over the day. What time do you wake up? When do you take your first dose? When do you take your next dose? When do you take your last dose?”

And that can be incredibly enlightening and helpful.

What is the Clinician's Role?

Use a risk-benefit framework

Judge the opioid treatment, *not* the patient



NOT

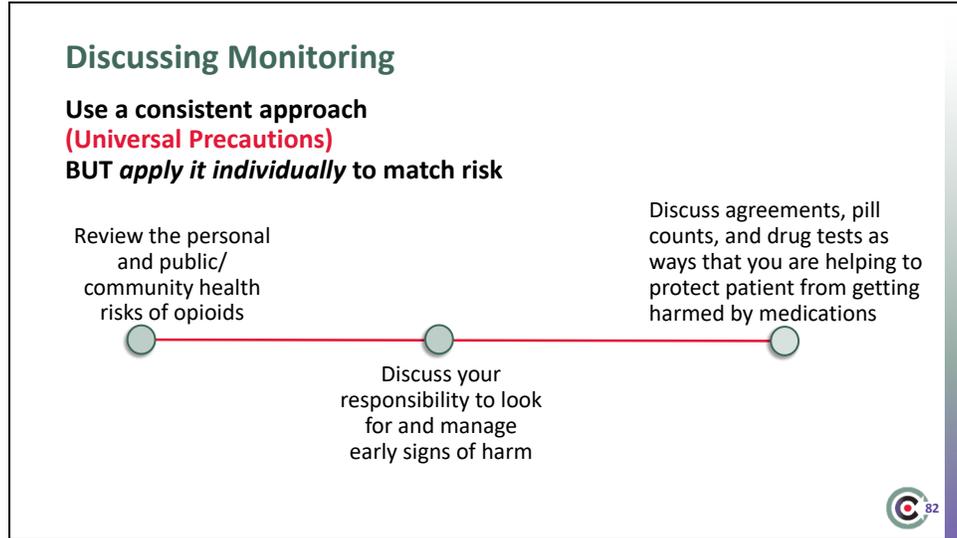


Nicolaidis C. Pain Medicine. 2011



So, talking about all these monitoring strategies, someone may say, “Well, boy, what’s my role here?” And your role is to still be a clinician. Using a risk-benefit framework, and judging the treatment, like we do all the time for any chronic disease management, we’re not judging the patient.

I am in no way asking you to be a police officer, a DEA agent, or judge, and I know sometimes it feels that way, but really, we’re clinicians. We’re trying to help our patients, both improve their life, but also, prevent them from being harmed from the treatments that we’re offering them.

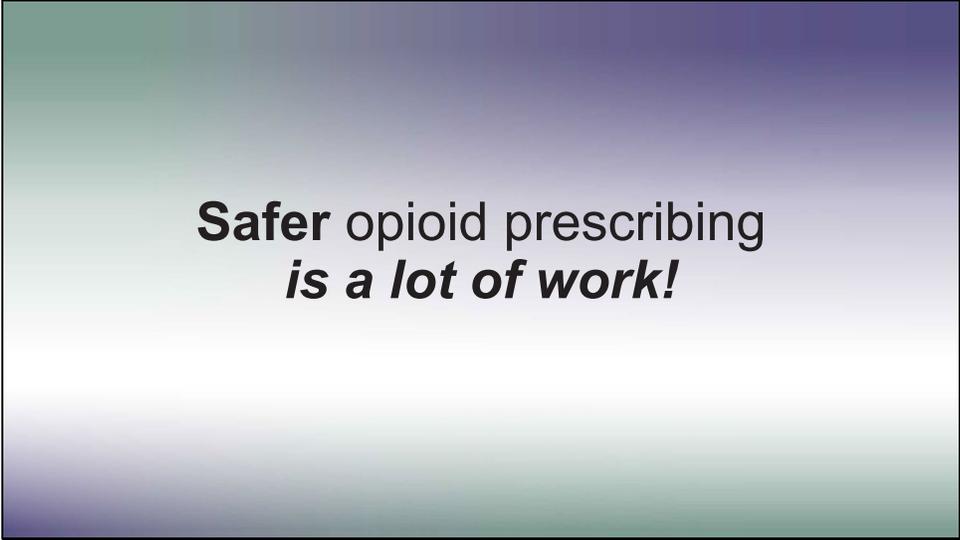


How do I discuss monitoring with my patients? I review the personal, and public, and community health risks, which they're very well aware of, usually.

I discuss that it's my responsibility to look for and manage any early signs of harm, and also that the agrees, pill counts, drug tests are simply ways that I can help protect them from being harmed from the medication that I'm prescribing for them.

In summary, I use a consistent approach that is universal precaution, so everyone has some level of precautions, but then I apply it individually to match that patient's risk.

Slide 83



Safer opioid prescribing
is a lot of work!

John Emery: Safer opioid prescribing is a lot of work. Can you talk about how you manage it in a busy primary care practice?

Implementing Safer Prescribing

- **Office controlled substance policies and procedures**
- **Patient registry**
Allows practice managers to track office-wide adherence to guideline-based practices
- **Utilize healthcare team**
Nurses, pharmacists, psychologists, medical assistants, front desk staff
- **Lists of referral and support resources:**
pain, mental health, addiction
- **Utilize DEA COVID-related policies** allowing for controlled substance prescribing via telemedicine without having to interact in-person with patients



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



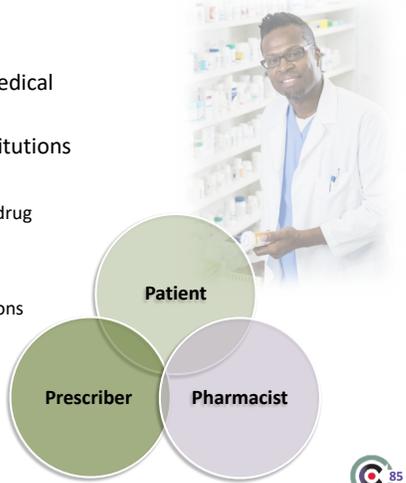
Daniel Alford, MD: There is no question it's a lot of work, but we do a lot of things in primary care that's a lot of work, but we figure out ways to do it. So, first, you want to make sure you've got an office-controlled substance policy and procedure that everybody agrees on and uses.

You could have a patient registry that allows practice managers to track adherence throughout your office to make sure that everyone is practicing guideline-based practices, and you want to utilize the whole healthcare team. We shouldn't do this alone. Nurses, if you've got primary care-based pharmacists, psychologists, medical assistants, front desk staff, everyone can help out.

You also want to have a list of referrals and support resources for pain specialists, mental health specialists, and addiction specialists, and the good news is that during COVID, the DEA has some policies that allow for controlled substance prescribing, via telemedicine, even without having to interact in person with patients. If you want to learn more about how to optimize your office systems, you can go to scopeofpain.org, and click on "Supplemental Training," and there's a free educational module on how to do that, how to optimize your office systems.

Community Pharmacist

- Ensure that prescriptions are for “legitimate medical purposes”
- 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 insurer formularies and prior authorizations
- Prescribers can help by including:
 - Diagnosis or indication on prescription
 - Parameters for when script should be filled

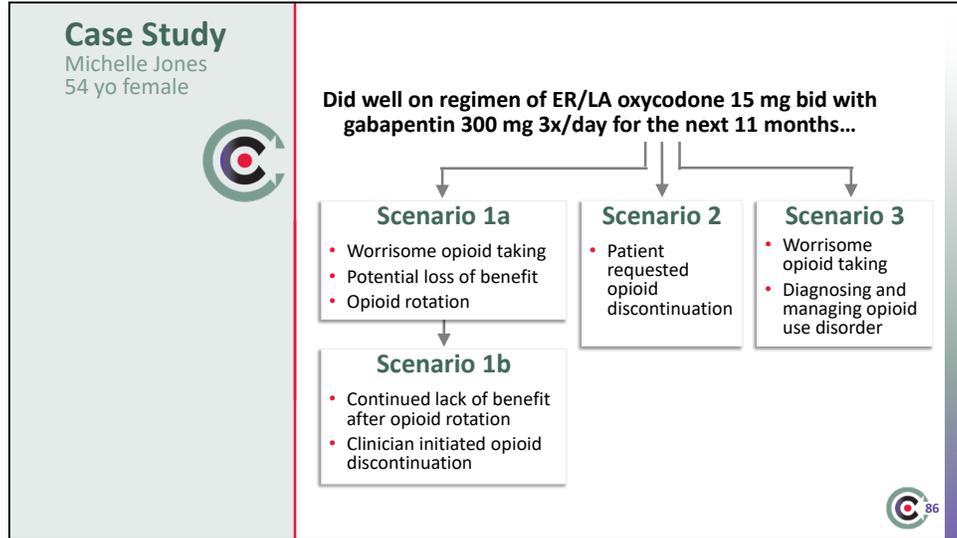


Gregory T, Gregory L. *J Pharm Pract.* 2020

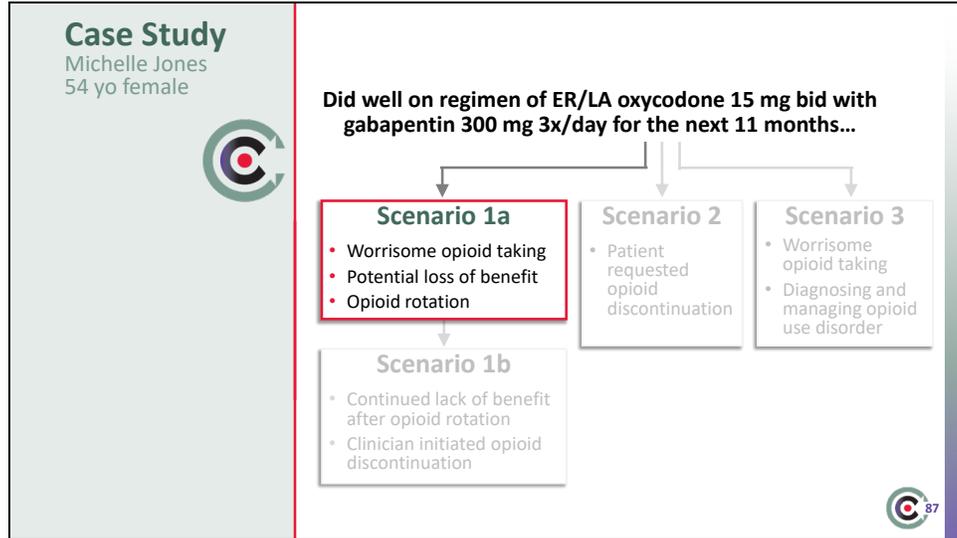
So, we also want to work collaboratively with our community pharmacists. Remember that pharmacists have a legal responsibility to ensure that every prescription that they dispense are issued for a legitimate medical purpose. Pharmacists are also medication experts, and they can help with medication choices, doses and substitutions.

Pharmacists have frequent contact with patients. They can educate patients on risks, on the proper use, storage, and disposal of opioids, as well as the use of naloxone. They'll also be checking the PDMP, and they can monitor patients for worrisome behavior, such as patterns of early refills, that might indicate misuse. They can identify potential drug-drug interactions, assist with formulation selections, and assist with navigating insurance companies' formularies, and prior authorization requirements.

We can help them do their job better, by communicating with them, such as listing the diagnosis, or indication for the opioid on the prescription, and also, listing parameters for when the script should be refilled.



John Emery: 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, opioid taper, and managing opioid use disorder.



Michelle seemed to be doing well on her pain treatment plan, including opioid therapy for her painful diabetic neuropathy, and chronic hip pain for the next 11 months.

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



Then, Dr. Alford was notified that Michelle was seen in the emergency room of a local hospital, requesting an early refill on her oxycodone after running out early. The ED physician noted that she was moderate to severe opioid withdrawal and gave her a prescription for enough oxycodone pills to last until our next appointment with Dr. Alford in one week.

<p>Case Study Michelle Jones 54 yo female</p>  <p>Post ED Follow-up</p>	<p>History since last visit</p> <ul style="list-style-type: none">• Foot pain worse in past month “10 out of 10 most days”• Extra oxycodone in the afternoon and ran out early• Requests increase in her dose• Concerned “body has become used to current dose”; doesn’t seem to work all day anymore• Husband says she has become “addicted”• Difficult to go to work due to severe pain• She is re-educated about risks including death of self-escalating her opioid dose 
--	---

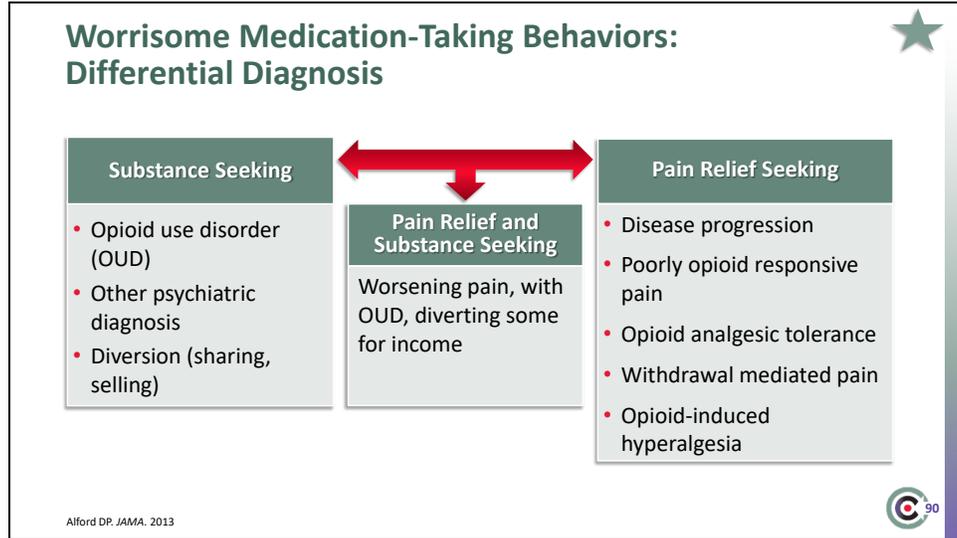
+++++

Daniel Alford, MD: Hi, Michelle. Wow, I was surprised to get a call from the emergency room doctor about your visit last week requesting an early refill of your oxycodone. Can you tell me about it?

Michelle Jones: Well, my foot pain has been so much worse that I started taking an extra pill in the afternoon. So, I ran out. I think I’ve gotten used to this dose, and it doesn’t work the way it used to, but now I’ve got my husband telling me I’m addicted, and I’m not, but the pain is so bad that it’s hard to get to work, and I can’t sleep, because even the sheets hurt my feet. I think I need a higher dose.

+++++

John Emery: Dr. Alford, what do you think is happening with Michelle, and how will you respond to her request?

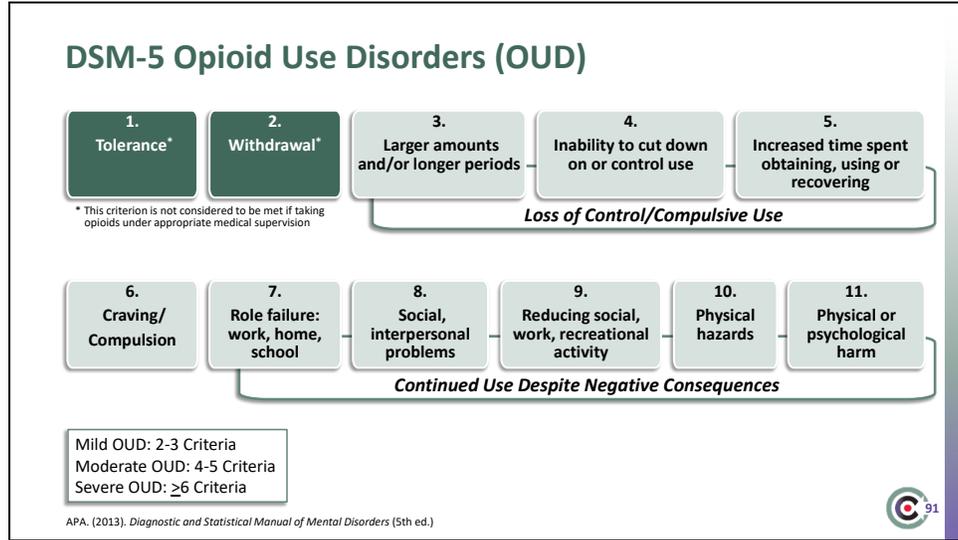


Daniel Alford, MD: The first thing I do is take a deep breath and think about the differential diagnosis for this worrisome behavior. Is it substance seeking? So, has she developed an opioid use disorder or addiction? Or maybe she's medicating some other psychiatric diagnosis. We know that opioids make people feel better, whether it's depression or anxiety, or maybe there's some diversion. Maybe she is sharing it with others.

Alternatively, maybe it's pain relief seeking. Maybe her neuropathy is worse, and her arthritis has worsened, or maybe her pain is just poorly opioid responsive. Maybe she developed opioid analgesic tolerance, or maybe she has withdrawal mediated pain, or maybe she has opioid-induced hyperalgesia.

Let me go back to those last two bullets. The first one is withdrawal-mediated pain. Remember, the patients who are on chronic opioids become physically dependent, and so, maybe there are certain times of the day where her opioid level drops, where she actually goes through some withdrawal, and that's experiencing as worsening pain. She takes her medication, and she feels better, but maybe she's treating withdrawal, and not actual pain. The opioid-induced hyperalgesia I'm going to talk more about in a subsequent slide.

But sometimes it's not even that clear-cut. Sometimes it's a combination of pain relief and substance seeking. For instance, maybe her pain has gotten worse. Maybe she has developed an opioid use disorder. Maybe she is diverting some, and taking some for her pain, so it can be much more complicated. But we should be thinking about it in terms of a differential diagnosis.



Let's start with opioid use disorder. Has she developed an opioid use disorder? We need to go to the DSM-5 to make that diagnosis. And there are 11 criteria. The first and second criteria are tolerance and withdrawal, and you'll notice down below it says, "These criteria cannot be considered if the patient is taking opioids under appropriate medical supervision," like our patient.

However, there are nine other criteria. Has she lost control, and using compulsively? Has she continued use, despite negative consequences? Has she stopped fulfilling her usual responsibilities? Is she using in hazardous situations? Is she craving, and so forth. So, you can see her the various criteria, and you only need two or three to have a mild opioid use disorder; four to five for a moderate OUD, and greater than or equal to six to have a severe OUD.

So, does she meet the cutoff for an opioid use disorder? We need to think about that.

Discussing Possible OUD

Opioid Use Disorders	Give specific and timely feedback about behaviors that raise your concern 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 outweighing risks
	"I cannot responsibly continue prescribing opioids as I feel it would cause you more harm than good."
	Always offer referral to addiction treatment



How do we discuss possible OUD with a patient? We want to give specific, and timely feedback about the behaviors that raise your concern for a possible OUD, such as she's lost control; she's using compulsively, and she continues to use despite harm. Remember that patients may suffer from both chronic pain and an OUD, and sometimes we just need to agree to disagree with the patient, if they don't agree with our assessment.

We need to remember that the benefits can no longer outweigh the risks if you're worried about an OUD diagnosis. I would say something like, "I cannot responsibly continue prescribing opioids as I feel it would cause you more harm than good." And then, always, always, always refer to addiction treatment, even if the person's not willing and able to accept that referral.

Opioid-Induced Hyperalgesia (OIH)

Paradoxical enhanced pain sensitivity in patients on chronic opioids	Underlying pathophysiology and true incidence is unknown
No official criteria or guidelines for diagnosing OIH Clinically pain is generalized, diffuse, ill-defined and not necessarily located at the source of original pain	
Increased dose may improve analgesia but only temporarily	No standardized approach on how to taper opioids to manage OIH

Yi P, Przybylowski P. *Pain Med.* 2015
Chang G, et al. *Med Clin North Am.* 2007
Lee M, et al. *Pain Physician* 2011
Eisenberg E, et al. *J Pain Symptom Manage.* 2014



I had mentioned opioid-induced hyperalgesia, and this is a paradoxical enhancement of pain sensitivity in patients who are on chronic opioids. Unfortunately, the underlying pathophysiology and the true incidence is unknown, and there are no official criteria or guidelines for diagnosing it. But what do you see? You see that their clinical pain is generalized, diffuse, ill-defined, and not necessarily located at the source of the original pain.

While an increase in opioid dose may improve analgesia initially, it will only be temporary, and there are no studies looking at opioid taper for opioid-induced hyperalgesia. So, when do I consider this diagnosis? Well, I only consider it when the patient isn't doing well. If they're doing well in terms of pain, function, and quality of life, then I'm not so worried about it.

But patients who aren't doing well, I absolutely consider it, and I'll even act upon it; that is, taper their opioids, based on the risk that they have developed this.

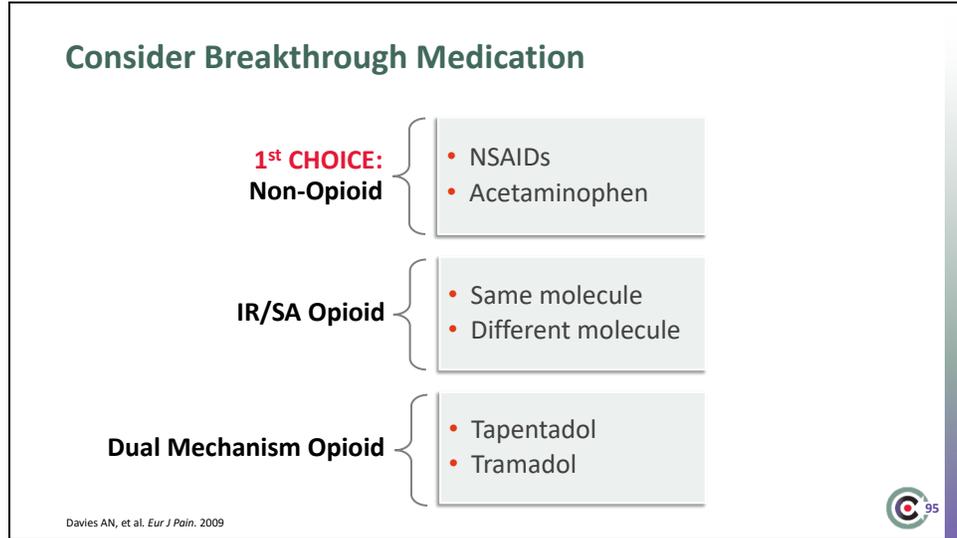
Lack or Loss of Benefit

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



If the patient has lack or loss of benefit, what are the next steps? I want to reassess the factors that affect their pain. I want to reattempt to treat any underlying disease and comorbidities, and I want to consider adding, or increasing nonpharmacological treatments, like acupuncture, or cognitive behavioral therapy, for example, consider adding breakthrough medications, or consider switching to a different opioid.



So, in terms of breakthrough medications, the first choice would be a nonopioid, like an NSAID or acetaminophen. Remember that even though the patient was on a long-acting opioid, I didn't initially feel the need to start breakthrough medications, but if I do, just because they're on a long-acting opioid doesn't mean they need a short-acting opioid for breakthrough medication, so I would start with nonopioids. But if that doesn't work, you certainly can use a short-acting opioid, either the same molecule, or a different molecule than what they're already on, or you could try one of the dual mechanism opioids, like tapentadol or tramadol.

Consider Switching Opioids

Switch to another opioid to:		
<ul style="list-style-type: none">• Restore analgesic efficacy• Limit adverse effects• Decrease overall MME		
Based on large intra-individual variation in response to different opioids	Different variants of mu-opioid receptors	Limited evidence as most trials were retrospective and studied small numbers of patients

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



So, in a patient like this, there are three possible benefits to switching opioids.

- One, you want to restore analgesic efficacy in someone who's lost efficacy.
- You want to try to limit any adverse effects.
- And then, finally, you want to decrease the overall morphine milligram equivalents

And I'll explain how that all happens. But remember, switching from one opioid to another, it's because of the large individual variation response to different opioids, because of the different variants of the mu opioid receptors, and the switching opioids, there's limited evidence, as most of the trials looking at it are retrospective with small numbers of patients.

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

Opioid	Conversion Factor*
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	5
Methadone	4.7
Morphine	1
Oxycodone	1.5
Oxymorphone	3
Tapentadol+	0.4
Tramadolx	0.2

www.cdc.gov

Treillet E, et al. *J Pain Res.* 2018
 Webster LR, Fine PG. *Pain Med.* 2012
 Pereira J, et al. *J Pain Symptom Manage.* 2001



But if you decide to do it, you're going to go to an opioid conversion table, or an equal analgesic table, and you need to remember their limitations. They're derived from relative potency ratios, using single-dose analgesic studies in opioid-naïve patients. They're based on limited doses, and ranges of doses, and therefore, they don't really reflect the clinical realities of the chronic opioid administration in the patient that we're sitting across from. They're often not reliable, due to individual pharmacogenetic differences, and most tables do not adjust for incomplete cross-tolerance.

So, what do I mean by that? If your patient is on a dose of oxycodone, like our patient, and they no longer have sedation or respiratory depression, because they're tolerant to it, if you give them the exact equal analgesic dose of another opioid, they could have sedation or respiratory depression because of the incomplete cross-tolerance to that adverse effect.

Case Study
Michelle Jones
54 yo female



Scenario 1a
Opioid Rotation

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

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

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

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



Now, I'm going to give you an example of how you would rotate or switch opioids in our patient, Michelle Jones. Remember, she's on long-acting oxycodone, 15 mg twice a day, or the equivalent of 45 morphine milligram equivalents. And I like to go to globalrph.com, which is really a fancy calculator that allows me to put in the opioid that the patient is on, so in this case it's oxycodone, and the total daily dose, 30 mg, and if she was on another opioid for breakthrough pain, I could add that, as well.

And then, notice here, it does ask you to reduce the new dose of medication for incomplete cross-tolerance. And I'm going to put in 33 percent, but the recommendations are usually 25 to 50 percent reduction. So, I'm putting 33 percent somewhere in the middle. And then, you put the opioid that you're switching her to, and in this case it's morphine. And then you say, "Calculate."

And the equivalent dose with that reduction for incomplete cross-tolerance is 30 mg of morphine. So, now I've converted her to long-acting morphine, 15 mg bid, which is 30 MME. So, you can see that we've decreased the overall MME.

Case Study
Michelle Jones
54 yo female



**Over the next
18 months after
the rotation to
morphine**

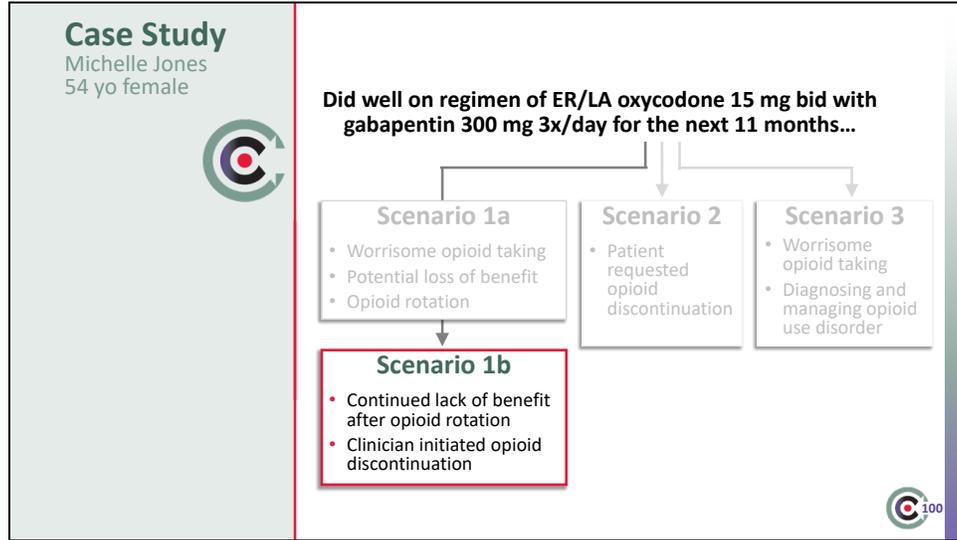
Scenario 1a

- Medication management
 - Continued ER/LA morphine 15mg 2x/d (30 MME)
 - Titrated gabapentin to 400mg 3x/day
 - Continued acetaminophen
 - Added nortriptyline 25 mg at night
- Continued acupuncture therapy and joined a monthly chronic pain support group
- PEG scores remained between 5-6/10
- Remained employed
- Remained adherent with the treatment plan and monitoring
- Continued with regularly scheduled follow-up visits



John Emery: Over the next 18 months, Michelle Jones' condition improved on a stable morphine dose of 15 mg twice a day, and she had no recurrent worrisome medication-taking behavior. Along with the morphine, her acetaminophen was continued, and her gabapentin was titrated up, and low-dose nortriptyline was added at night for her neuropathic pain.

Michelle continued acupuncture therapy and joined a monthly chronic pain support group. Her individual PEG scores remained between 5 and 6 on a 10-point scale. She remained employed and remained adherent with treatment and monitoring. She continued with her regularly scheduled follow-up visits.



In scenario 1B after being rotated to morphine and maintained on gabapentin, acetaminophen, and nortriptyline, Michelle's pain remained out of control.

Case Study
Michelle Jones
54 yo female



**After rotation
from oxycodone
to morphine...**

Scenario 1b

- Her pain remained out-of-control (PEG scores 9-10/10)
- After one morphine dose increase, **she requested to be converted back to oxycodone**
- She continued to do poorly: on medical leave from work and spending most of the day in bed (according to her husband)
- 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 cannabis to treat her pain



In scenario 1B after being rotated to morphine and maintained on gabapentin, acetaminophen, and nortriptyline, Michelle's pain remained out of control. with PEG scores between 9 and 10 out of 10, despite one trial dose increase of the morphine, she demanded that she be changed back to oxycodone, and at a higher dose. After being converted back to oxycodone, her pain did not improve.

She is now on medical leave from her job, and according to her husband, spends most of the day in bed. She has been adherent with urine drug testing and pill counts. Clinic staff reported on multiple occasions that she was rude, and confrontational when she tried to be seen without an appointment. She states that she is now smoking marijuana to help with her pain.

Dr. Alford, what do we know about marijuana and pain, and what should be the next steps?

Cannabis and Pain

Cannabis

- Contains >60 pharmacologically active cannabinoids including psychoactive THC and cannabidiol (CBD)
- Schedule I controlled substance (no currently accepted medical use)
 - Products with less than 0.3% THC are not considered a controlled substance



- Meta-analyses found moderate-quality evidence that cannabis and cannabinoids can be effective for treatment of chronic pain, particularly neuropathic pain
- Observational studies of impact of cannabis on opioid use are mixed, some show improvement in pain and decrease in prescribed opioids with medical cannabis use while others do not
- Double-blind, placebo-controlled trials are needed

Whiting PF et al. JAMA 2015
Nugent SM et al. Ann Intern Med 2017



Daniel Alford, MD: Well, cannabis and pain is being looked at more and more these days, because many states have now legalized it. Remember that cannabis contains more than 60 pharmacologically active cannabinoids, including psychoactive THC, and cannabidiol, or CBD. There's moderate-quality evidence that cannabis and cannabinoids can be effective for treatment of chronic pain, particularly neuropathic pain.

The strongest evidence is for oral products with high THC to CBD ratios that demonstrate a small to moderate short-term – less than six months – improvement in pain severity and overall functioning, but with increased risk of dizziness and sedation.

What we do know is that high-quality research is really needed to understand the pharmacology of cannabis and cannabinoids, the type of pain and patient characteristics where there is benefit or harm from a particular cannabinoid compound. So, we really have a lot more to learn, but it does seem like there could be some short-term benefit for some patients, but not all.

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

Now, back to our patient about continued lack of benefit. Remember that not all chronic pain is opioid-responsive, that more opioid is not always better, and more opioid may increase the risk of adverse effects, and that some chronic pain actually improves after an opioid taper.

Discussing Continued Lack of Benefit

- Stress how much you believe/empathize with patient's pain severity and impact
- Express frustration re: lack of good pill to fix it
- Focus on patient's strengths
- Encourage therapies for "coping with" pain
- Show commitment to continue caring about patient and pain, even without opioids
- Schedule close follow-ups during and after taper



How do we have this difficult conversation with our patients about continued lack of benefit?

First, you want to stress how much you believe the pain severity, and also, be empathic for their suffering. You want to express the frustration that the medication didn't work to help their problem. You want to focus on the patient's strengths and ability to cope with their pain. You want to show a commitment to continued caring for the patient, and pain, even without opioids. And finally, you want to schedule close follow-ups during and after a taper.

Discontinuing Opioids

You are **NOT**
abandoning
the patient,
you are
ABANDONING
THE OPIOID

- 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 setting of benefits
- Need to determine how urgent the discontinuation should be based on the severity of the risks and harms
- Document rationale for discontinuing opioids
- Determine if the opioid needs to be tapered due to physical dependence



Now, in terms of discontinuing opioids, you do not have to prove with 100 percent certainty that the person has addiction, or that they're diverting, because that can be really hard to do. You only need to assess and reassess the risk-benefit ratio. If the patient is unable to take opioids safely, or if they're nonadherent with monitoring, then discontinuing opioids is completely appropriate, even in the setting of benefits. You need to determine how urgent the discontinuation should be, based on the severity of the risks and harms. How worried are you?

You need to document the rationale for discontinuing opioids, and then, even determine whether or not the opioids need to be tapered due to physical dependence. Maybe the patient is taking it so intermittently, that they're not physically dependent, and therefore, you won't need to taper. A very important take-home message here is that you are not abandoning the patient when you're tapering opioids. You're abandoning the opioid, either because it wasn't helping, or it's causing them harm.

Opioid Discontinuation Risks

- Observational studies identified harms (suicide and overdose) associated with opioid tapering and discontinuation^{1,2,3,4}
- A comparative effectiveness study of ~200,000 individuals on stable* long-term opioid therapy, found opioid tapering was associated with a small absolute increase in opioid overdose or suicide compared with maintaining stable opioid dosages⁵

*no evidence of opioid use disorder or opioid misuse

1. James JR, et al. *J Gen Intern Med.* 2019
2. Mark TL, Parish W. *J Subst Abuse Treat.* 2019
3. Oliva EM, Bowe T, Manhapra A, et al. *BMJ.* 2020
4. Hallvik SE, et al. *Pain.* 2022
5. Larochelle MR et al. *JAMA open.* 2022

Tapering/discontinuation **should not** be considered a harm reduction strategy for patients receiving **stable** long-term opioid therapy **without evidence of misuse**⁵

Patients being tapered because of lack of benefit or misuse should be monitored closely for suicide and overdose risk



Keep in mind there have been some recent studies looking at the risks of discontinuing opioids. There have been some observational studies that have identified harms, namely suicide and overdose, that are associated with opioid tapering, and discontinuation.

But recently, there was a comparative effectiveness study of around 200,000 individuals who had been on stable long-term opioid therapy and found that opioid tapering was associated with a small, absolute increase in opioid overdose or suicide, compared to those that were maintained on stable opioid dosages.

So, keep in mind, based on these studies that patients being tapered because of lack of benefit or misuse, should be monitored closely for suicide and overdose risk, and that tapering opioids, or discontinuing opioids should not be considered a harm reduction strategy for patients who are on stable doses without any evidence of misuse.

Risk Benefit Framework

Benefits	Risks/Harm
Pain	Misuse
Function	Addiction, Overdose
Quality of Life	Adverse Effects



Useful to avoid “But I really, really need opioids.”
“Don’t you trust me?”

pitfalls: “I thought we had a good relationship/I thought you cared about me.”
“If you don’t give them to me, I will drink/use drugs/hurt myself.”
“Can you just give me enough to find a new doc?”

Response: **“I cannot continue to prescribe a medication that is not helping you (or is hurting you, or both).”**



It's helpful to keep the risk-benefit framework in mind when a patient, who you're planning on stopping the opioids, or tapering the opioids says to you, "But I really, really need the opioids," or, "Don't you trust me?" or, "I thought we had a good relationship; I thought you cared about me. If you don't give them to me, I'll drink, or use drugs, or hurt myself, and can't you just give me enough until I find a new doc?"

And what you need to say is, "I cannot continue to prescribe a medication that is not helping you, or is hurting you, or both."

Case Study
Michelle Jones
54 yo female



Scenario 1b

- Despite the PCPs 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 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...



John Emery: Despite Dr. Alford’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 nonopioid pain treatments, including cognitive behavioral therapy, Michelle keeps on insisting that she needs higher-dose oxycodone.

+++++

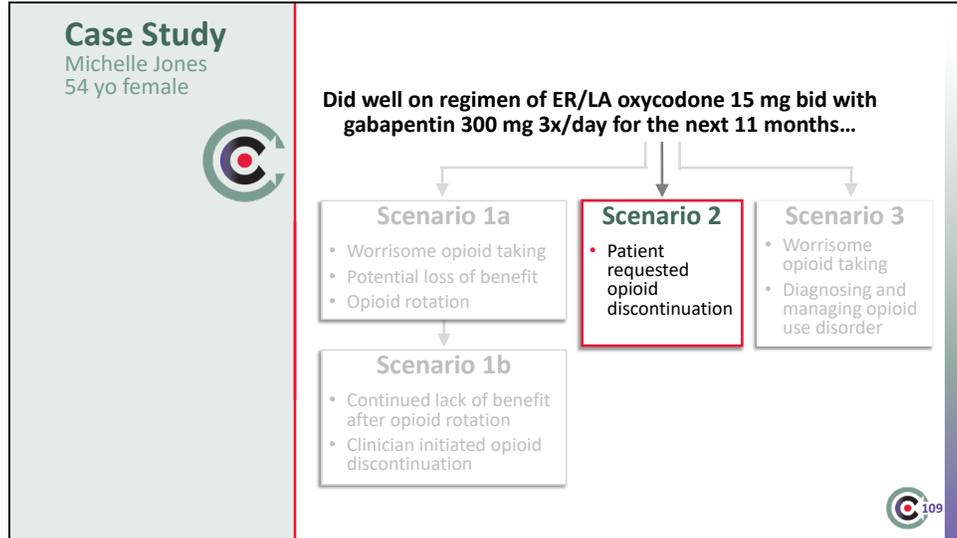
Daniel Alford, MD: So, Ms. Jones, it seems like we’re not going to agree on a treatment plan moving forward. To make sure I know that you understand why I’m suggesting to make these changes, please tell me in your own words why I think tapering the oxycodone is really the best approach.

Michelle Jones: Well, it’s because you don’t think it’s helping me, but I disagree. All I need is a higher dose of oxycodone. It seems you just don’t understand me, so I’m going to need to find a new doctor.

Daniel Alford, MD: Well, ultimately, that is your choice, but I just want you to know that if you change your mind, I’m happy to continue caring for you, and trying to control your pain, but I just won’t be using opioids.

+++++

John Emery: Ms. Jones storms out of the office, and states that she will be calling Patient Advocacy.



In the next scenario, we return to Michelle, who seemed to be doing well on her pain treatment, including oxycodone for her painful diabetic neuropathy, and chronic hip pain for the next 11 months. But then, she started to struggle and become frustrated with the rules and stigma of taking opioids.

<p>Case Study Michelle Jones 54 yo female</p>  <p>How will you help her taper off oxycodone?</p> 	<p>Scenario 2</p> <ul style="list-style-type: none">• Presents for an urgent visit after she was unable to get her oxycodone refilled due to her insurance’s new prior authorization requirement<ul style="list-style-type: none">– “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:<ul style="list-style-type: none">– “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!” 
---	--

+++++

Daniel Alford, MD: Hi, this is Dr. Alford calling for Michelle Jones.

Michelle Jones: This is she. Oh hi, Dr. Alford. Thanks so much for returning my call. The pharmacy won’t refill my prescription. They said that they can’t put it through my insurance. New rules, I guess. The company just refuses to pay even though I’ve been on this medication for a while. I’m just so sick of this. Everyone treats me like I’m a criminal, or a suspect, just because I need these meds. Even my husband is giving me the side eye now.

I hate being put through the ringer by people here. Come on, drug tests? Dr. Robertson never made me do that. These things are ruining my life. I just tried to stop taking them myself, but oh, my Lord, I got so sick. I just want to get off them.

Daniel Alford, MD: Okay, Michelle. I hear you. I completely understand the frustration. The insurance company rules sure don’t make it any easier, and I’m not surprised you felt sick when you stopped taking the medication, because your body is absolutely used to taking them. So, let’s talk about how we can taper you off these medications safely to minimize any discomfort, and try you on some other treatments for pain.

+++++

John Emery: Dr. Alford, how do you taper someone off opioids?

Tapering Opioids

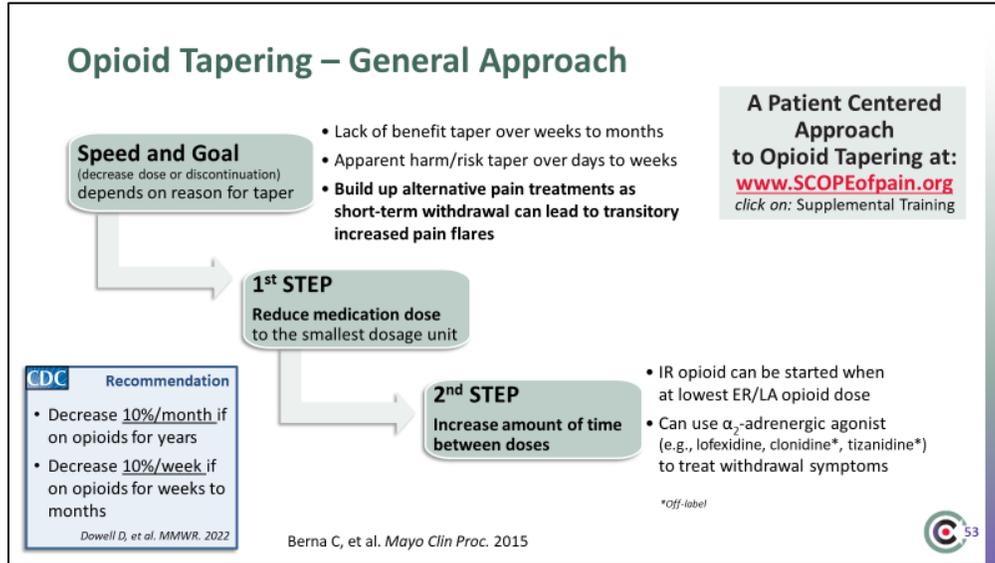
- No validated protocols in patients on opioids for chronic pain
- **Very low-quality evidence**¹ suggests several types of opioid tapers may be effective and that pain, function, and quality of life may improve for some patients with decrease opioid dose
- Study² found 62% of patients in a pain clinic completed a voluntary, patient-centered opioid taper over 4 months with >50% dose reduction
 - Success was not predicted by starting dose, baseline pain intensity, years prescribed opioids or any psychosocial variable
 - Neither pain intensity nor pain interference increased with opioid reduction
- Study³ of over 100,000 patients on long-term opioids
 - Annual tapering increased and more likely in women and those on higher opioid doses
 - 19% had maximum dose reduction rate exceeding 10% per week

¹Frank JW, et al. *Ann Intern Med.* 2017
²Darnall BD, et al. *JAMA Intern Med.* 2018
³Fenton JJ et al. *JAMA Network Open.* 2019



Daniel Alford, MD: It's a common question that I get asked, and there are no validated protocols in patients who are on opioids for chronic pain, and there was a systematic review that found very low-quality evidence that suggested several types of opioid tapers may be effective, and that pain function, and quality of life may actually improve for some patients who decrease their opioid dose. Remember that tapering is not always to get to zero, but maybe it's just to get to a lower dose.

There was one study recently that found that almost two-thirds of patients at a pain clinic who wanted a voluntary taper, who completed this patient-centered taper over four months, were able to reduce their opioid dose by 50 percent. The success was not predicted by the starting dose, the baseline pain intensity, the years they were prescribed opioids, or any other psychosocial variable, and neither their pain intensity, nor their pain interference actually increased with the opioid reduction.



So, the general approach to tapering includes first you need to decide how quickly you want to do it, and if it's lack of benefit, then you can taper over weeks to months. But if you're worried about risk or harm, it's going to be over days to weeks. You're going to do it much more quickly.

The first step is to reduce the medication dose to the smallest dosage unit, and if somebody is on long-acting opioids, and you've gotten to the lowest dosage unit, you might need to convert to short-acting opioids to get to even lower doses. Remember that if someone has withdrawal during a dose decrease, you could use an alpha-adrenergic agonist like lofexidine, or off-label use of clonidine or tizanidine to treat the withdrawal symptoms.

But once you've gotten to the lower dose, you want to start increasing the amount of time between doses or remember to build up alternative pain treatment modalities as short-term withdrawal will absolutely lead to transitory increase in pain. If you want to learn more, go to scopeofpain.org, and click on "Supplemental Training," and there's a free training on tapering.

Case Study
Michelle Jones
54 yo female

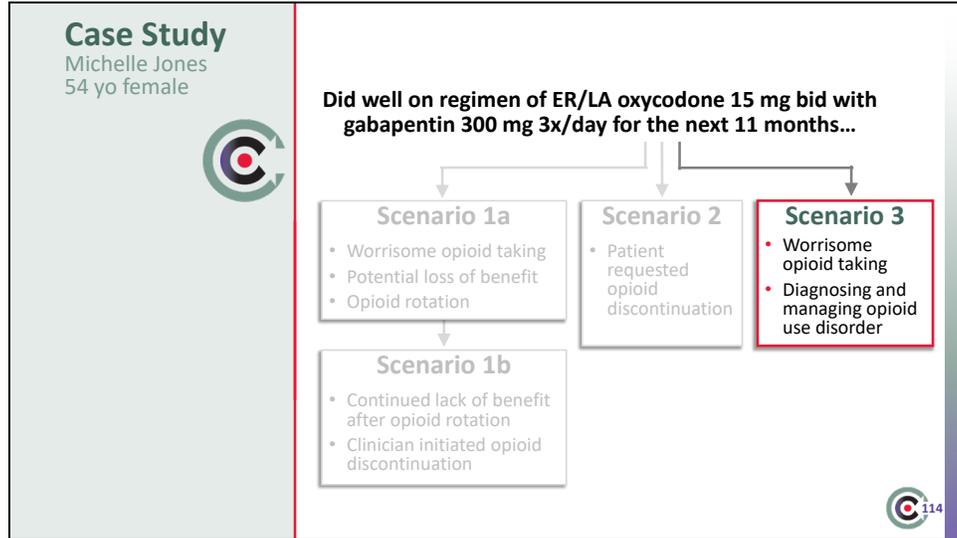


Scenario 2

- Over 6 months she successfully tapered off oxycodone
- Over following 6 months, her neuropathic pain was moderately well controlled on combination of nortriptyline 25 mg at night, gabapentin 600 mg tid and capsaicin cream 3-4 times per day
- 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



John Emery: Over six months, Michelle successfully tapered off the oxycodone. Her neuropathic pain was moderately controlled on a combination of acetaminophen, nortriptyline, gabapentin, and capsaicin cream. Michelle joined a monthly chronic pain support group. Her individual PEG scores remain between 5 and 6 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 the next 11 months. Her urine drug tests consistently returned expected results, except once, when the UDT was opiate positive, but negative for oxycodone, raising concerns for opioid misuse, including possible diversion.

Case Study
Michelle Jones
54 yo female



Scenario 3

- UDTs were consistently positive for oxycodone as expected **except** once her UDT was opiate positive but **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



+++++

Daniel Alford, MD: Michelle, your recent drug test didn't have any oxycodone in it. Can you tell me about it?

Michelle Jones: I have no idea why the test results came back that way. I've been taking the meds exactly like you told me to, and I never gave any of the oxy to anyone else.

Daniel Alford, MD: Well, unfortunately, I wasn't able to do a confirmatory test to check the result, but I do want to tell you that I'm worried, but this is not the first concern I have. Remember that the last couple of appointments, you were supposed to bring in your pill bottle, so I could do a pill count, and you told me you forgot them, and as we discussed early on, this puts you at greater risk for harm from these potentially dangerous medications.

So, what I need to do moving forward is to monitor you more closely. That includes doing more frequent urine drug testing.

+++++

John Emery: There were no additional unexpected test results over the next two months. Dr. Alford, how do you talk to patients who you're worried may be diverting some of their opioid pain medications?

Discussing Possible Diversion

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

Zacny J, et al. *Drug Alcohol Depend.* 2003
*Setnik B, et al. *J Opioid Manag.* 2015



Daniel Alford, MD: Well, remember that prescription drug diversion is one form of opioid misuse, and it's defined as giving, selling, or trading prescription medications. And a survey looking at this issue found that family and friends are the most common source of diverted opioids. You want to discuss why you're concerned about diversion, for instance, is the urine drug test negative for the prescribed opioid, or nonadherence with pill counts, and then you want to discuss your inability to continue to prescribe opioids if the opioids are being diverted to others.

<p>Case Study Michelle Jones 54 yo female</p>  <p>2 months later... brought to ED by ambulance after suffering an opioid overdose</p> <p>How will you manage this patient?</p> 	<p>Scenario 3</p> <ul style="list-style-type: none">• Husband found her unresponsive, administered intranasal naloxone with brisk response and called 911• In the ED, husband reported that his wife's has been taking more oxycodone, and taking some of her father's morphine• Husband said he has been in denial of how bad his wife's problem had gotten. He reports 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 the teapot she was using• He heard a staff person in the ED refer to his wife as an "addict" and "drug abuser" 
--	---

John Emery: Two months later, Michelle is brought to the emergency department 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 has been sleeping a lot and calling in sick to work.

He acknowledges that he's been denying Michelle's problem to himself, as he's immersed himself in work. He reports Michelle has not been able to shop, or cook, or clean, and that he was rationalizing, assuming it was 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 is upset by these characterizations. Dr. Alford, what are the next steps for Michelle?

Language and Stigma

Stigmatizing Language	Non-Stigmatizing Language
Addict, substance abuser, alcoholic	Person with a substance use disorder (SUD)
Substance abuse	Substance use
Clean, clean urine	Person with SUD in remission
Dirty, dirty urine	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.”

Zwack J, Appleseith H, Arndt S. Subst Abuse Treat Prev Policy. 2020



Daniel Alford, MD: Well, first I want to address the language that was used in the emergency department, and I think it was very stigmatizing, and I would encourage people to use less stigmatizing language. For instance, instead of saying someone is an addict, or a substance abuser, or an alcoholic, I would suggest saying it's a person with a substance use disorder.

As opposed to saying substance abuse, I would say substance use. Instead of saying clean, or clean urine, I would say a person who has substance use disorder in remission. As opposed to saying a dirty urine, I would say the person has active substance use. So, I think this quote summarizes my message here, which is, “Stigma surrounding substance use disorder is actually perpetuated by the stigmatizing terminology used in healthcare settings, by the news, and other media, and by society as a whole.

So, I think we can do a better job of using more medical terminology when we describe patients who have this problem.

Treatment Gaps Following Opioid Overdose

Opioids were dispensed to 91% of patients after a nonfatal overdose¹
n=2848

- **7%** had repeat opioid overdose
- At 2 years, cumulative incidence of repeated overdose was **17%** for patients on **high opioid dosages** after the index overdose

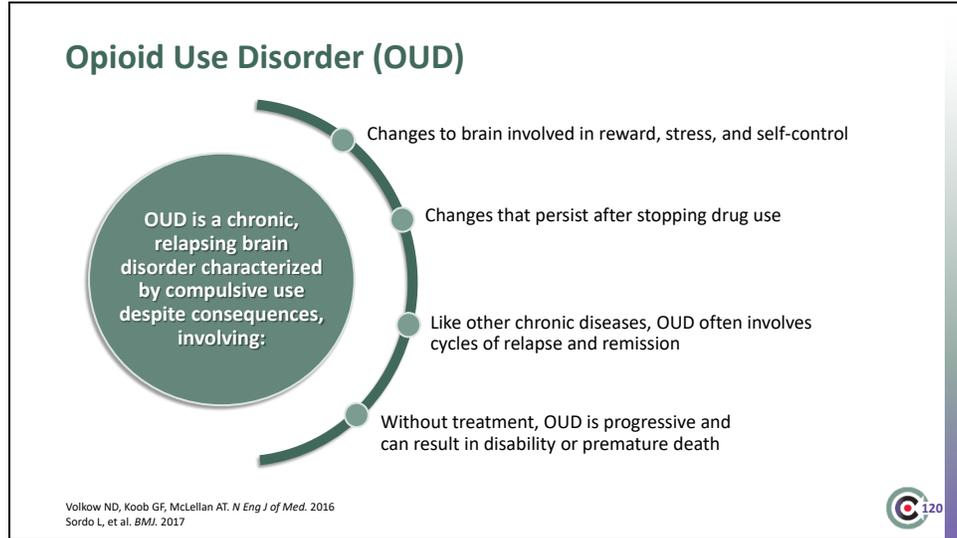
Less than a third of opioid overdose survivors receive medications for OUD (MOUD) in the subsequent 12 months²
n= 17,568

- Receipt of MOUD was associated with decreased all-cause and opioid-related mortality

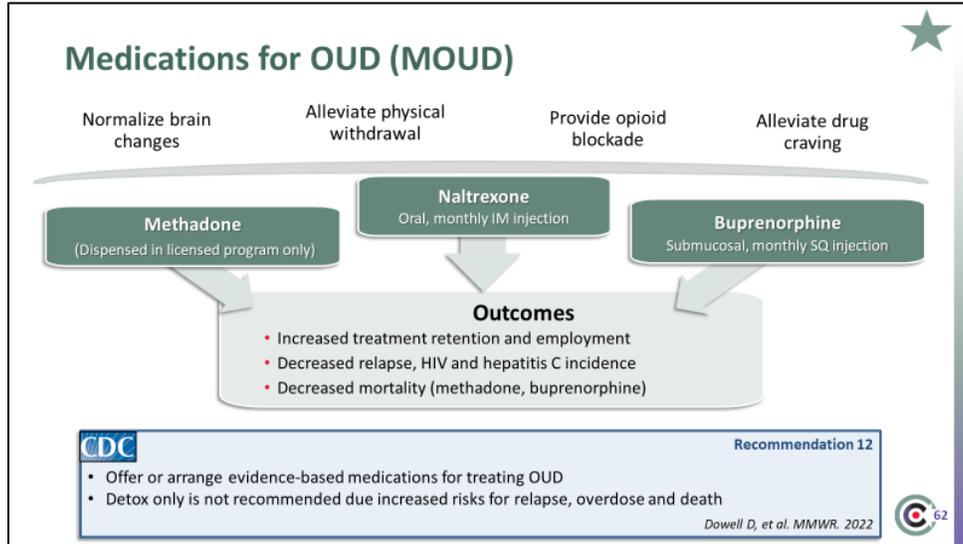
1. Laroche MR, et al. *Ann Intern Med.* 2016
2. Laroche MR, et al. *Ann Intern Med.* 2018

There have been identified treatment gaps following opioid overdoses. In this study, opioids were continued to be dispensed in over 90 percent of patients after a nonfatal overdose, and of those, 7 percent had a repeat overdose, and at two years, the cumulative incidence of repeat overdose was 17 percent in patients who were on high opioid doses after that index overdose, so it's a really high-risk patient.

Moreover, after an opioid overdose, less than a third of those survivors received a medication for their opioid use disorder in the subsequent 12 months, and those that did get a medication, it was associated with a decrease in all-cause opioid-related mortality. So, it's very important that these individuals get put into treatment, that is started on a medication that can be lifesaving.



Remember that opioid use disorder is a chronic, relapsing brain disorder, characterized by compulsive use, despite negative consequences, involving changes to the brain involved in the reward, stress and self-control pathways, changes that persist after stopping drug use, and like other chronic diseases, opioid use disorder often involves cycles of relapse and remission, and without treatment, it is progressive, and can result in disability, or premature death.



We are fortunate that there are a number of evidence-based medications for treating this disorder, and these medications do the following: They sometimes alleviate the physical withdrawal; they alleviate drug craving; they provide opioid blockade, that is if someone uses an opioid on top of these treatments. They do not get reward. It also normalizes the brain changes that have occurred.

And the choices include methadone. Remember methadone for the treatment of OUD can only be dispensed from a licensed treatment program. It is illegal for you to prescribe methadone from your primary care practice for the treatment of OUD, even though you can prescribe it for pain, you cannot prescribe it for treating OUD.

What about buprenorphine? Only waived clinicians can prescribe buprenorphine for the treatment of OUD. Buprenorphine comes in submucosal formulations, as well as a monthly subcutaneous injection.

And then, thirdly, there's naltrexone, which is an opioid antagonist, which comes in an oral formulation, as well as monthly intramuscular injections. The outcomes for these medications include increased treatment retention and employment, decreased opioid use, decreased HIV and hepatitis C incidence, and a decrease in opioid-related all-cause mortality for methadone and buprenorphine, in particular.

Case Study
Michelle Jones
54 yo female



Over the next 6 months...

How will you manage this patient perioperatively?



Scenario 3

- PCP who is waived to prescribe buprenorphine for the treatment of OUD continues buprenorphine started in the ED but doses it TID to treat both pain and OUD
- 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



John Emery: Dr. Alford continues the buprenorphine started in the ED, but doses it three times per day to treat both 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. How should Michell's pain, and OUD be managed before and after her surgery?

Acute Pain in Patients on MOUD: Systematic Review

There is a growing consensus on perioperative management of patients on MOUD

Best available evidence suggests:

- 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 patients daily MOUD
- Patients taking MOUD may need higher doses of opioid analgesics
- Ineffective pain management can result in disengagement in care

Veazie S et al. J Gen Intern Med. 2020
Kohan L, et al. Reg Anesth Pain Med. 2021



Daniel Alford, MD: There was a systematic review that looked at treating acute pain in patients on medications for OUD. And there is a growing consensus on the perioperative management of these patients.

The best available evidence suggests that patients with an OUD history are often more sensitive to painful stimuli, that we should continue the methadone or buprenorphine throughout the perioperative period, that we should treat their pain with analgesics on top of the patient's daily medication for their OUD. The patients taking MOUD may need higher doses of opioid analgesics, and that ineffective pain management in these patients can result in disengagement and care.

Case Study
Michelle Jones
54 yo female



**Over the next
12 months...**

Scenario 3

- She did well postoperatively with improved pain control of her right hip
- Her painful diabetic neuropathy well controlled on combination of buprenorphine 4 mg sublingual 3x/day, duloxetine 30 mg 2x/day and nortriptyline 25 mg at night (Note: gabapentin discontinued due to misuse risk¹ and overdose risk when combined with opioids²)
- PEG scores remained between 5-6/10
- OUD in sustained remission with MOUD and outpatient addiction counseling
- Remained employed
- Continued with regularly scheduled follow up visits

1. Hill J, Alford DP. *Semin Neuro.* 2018
2. Goodman CW, Brett AS. *N Engl J Med.* 2017



John Emery: 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, duloxetine, and nortriptyline. Her gabapentin was discontinued, due to the misuse risk. Her PEG scores remain between 5 and 6 on a 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.

Dr. Alford, can you please summarize what we've learned?



SCOPE of Pain
Safer/Competent Opioid Prescribing Education

SUMMARY Part 2

- Employ universal precautions but individualize care based on risk
- Continue or modify opioid treatment based on clinical indication and response
- Optimize office systems to involve the entire healthcare team including community pharmacists
- Document benefits, risks and harms and rationale for the plan of care
- Worrisome opioid-taking behavior can signify pain-relief or substance-seeking behaviors or a combination of both
- Fully assess and then respond to worrisome behaviors
- Decisions to continue or discontinue opioids should be based on reassessment of the risks and benefits of the treatment and should be well-documented
- Continue MOUD during the perioperative period



Daniel Alford, MD: Sure. So, we want to employ universal precautions, but we want to individualize care, based on a patient's risk. We want to continue or modify opioid treatment, based on the clinical indication and response to that treatment. We want to optimize office systems to involve the entire healthcare team, including our community pharmacist.

We should document benefits, risks, and harms, and the rationale for our plan of care. Worrisome opioid taking behavior can signify pain relief, or substance-seeking behaviors, or a combination of both. We need to fully assess them, and then respond to these behaviors in order to keep our patients safe. Decisions to continue or discontinue opioids should be based on a reassessment of the risks and benefits of the treatment and should be well-documented.

Remember that use of medications for OUD decreases all-cause mortality, and that we should continue these medications during the perioperative period.



SCOPE of Pain
Safer/Competent Opioid Prescribing Education

Post-test and Evaluation

- Complete the post-test with a cumulative score of $\geq 70\%$
- Complete the evaluation
- Download your certificate, worth:
 - 2 *AMA PRA Category 1 Credits*[™]
 - 2 nursing contact hours, or
 - 2 ACPE credits



John Emery: Thank you for participating in this SCOPE of Pain online activity. Please complete the posttest, and an evaluation, and you'll be able to download your certificate. Also, be sure to visit our resources page, 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.