SCOPE of Pain
Safer/Competent Opioid Prescribing Education

Transcript

Part 1

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

This web-based program consists of two parts that follow the case of Michelle Jones to discuss management of acute and chronic pain. Occasionally, within the program, you'll be asked quick polling questions, which focus on the more challenging aspects of the case. After each one-hour part, you'll 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. You'll find a wealth of materials available at the *SCOPE of Pain* website, including a downloadable transcript, a PDF of the slides, and a comprehensive resource and reference document with a complete bibliography. As well, you'll find clinical resources available for your use, audio micro-cases for quick study, a number of supplemental educational activities, and a trainer's toolkit for your use, if you're training your colleagues.

We'll be discussing this case with Dr. Daniel Alford, Professor of Medicine at Boston University, and Director of the Clinical Addiction Research and Education Unit at Boston Medical Center, and Dr. Erica Bial, an interventional pain specialist in private practice, and visiting lecturer at Tufts University.

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.

Through the case presented in this program, learners will be able to assess pain and function; educate patients about opioid risks and limitations of benefit; assess for prescription opioid misuse risk; develop patient-centered treated 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.

SCOPE of Pain covers strategies for the safer use of opioids for managing acute and chronic pain by reviewing best practices and sharing clinical pearls. As well, the content counts towards the eight-hour DEA pain and addiction education requirement, as outlined in the Medication Access and Training Expansion or MATE Act and aligns with the 2022 CDC Clinical Practice Guideline for Prescribing Opioids for Pain. Throughout the presentation, you'll see blue boxes with the CDC recommendations that

address specific content on the slide. This training does not cover palliative care, or end of life pain management, due to the differences in overall treatment goals.

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

Dr. Alford: Sure. So, let's start with the definition of pain, and pain is defined as an unpleasant sensory and emotional experience. And we start with acute pain: Acute pain is a life sustaining symptom. It's adaptive, and it elicits motivation to minimize further harm, and allows for healing.

Chronic pain, however, is pain that persists beyond the expected healing. Some define it as more than three months, and there really is no benefit. And really, it can be a disease in and of itself. It's maladaptive, and it's influenced by genetic and epigenetic factors. And let's talk about how it's categorized, because that influences how we work it up, how we treat it, and what the prognosis is.

So, let's start with nociceptive pain, and that's tissue or potential tissue damage, including somatic, which includes bones, joints, and muscle, and visceral, including mucosal injury, obstruction/distention, and ischemia.

So, second, neuropathic pain, which is disease or injury affecting the somatosensory nervous system, including central, which includes traumatic, vascular, and neurodegenerative, and peripheral – infection, compression, traumatic, and ischemic injury.

Third, nociplastic. This is abnormal processing of the pain signals at multiple levels of the nervous system without clear evidence of tissue damage or discrete pathology. And this includes diffuse sensitization, like fibromyalgia, functional visceral pain, like irritable bowel syndrome or bladder pain syndrome, and regional somatic sensitization, like complex regional pain syndrome.

Sometimes, there is a mixture of all of these, or some of these, and that's called mixed pain, a combination of different types of pain, such as nociceptive, neuropathic, or nociplastic that occurs simultaneously in the same area of the body.

Pain is common. Twenty-one percent of US adults, about 50 million individuals, report pain on most days or every day. And we know that up to 60 percent of Emergency Department visits are for pain-related complaints, and it's actually one of the most common reasons people seek medical care in the first place. It's incredibly expensive. It costs billions of dollars per year in medical costs, lost wages, and lost productivity.

We also know that pain contributes to disparities, by disproportionately impacting women, the elderly, racial and ethnic minorities, those with lower socioeconomic backgrounds, military veterans, and those that live in rural communities.

There are lots of barriers to adequate pain care, including an over-burdened primary care provider system with competing priorities, inadequate training in managing patients with chronic pain, lack of decision support for chronic pain management, financial misalignment favoring the use of medications. It's a whole lot easier for me to prescribe a medication, than it is for me to refer somebody for multimodal care, lack of access to pain specialists, and comprehensive pain care, and finally, negative attitudes and disparities in pain care.

Let's talk a little bit more about disparities in pain care. Racial minorities and vulnerable populations experience additional suffering because of inadequate pain care from disparities in access and treatment. And these can be broken down into patient factors, clinician factors, and system factors.

Let's talk about patient factors. Well, certainly, language barriers, cultural differences in communication and beliefs, and health literacy can all lead to poor pain treatment outcomes. What about clinicians? Well, certainly misconceptions, negative attitudes, stereotyping, and implicit bias can result in racial and ethnic disparities in how pain is assessed and treated. And then, what about systems? Well, systems include lack of geographic and/or financial access to care, and poor socioeconomic status.

What about trends in opioid prescribing? Well, I'm sure you're all aware of the fact that we became very opio-centric, and prescribed many opioids starting in the 1990s, and it peaked at around 2011. We became overly opio-centric for both treating acute and chronic pain. But you can see at around 2011 and in 2012, we started to decrease opioid prescribing. And whether this is due to more judicious prescribing, or more fearful prescribing, it's unclear, but the bottom line is prescribing has decreased. There are also racial differences in opioid prescribing. Compared to White patients, Black and Hispanic patients are less likely to receive opioid analgesics for pain, and when they do, it's at a lower dose.

So, let's move on to trends in opioid overdose deaths. And there really were three waves. The first wave started in the late 1990s-early 2000s, and it was predominantly caused by the natural and semi-synthetic opioids, or prescription opioids. That, in about 2013, was starting to be overrun by heroin-associated overdose deaths, and then, the third wave started in about 2015-2016, which was including the illicitly manufactured fentanyl analogs, or the synthetic opioids, and they have predominantly been responsible for opioid overdose deaths since around 2015. There are racial differences in overdose deaths. Whites had an early period of acceleration between 1999 and 2016 with a decreased rate of change starting in 2016. American Indian/Alaska Natives, and non-Hispanic Black persons experienced the highest increase in drug overdose death rates, starting in 2019.

John Emery: Thank you. Now we'll move to Part One: Understanding Pain and Opioids. Meet Michelle Jones. At 36, she was in a motor vehicle crash, resulting in a right hip fracture. After successful surgery, her pain was managed with nerve blocks and intravenous hydromorphone. Dr. Bial, 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?

Dr. Bial: I'd be happy to. So, when we're assessing acute pain, we first and foremost want to describe it thoroughly, and a convenient acronym for how to remember all of the features that we may want to capture in describing and understanding a patient's pain is SOCRATES. So, S for Site. Where is the pain? O, its Onset. C, its Character. Is it sharp, dull, something else? R, does it Radiate? A, does it have Associations, other symptoms that come along with it? T, its Time course. E, Exacerbating and ameliorating factors. And S, its Severity.

Now, when we're thinking about assessing a pain's severity, particularly when we're assessing acute pain, we often use pain intensity scales. So, these are things that we're all familiar with, things like a visual analog scale, emoji-based visual analog scale, so from the happy face to the crying face, as well as what most of us probably use when assessing adults, a numerical rating scale. So, "On a scale from zero to 10 with zero being no pain at all, and 10 being the worst possible pain, how strong is your pain?" We

need to recognize that many factors influence self-reported pain, including gender, social supports, clinician characteristics, and I think most importantly, trust.

So, there are a number of risk factors for the developing of chronic postsurgical pain, and we're using postsurgical pain here as an example, but really talking about recognizing early on, perhaps at the stage of acute pain those risks that might yield conversion to a chronic pain syndrome. Ultimately, these relate to alterations in expression of neurotransmitters, receptors, and ion channels, and changes in the structure, connectivity, and survival of neurons. And there are a number of factors that might contribute in three broad categories. So, patient-related factors in the example of postsurgical pain, intraoperative variables, as well as the patient's experience of postoperative pain.

So, think first about patient-related factors, and some of these might be surprising, things like younger patients, female patients, and patients with a history of anxiety, depression, catastrophizing, the presence of a pre-existing pain syndrome, or preoperative opioid use, all increase the risk of that conversion from acute to chronic pain.

There are intraoperative variables that also make a difference. So, what was the surgical procedure and the particular technique that was employed? Whether there was nerve ligation, or nerve injury, whether there was ischemia to the operative site, as well as the modality of the anesthetic used.

And then, the postoperative pain experience, also, has an influence. So, patients who experience uncontrolled high-intensity pain or a longer duration of postoperative pain are at increased risk for developing chronic pain.

Another useful tool is the STarT MSK Screening Tool, and this allows us to get a sense of the risk of progression from acute to chronic musculoskeletal pain, but I think recognizing the criteria included can be useful in many other examples. So, this helps us to identify modifiable risk factors, which are typically biomedical, psychological, or social for the development of chronic musculoskeletal pain disability. And this score just helps us to stratify risk. So, low, medium, high. The important thing to recognize here is that there are two big categories. So, the characteristics of the pain itself, but then the larger, more important potential predictor, all relate to catastrophizing: the patient's beliefs about the pain, and how it may become chronic or further impair them.

So, let's look quickly at this. In terms of the pain characteristics we ask, "In the last two weeks, has your pain been troublesome, joint or muscle pain in more than one part of the body? Have you been only able to walk short distances because of your pain?" So, thinking about function. "Dress more slowly than usual, because of your pain?" Again, focused on function. Or, "Are you having other important health problems?" So, the presence of comorbidities.

But the remaining questions are really focused on catastrophizing. So, "In the last two weeks, do you feel it is unsafe to be physically active? Do you have worrying thoughts about your pain a lot of the time? Are you concerned that your pain condition will last a long time? Have you stopped enjoying all the things you usually enjoy?" So, thinking about anhedonia. And then, "How bothersome has your pain been? Not at all, slightly, moderately, very much, or extremely?"

John Emery: After her surgery, Michelle was discharged with home-based physical therapy and orthopedic follow-up. She received a prescription 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. Bial, is there a correct amount 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?

Dr. Bial: So, the right amount of opioid leads me to a conversation about opioid overprescribing for acute pain, which we know is a real issue. Overprescribing occurs frequently. Postoperatively, we know that over 70 percent of patients took half or less of their opioids. After an ED visit, for example for renal colic, or for fracture, 93 percent of patients had leftover pills, and 52 percent of pills were unused.

Now, there are risks associated with overprescribing. We know that the source of prescription opioids misused, 39 percent of the time is from a family member, or a friend, and 44 percent of the time is from a single prescriber. There is overprescribing risk, even in opioid-naïve patients. We know that 3 to 5 percent of opioid-naïve patients receiving an opioid will become long-term – so, greater than three months – opioid users. And the risk factors for this are a little different. This would include patients who are male, over the age of 50, with underlying mental illness, or a history of substance use disorder. Since 2012, there has been a decrease in new opioid prescriptions for more than a seven-day supply.

Going back to your question, "How do we treat acute pain?" It may come as a surprise to many that oftentimes opioids are not required. So, there was a somewhat recent study looking at acute dental pain, so of molar extractions. And what they found is patients who were prescribed a nonsteroidal anti-inflammatory medication along with acetaminophen actually had more effective pain relief when compared to oxycodone alone, or oxycodone in combination with acetaminophen.

A somewhat different example, but in the presence of acute musculoskeletal pain, there was also found to be no significant difference in pain reduction with opioids alone, versus NSAID plus acetaminophen, or multiple opioid-plus-acetaminophen combinations. So, no distinct advantage of using those opioid preparations.

In acute pain guidelines, we now recommend a multimodal and individualized approach. Some minor surgeries are entirely appropriate to discharge a patient from the hospital, or in the postoperative period, with nonsteroidal anti-inflammatory medications with or without acetaminophen for its synergy, or very limited opioids before we transition to a non-opioid regimen, and this is consistent with the CDC's recommendations number 1 and 6, which are that in the setting of acute pain, we want to maximize non-pharmacologic and non-opioid approaches. We should really only consider opioids if the benefits outweigh the risks. We should discuss realistic benefits and the known risks with patients, and we should ideally prescribe no greater quantity than that which is needed for the expected duration of the severe pain.

Recently, ketamine has become more commonly used for acute pain. This was developed in the 1960s as a dissociative anesthetic, and in subanesthetic doses, it is actively being studied, and more recently employed for the treatment of perioperative pain, neuropathic and nociplastic pain disorders, as well as depression and substance use disorders. What's interesting about it is that it is analgesic, as well as dissociative without respiratory depression. As an analgesic in the Emergency Department and in perioperative settings, it's often used parenterally. Low-dose ketamine does safely reduce pain more rapidly, but in a less sustained way, than morphine, and it's known to be opioid-sparing. So, in those situations where one needs to use an opioid, it can decrease opioid requirements.

Unfortunately, its use is limited by low-oral bioavailability. There's very limited evidence for its use in outpatient treatment of chronic pain, although for sure people are studying this, and using it off-label. Some situations of outpatient use, such as intranasal, is complex, because it's difficult to formulate, and administration and monitoring requirements are also challenging. There are some pretty remarkable dose-dependent adverse effects. These can include things like hallucinations, agitation, anxiety, dysphoria, as well as euphoria, and it definitely has a misuse potential, due to psychoactive effects, and can also be bladder toxic.

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 18 years later, when she presents for an initial appointment with a new primary care physician, Dr. Alford.

[Music Plays]

Dr. Alford: Good morning, Ms. Jones. I'm Dr. Alford. It's nice to meet you. Ah, let's see, what brings you here today?

Michelle Jones: Hi, Dr. Alford. Great to meet you, as well. Boy, I had a hard time getting an appointment with you. You must be really busy. I made an appointment, because my doctor – my old doctor, Dr. Robertson – retired. Basically, I'm here because of my blood pressure and diabetes, and the pain in my feet and hip. Here, I brought my old medical records for you.

Dr. Alford: Great, great. Thanks. That's helpful. So, 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? Oh, it started after your accident, and you had surgery. Okay. It looks like your diabetes, blood pressure, and cholesterol seem to be under good control with the medications you're on, and your kidney function seems stable. I see you're on a couple of different pain medications, too.

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

Dr. Alford: Okay. Well, we'll definitely get to talking about your pain, and your pain medications, but before we do, can you tell me a little bit about yourself? I mean, how about your home? Are you working?

Michelle Jones: Well, I'm married. We don't have any kids. I'm a paralegal downtown. These days I'm working just part-time, exit strategy, thinking about retirement.

Dr. Alford: Okay. Thanks. I also have some health behavior questions that I ask all my patients. So, do you smoke?

Michelle Jones: Nope, never have. And I know what you're going to ask. I drink socially. I don't use drugs. Honestly, my biggest vice is food. I know I need to lose some weight.

Dr. Alford: Yeah. Okay. Well, any medical problems run in your family?

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

Dr. Alford: Yeah. That must have been difficult.

Michelle Jones: It was tough. Yeah.

Dr. Alford: Okay. So, tell me what's going on with your pain.

Michelle Jones: So, even now – it's been 18 years since that car crash – my hip still hurts, especially when I try to move a lot. It's really bad when I stand up after sitting. Dr. Robertson told me that I now have bad arthritis in that hip, and I may need a replacement. I'm not looking forward to that one.

And my feet are terrible. I always have burning and tingling, and they get numb sometimes. There are days when I can't put my shoes on, because of the pain. It's really almost impossible to get to work sometimes.

Dr. Alford: Wow. Yeah. No, it sounds pretty severe. Can you tell me about your pain medications? How are they working?

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

Dr. Alford: Yeah. It sounds like you're very uncomfortable, and so, can you tell me on a scale of zero to 10, where zero is no pain at all, and 10 is the worst pain imaginable, where would you rate your pain overall, right now?

Michelle Jones: Wow. Jeez, it is a 20!

[Music Plays]

John Emery: Dr. Alford, now you've met Michelle Jones. What might it mean when a patient reports their pain beyond the scale, like in this case?

Dr. Alford: Yeah. In my experience, this is not uncommon, and I believe it has to do with mistrust. Patients may assume that you do not believe the severity of their pain complaints, and this is demonstrated by either exaggerating the pain score or exaggerating functional limitations.

So, how do we build trust? Well, after you've done a complete and thorough pain history, a focused physical exam, and appropriate diagnostic testing, I think we should show empathy for the patient's experience by saying things like, "It must be difficult to enjoy life with such severe pain." I think 100 percent of the time, we should validate that we believe their pain and suffering is real, saying things like, "I believe you and I want to help." There is zero percent risk in validating and believing someone's pain complaint. Why? Because just because you believe the severity of a patient's pain complaint, it does not mean that opioids are indicated. And that's really where our clinical acumen comes in, where we use a risk-benefit framework – that we're going to be talking a lot about – to make that determination. What is the safest and potentially the most effective treatment for this patient's pain?

So, how do we assess chronic pain? Well, we heard about assessing acute pain using unidimensional scales, like the numeric rating scale, but really, they are of limited value for assessing chronic pain. We're much more interested in a multidimensional instrument, and they're certainly out there, like the McGill Pain Questionnaire, the Graded Chronic Pain Scale, as well as the Brief Pain Inventory, but in my practice, they're impractical for routine use. They're too long. If you can use them, that's great, but in my practice, I'm unable to use them.

However, there is a great tool that is a brief, multidimensional tool, called the PEG Scale, which stands for Pain, Enjoyment, General Activity Scale. And the questions are, "What number best describes your pain on average in the past week? Zero is no pain; 10 is pain as bad as you can imagine. Two, what number best describes how, during the past week, pain has interfered with your enjoyment of life? Zero, it doesn't interfere; 10 completely interferes. What about interfering with your general activity? It doesn't interfere; completely interferes." And really, what we're measuring here is pain, enjoyment of life, which is a quality-of-life measure, and general activity, which is measuring function.

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

[Music Plays]

Dr. Alford: I absolutely believe that you have terrible pain, and absolutely hear that you're suffering a great deal, and it must be really hard. And I can't imagine what it feels like on a daily basis.

Michelle Jones: It is really hard.

Dr. Alford: At this point, it would really be helpful if you could tell me your pain level within the scale, so I can follow it over time. So, remember that 10 is the most severe pain possible. So, what number best describes your pain on average in the past week, again where zero is no pain, and 10 is the worst pain that you can imagine.

Michelle Jones: [Sighs] It really is terrible. I really would have to say it is the worst. It's a 10.

Dr. Alford: Okay. Well, what number best describes how during the past week your 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 – it's ruining my life right now. I'd have to say maybe not quite a 10. I'll call it a 9.

Dr. Alford: Okay. And what about interfering with your general activity? Zero, it doesn't interfere at all; 10 it completely interferes with your general activity?

Michelle Jones: That is also a 9. I really can hardly do anything.

[Music Plays]

John Emery: Michelle's physical shows no acute distress, and normal vitals with a body mass index of 32. Her cardiopulmonary and musculoskeletal exams are normal, 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. Dr. Bial, let 's turn back to you. What is the best treatment approach, as you think about managing a patient's chronic pain?

Dr. Bial: It's a great question. I think the first step is actually to take a step back, and recognize that medication management is far, far from the only approach, and that we really want to take a multidimensional approach to all chronic pain. And broadly, we can divide this into four big categories. So, the physical and restorative approaches to pain; behavioral and complementary and integrative approaches to pain, procedural things, things that I might do for work, as well as medications.

And there are multiple benefits to trying to take a multimodal approach. So, when we think about things that might fall into the physical and restorative category, things that both help to restore function, and cultivate wellbeing, like therapeutic exercise, massage, traction/stretching, heat or cold, chiropractic care, therapeutic ultrasound, bracing, orthotics, TENS units, other approaches that also give patients a sense of self-efficacy. These are things that most of the time, really strongly contribute to self-care.

Also, let's not discount the importance and the tremendous value of behavioral, as well as complementary and integrative approaches, so things like cognitive behavioral treatment, acceptance and commitment therapies, mindfulness, stress reduction, meditation, acupuncture, yoga, tai chi. These have all been demonstrated to have very strong, legitimate benefits that rival those that we can achieve, for example, with medications.

Sometimes, though, we do need to reach for medications, and we should still be thinking broadly, using medications that are not merely opioids, but also considering acetaminophen, the NSAIDs, anticonvulsants, antidepressants, topical agents, as well as opioids and others.

And finally, if other approaches have not been effective, we need to consider procedural approaches, so things like nerve blocks, steroid injections, radiofrequency ablation, trigger injections, sometimes things as invasive as neuromodulation, or intrathecal pumps, or other stimulators.

What may be very surprising is that multimodal approaches are more cost-effective than single modality options, but study duration on all treatments for chronic pain are less than 12 months, and the vast majority are less than 12 weeks, barely even meeting the criteria for chronic pain.

So, when should you get help from a pain specialist? When should you call me, or one of my many colleagues? Well, there are a lot of good reasons, and the first one is that you need help, and that you recognize it. If you feel unsure of the pain diagnosis, if you're unsure about what other options might be available, or even if you just want a second opinion, whether that's with regard to opioids for an individual patient, or for other approaches that may be available.

But I do think it is critically helpful to the patient's experience that you need to know what services your pain specialist offers, and if you don't have a pain specialist available, get a second opinion from your colleagues, get a fresh pair of eyes on the patient. Also, be sure to remain up to date with local or state requirements requiring pain specialist referrals.

So, thinking about the non-opioid pharmacotherapies, or what should ordinarily be a first step when we are choosing medication management, I usually think first about the NSAIDs, so whether that's the

salicylates, the nonacetylated salicylates, and/or acetaminophen. We need to recognize that the NSAID category includes both the nonselective and the selective COX-2 inhibitors, and that these offer the benefit of being anti-inflammatory, as well as analgesic and antipyretic. Acetaminophen is analgesic and antipyretic, but considerably less effective than full-dose NSAIDs in relieving chronic pain, but it has fewer adverse effects, probably because it is less anti-inflammatory.

There are some general considerations. We know that the non-opioid pharmacotherapies do have a ceiling analgesic effect, meaning that you can keep prescribing more and more of the medication, but beyond a certain point, we achieve no further benefit, but we increase the risk of toxicity. But they have no known analgesic tolerance. They do have an additive, and likely synergistic role, so it's not unreasonable to administer both an NSAID together with acetaminophen. Some patients may respond better to one NSAID than another, but they carry risks: Common side effects, GI, renal, and cardiovascular effects, particularly at high NSAID doses.

There are additional non-opioid pharmacotherapies, and these are really the mainstays of pharmacologic treatments for neuropathic and nociplastic pain syndromes, including antidepressants, so the tricyclics, and the SNRIs. You might notice the SSRIs are not really on this list. The anticonvulsants, very classically, we use the gabapentinoids and carbamazepine, particularly for neuropathic and nociplastic pain syndromes.

Sometimes, there's utility to the antispasmodics or muscle relaxants, as well as local anesthetics. But just a word of caution: there is, indeed, misuse and addiction potential with the gabapentinoids, as well as with a number of the muscle relaxants. So, for example, carisoprodol metabolizes into meprobamate, which is a barbiturate-like drug. There is also the added burden of anticholinergic side effects. So, for example, when you're giving the tricyclics, as well as cyclobenzaprine.

So, turning our attention to the opioids, I think it is important to be clear in our language about the use of the term "opioid" versus "opiates." They are not interchangeable. The opiates specifically, are a subcategory of the opioids that are our natural opioids. So, these are things that are morphine or codeine. Then, there are semisynthetic opioids that are biologically related to the opiates: Hydrocodone, hydromorphone, and oxycodone. In contrast to many of the synthetic opioids, which are chemically distinct in terms of their molecular structure from the opiates, things like methadone, meperidine, and fentanyl.

So, how do the opioid analgesics work? Well, they work in multiple points along the pain pathway. So they turn on descending inhibitory systems, the hush message coming down from the brain. Additionally, they prevent ascending transmission of pain signals, so they also quiet the upgoing pain response to the brain. They inhibit the terminals of C-fibers in the spinal cord, so that first synapse, and they inhibit activation of peripheral nociceptors themselves.

But responses are variable, so not all patients respond to the same opioid in the same way. This probably related to the fact that there are greater than 3,000 recognized polymorphisms in the human MOR gene, and that there are also single nucleotide polymorphisms or SNPs, which affect opioid metabolism, transport across the blood brain barrier, as well as activity at receptors and ion channels. Additionally, opioids activate the reward pathway in the brain.

Just to quickly touch upon the difference between opioid tolerance and physical dependence, we should recognize that both tolerance and physical dependence are physiologic adaptations to chronic opioid

exposure. They're not moral failings on the part of the patient. These are physiologic responses to that opioid exposure.

So, thinking first about tolerance, this is when we experience an increased dosage needed to produce a specific effect. So, tolerance can develop very readily for CNS and respiratory depression. The patient takes large doses of opioids over time, and they'll be tolerated to those side effects, but much less so for constipation. And it's unclear about analgesia. In contrast, physical dependence is when signs and symptoms of withdrawal by abrupt opioid cessation, or a rapid dose reduction, or exposure to an opioid antagonist can be elicited.

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

Dr. Alford: This is a very important question, and pretty much everything you need to know is on this slide. What is the opioid efficacy for chronic pain? And if you start at the left, there are a number of meta-analyses that show that opioids versus placebo, looking at just high-quality studies, show that opioids have a statistically significant, yet small improvement in pain and physical functioning. What about opioids versus non-opioids? Well, those are only low- to moderate-quality studies, and they show similar benefits. What's important to note, however, is that the duration of these studies are only three to six months, so there are really no long-term studies looking at this question.

There was a randomized controlled trial that found that opioids were not superior to non-opioids for improving musculoskeletal pain-related function over 12 months. So, a good, long study. However, with any RCT, you need to look at the methods to see if it's generalizable to the patient sitting across from you. And I would say there are some limitations to generalizability. Why? Because they excluded patients who are already on long-term opioids, so our patient in this case would not have been included in the study. And of those that were eligible, 89 percent said, "No, thank you. I don't want to be enrolled in this study, where I would be randomized to an opioid or a non-opioid." So, of the 11 percent that said, "Sure, sign me up," there was no difference between opioids and non-opioids.

There were two longer-term follow-up studies that found 44.3 percent on chronic opioids for chronic pain had at least 50 percent pain relief. So, if that is your outcome measure – 50 percent pain relief – about half achieved it.

What about opioid safety and risks? Well, the good news is that allergies are rare, but we've learned over time that there is opioid-induced immunosuppression. We first learned that in animal models, but more recently in observational studies, we have found that humans have an increased risk of invasive pneumococcal disease and an increased risk of community-acquired pneumonia when on chronic opioid therapy.

What about organ toxicities? Well, we're very familiar with the organ toxicities of NSAIDs and acetaminophen, but what about opioids? Well, really, the focus is on suppression of the hypothalamic-pituitary-gonadal and adrenal axes, leading to menstrual irregularities, reduced fertility, and erectile dysfunction, but also, problems with bone health, osteoporosis, problems with fatigue, obesity, and metabolic syndrome.

Adverse effects are quite common, including nausea, sedation, urinary retention, and sweating, and as was mentioned earlier, constipation, because you've got a hypodynamic bowel, and dry stool. What

about pruritus? Well, that's because of a histamine release. It's not an allergy, and finally, we worry about respiratory depression.

How do we manage these opioid adverse effects? Well, nausea and vomiting usually resolve in a few days. We certainly can use an antiemetic, or sometimes we need to try a different opioid. Sedation? We have to decrease the dose. And this mostly happens during dose initiation or changing a dose. Constipation? It really is the most common and should be anticipated. We should use stool softeners, osmotic stimulants, peripherally-acting opioid antagonists. Sometimes we need to switch to a different opioid, but we really should avoid bulking agents, because, again, we have a hypodynamic bowel. Pruritus, you can certainly switch to a different opioid or use a non-sedating antihistamine. And then, urinary retention, especially in our male patients with BPH, sometimes we need to switch to a different opioid.

There are specific patient considerations when prescribing opioids. Let's start with age. Well, with age, there's always a decline in therapeutic index with any medication that we're prescribing, and a predisposition to adverse drug effects. But when we're prescribing opioids, we need to worry about the fall risk and worsening cognitive function.

But there's also things to consider when patients have medical comorbidities, for instance liver disease, and that's going to decrease opioid clearance. Morphine, oxycodone, hydromorphone are all implicated. We need to reduce the dose or prolong the dosing interval.

What about kidney disease? Well, that's going to decrease opioid excretion, and preferred are hydromorphone, fentanyl, buprenorphine, and methadone. Oxycodone should be considered second line, due to its active metabolites, and morphine and codeine are not recommended, due to its active metabolites.

We also need to consider drug-drug interactions. So, the mechanism really includes inhibition or induction of the cytochrome P450 system. Opioids that are metabolized by cytochrome P450 include codeine, oxycodone, hydrocodone, fentanyl, tramadol, and methadone, and these have numerous drug-drug interactions that can reduce or increase opioid effects.

Opioids that are not metabolized by cytochrome P450 include morphine and hydromorphone, and they, therefore, have fewer drug-drug interactions. It's going to be hard to remember all of these, so a helpful resource is called "DailyMed," which is a National Library of Medicine or NIH resource that talks about each medication and the potential drug-drug interactions.

We also need to worry about CNS depressants, because they may potentiate opioid effects on sedation and respiratory depression. CNS depressants include benzodiazepines, alcohol, and cannabis, for example. Alcohol may also rapidly release an opioid in a long-acting formulation, and that's called a "dose dump," or increase drug levels, even without dose dumping. And then, opioids can reduce the efficacy of diuretics by inducing the release of ADH or antidiuretic hormone.

This is all consistent with Recommendation 11 of the CDC Guideline, which talks about using caution when concurrently prescribing opioids with sedatives, like benzodiazepines.

So, what is the rate of problematic opioid use in patients taking opioids for chronic pain? Well, if we look at a systematic review of 38 Studies, about a quarter took place in primary care, half in pain clinic

settings, and the rest in other subspecialty clinics. They found that the misuse rates were somewhere between 21 and 29 percent. Well, misuse was defined as use contrary to the way it was prescribed, that is taking it for some other reason. For example, you're prescribing it for someone's back pain, and they took it for their headache. That would be considered misuse.

What about addiction rates? Well, that was somewhere between 8 and 12 percent. And addiction was defined as pattern of continued use with experience of, or potential for harm.

Now, we also need to worry about collateral risk, that is, risk to others. That includes young children, who may ingest an overdose, adolescents who may experiment, leading to overdose and addiction, and other household contacts, and the question is how do we mitigate that risk? We talk to our patients about safe storage, including using a lockbox, asking the pharmacy for child-resistant packaging, safe disposal, and you can go to this DEA website to find the latest recommendations around disposal. And we want to talk to our patients about overdose prevention, and we want to co-prescribe naloxone, just in case it occurs. There's more information on naloxone co-prescribing at the website www.prescribetoprevent.org. And this, again, is consistent with Recommendation 8 of the CDC Guideline, "Use strategies to mitigate risk, including naloxone co-prescribing."

I now want to touch upon higher dose opioids. First, there is a critical lack of high-quality evidence about the efficacy of high-dose opioids for chronic pain, and we know that higher doses are associated with some negative consequences, including overdose risk. And if you look at this graph to the right, you can see four different population-based studies, and they all show the same trend, that is, a dose-dependent effect on increased risk. Overdose risk increased by about two-fold at about 20 to 49 morphine milligram equivalents, and up to nine-fold once you got at 100 or greater morphine milligram equivalents. But we know higher doses are also associated with hyperalgesia, that is, an increased sensitivity to pain, reduced function, and immunosuppression.

So, for patients on higher-dose opioids, we should manage them as higher risk. That includes increased monitoring and support. This is consistent with Recommendation 4 of the CDC Guideline. That is, when starting opioids, prescribe the lowest effective dosage, use caution at any dosage, carefully evaluate benefits and risks when considering increasing dosages, and avoid increasing dosages above levels with diminishing benefit relative to risk.

John Emery: So, for any given patient on opioids, like Michelle 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?

Dr. Alford: So, there is, and when we talk about harm, I'm really talking about misuse, overdose, and addiction. So, what are the risk factors? I like to think of it in two buckets. The first are medication factors. That includes higher opioid dose, long-term opioid use – that's defined as greater than three months – being on an extended release/long-acting opioid, and the initial two weeks after starting an extended release/long-acting opioid. And then, as we discussed, being on an opioid with some other sedative.

And then, there are patient-related factors. That includes having a mental health disorder, including depression or anxiety; having substance use disorder, and that could be alcohol, even tobacco, illicit and prescription drug; having a family history of substance use disorder; a history of an opioid overdose; and sleep-disordered breathing.

Because sleep-disordered breathing is so important, let's just talk about a screening questionnaire to screen our patients for it, and that is the STOP-BANG Questionnaire. It's pretty easy to use. STOP stands for Snore. Does the person snore loudly? T is for are they often Tired, fatigued, or sleepy during the day? Has anyone Observed – that's the O – observed them stopping breathing during their sleep? And do they have, or have they been treated for high blood Pressure? And that's the P.

And then BANG is BMI more than 35, Age over 50, a Neck circumference of greater than 16 inches, and being male (Gender), and you can classify your patients as high risk for sleep apnea, intermediate risk, and low risk, based on their scoring.

We know that there are lots of psychiatric comorbidities in patients with chronic pain, and that there's a bidirectional relationship. What are those psychiatric comorbidities? We're talking about sleep disorders, depression, anxiety, personality disorders, PTSD, and substance use disorders. They are common. And the bidirectionality includes that pain makes these conditions worse, and these conditions make pain worse. So, it behooves us to look for them in all of our patients who have chronic pain, and comanage them.

So, how do we screen for these comorbidities in a busy, primary care practice? Well, there are some brief screening tools, including for depression, using the Patient Health Questionnaire 2, or two-item screener, PHQ-2. Or screening for anxiety, using the GAD-2, that's two items. Screening for PTSD using the Primary Care PTSD Screen for DSM-5, that's five items. Screening for sleep disorders, using the Insomnia Severity Index, that's three items. And screening for suicidality, that's a four-item screener.

What about screening for substance use? And I'm going to go into this in a little more detail, because this is probably a screener that you're not familiar with, and it's called the TAPS, which stands for Tobacco, Alcohol, Prescription Medication, and Other Substance Use Tool, and it's all about, "In the past 12 months how often have you…," and you'll notice they ask it in a normative way, "How often?" They don't say, "Do you?" They say, "How often have you used tobacco or other nicotine? Had five or more drinks in a day for men, four or more drinks in a day for women? Used any prescription medication, just for the feeling, more than prescribed, or that were not prescribed for you, or used any illicit drugs, including marijuana, cocaine or crack, heroin, methamphetamine, hallucinogens, or ecstasy."

John Emery: As we know, Michelle doesn't smoke. She screens negative for sleep-disordered breathing and insomnia, as well as for depression, anxiety, and substance use. Dr. Alford, how do you decide, in general, whether to prescribe opioids for chronic pain, and how do you manage patients like Michelle, who are already taking opioids that were already started by another clinician? And finally, how would you assess a patient like Michelle for prescription opioid misuse risk prior to prescribing?

Dr. Alford: So, this is a fundamental question we need to ask whenever we're thinking about prescribing opioids, that is, is the pain severe? Also, does the pain have a significant impact on function, and quality of life, and is the pain a type that's potentially opioid-responsive? And we know that nociceptive or neuropathic pain may respond to opioids, but less so for nociplastic pain and headache syndromes. Did the patient have inadequate benefit from non-opioid modalities? And like in this case, if the patient is already on opioids, is there documented benefit? And that includes pain, function, and quality of life.

So, just to talk about opioids in chronic pain, and put it all in perspective, remember that the efficacy of long-term opioid therapy for chronic pain has been inadequately studied, and that opioid prescribing

should be more judicious, that opioid misuse can be fatal, especially when we're talking about overdose and opioid use disorder, that opioids for chronic pain are indicated only after alternative, safer options have been found to be inadequate, and they're really only one tool of a multimodal approach for managing severe, chronic pain. And this is consistent with Recommendation 2 of the CDC Guideline.

I want to touch upon patients who you may inherit, who are already on long-term opioid therapy from a previous clinician, and sometimes these patients are called "legacy patients," or "opioid orphans." You want to review the case with the former clinician, if possible. You want to review the prescription history by looking at the prescription drug monitoring program. You want to assess the patient for an opioid use disorder and treat or refer specialty care if indicated. You want to consider prescribing a therapeutic bridge for the patient until a plan of care is determined, given the risks associated with stopping an opioid therapy abruptly. And you definitely want to document the rationale for your treatment plan, and what the next steps will be.

This is consistent with Recommendation 5 of the CDC, where they specifically say, "If a patient's already on opioids, carefully weigh the benefits and risks. If the benefits are greater than risks, continue opioids, and optimize other therapies, but if the risks are greater than benefits, optimize other therapies, and gradually taper opioids to lower dosages. And unless there's life-threatening issues, like impending overdose, do not discontinue abruptly, or rapidly reduce opioids from higher dosages."

We're going to be talking a lot more about this later in the course, but how do you assess for opioid misuse risk prior to prescribing? Well, you want to take a medication-taking history. Has the patient shown loss of control, compulsive use, continued use despite harm? You want to do urine drug testing to confirm the substance use history. You want to check the prescription drug monitoring program to confirm the medication and prescriber history. You certainly want to try to speak to the previous clinicians, and co-care providers, to find out if there's a history of any concerning medication-taking behaviors (early refills, lost prescriptions). You want to review old medical records, any history of unsafe medication use. And there are some screening tools looking for opioid misuse risk that have been validated, but there is no gold standard, and they all lack robust evidence supporting their use. And they're listed here, and the one that's probably most commonly used is the ORT, or the Opioid Risk Tool.

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

[Music Plays]

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

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

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

Dr. Alford: Oh, please don't think that. It's just that these medications can cause serious problems for some people, and I really want to make sure that you're safe.

Michelle Jones: Okay. I get it. I keep reading about people overdosing, and people with pain being shut off from their medications. It really is an awful situation. I'll see you in a couple of weeks.

[Music Plays]

John Emery: Michelle's problem and medication lists are reconciled, and Dr. Alford 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's no evidence of misuse of her prescription opioid.

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

Dr. Bial: Yes. So, we've discussed that opioids should not be first-line treatment option, that they're just one tool in a multimodal approach, that side effects are common, but they can be managed. Recognizing that opioids carry significant risks, including addiction, overdose, and death, and that misuse risk can be assessed using a systematic approach, which includes screening for comorbidities.

End of Part 1

Part 2

John Emery: Welcome back to Part Two of SCOPE of Pain. Two weeks have gone by. Now, let's return to Michelle Jones and her second appointment with Dr. Alford.

[Music Plays]

Dr. Alford: Good to see you again, Michelle. I normally try to speak with patients' previous doctors, but unfortunately, I was unable to reach Dr. Robertson, but your old records and the urine test results from the last visit were completely helpful, so thanks.

Michelle Jones: Yeah. I think Dr. Robertson moved away when he retired.

Dr. Alford: Okay. Let's review how you're doing now. Remember those questions that I asked last time: What number best describes your pain on average in the past week, again, where zero is no pain; 10 is pain as bad as you can imagine.

Michelle Jones: Well, I'd say that my pain is pretty much a 6 most of the time, except right before I'm ready to take my next pill, when it definitely shoots up to a 9. But I've been taking them just as you told me to.

Dr. Alford: Okay. Well, what number best describes how during the past week, pain has interfered with your enjoyment of life? Remember zero, it doesn't interfere at all; 10 it completely interferes with your enjoyment of life.

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

Dr. Alford: All right. Well, what about interfering with your general activity?

Michelle Jones: That's also a 6. Really, my pain is always there. It never goes away.

Dr. Alford: Okay. Tell me, do the pills make you tired at all?

Michelle Jones: No. Not at all. They really just help me get through the day.

[Music Plays]

John Emery: Dr. Bial, should Dr. Alford make any changes to Michelle's opioid prescription? What do you consider when thinking about the different opioid choices? Are some more effective and safer than others?

Dr. Bial: It's hard to say. We have a number of important choices to make, and I think one of the first ones is about the use of a short-acting or immediate-release opioid versus a long-acting, or an extended-release opioid. And I think it's incredibly important to recognize that most of the medications that would fall in either bucket are actually the same substance. So, for example, morphine, hydrocodone, and oxycodone are all available both in immediate-release, and extended-release formats. What really differs is the formulation. Codeine is only available as an immediate-release opioid, and methadone by its very nature is considered an extended-release opioid.

So, how do we choose between a short-acting and a long-acting opioid? I think that this is critically important to remember, which is that when starting opioids, we should always use the immediate-release, rather than an extended-release, or long-acting format. And that's consistent with the CDC's Recommendation Number 3.

So, we should choose immediate-release or short-acting opioids when the patient is opioid-naïve, or no opioid tolerance exists, which might not quite be the same thing. Also, when that fits the pattern of the patient's pain most appropriately. So, if the patient has intermittent or occasional pain, if what they really require is PRN dosing, then we should be matching that pain pattern to the pattern of the duration of action of the medication.

In contrast, extended-release or long-acting opioids can be very useful, so long as opioid tolerance exists, and again, matching the pattern of the patient's pain. So, when the patient has a constant, severe, or around the clock pain, then scheduled dosing might best fit that situation, or when we need to stabilize pain relief, such as when a patient is using multiple doses a day of short-acting opioids.

But, again, recalling that what differs is usually not the drug, but the formulation, that long-acting opioids must not be broken, chewed, or crushed. We should also remember the old school pharmacy adage that we should always start low and go slow.

So, how do we choose? Which is better in terms of the use of short-acting versus long-acting opioids? And at the end of the day, there's really insufficient evidence to determine whether long-acting opioids are either more effective or safer than short-acting, or immediate-release opioids. There's considerable debate, also, about whether bolus dosing or continuous exposure is more likely to result in analgesic tolerance, hyperalgesia, or addiction.

So, at the end of the day, given that we have so many clinical questions as yet unanswered, the answer is only to individualize treatments. You want to choose the options in an individualized way that best meet the patient's needs.

So, thinking about some of the longer-acting opioid options available, I'd like to turn our attention to transdermal fentanyl. So, fentanyl is dosed in micrograms. Incredibly potent substance. It's very slow in peak onset, so if you apply the patch, it will take 24 to as much as 72 hours before the patient achieves that steady-state dosing. Similarly, there's a delayed offset, so if the patient peels that patch off, the drug is still available, given that it has a serum half-life of 17 to 26 hours. Why? Well, sustained-release requires predictable blood flow, and adequate subcutaneous fat, because the way that transdermal fentanyl works, is through the buildup of a depot in the subcutaneous tissue from which the body is then dosed with the fentanyl, which is, in fact, short-acting. Absorption is increased with fever or broken skin, as a result, and decreased with tissue edema. Just as a point to remember, that some formulations of transdermal fentanyl have a foil backing, and they might not be compatible with MRI.

Buprenorphine is another special opioid that's worthy of independent conversation. So, buprenorphine is a partial agonist, and it has formulations approved for the treatment of pain OR opioid use disorder. Now, when we're using buprenorphine for pain, we dose this in micrograms. It's important to recognize that because it is a partial agonist, exposure to buprenorphine can precipitate opioid withdrawal if it's initiated while a full opioid agonist is highly bound. So, for patients that you might be rotating to buprenorphine, for example, you want to taper their prior opioid to fewer than 30 MMEs before starting buprenorphine. This is available as a buccal film, and that film should not be cut, chewed or swallowed, as well as a transdermal patch. This is a seven-day application of the patch, and it's important in order to avoid skin site reactions that sites need to be rotated, and we need to wait a minimum of three weeks before reusing the same site.

Now, in contrast, when we use buprenorphine for opioid use disorder, we're dosing that in milligrams. This is usually administered as a sublingual tablet or film, or now available as a subcutaneous injection, which can be weekly or even monthly. Some formulations will contain naloxone (sequestered). There is an induction procedure to avoid precipitating opioid withdrawal. Usually, when we are using buprenorphine for opioid use disorder, it's dosed just once a day. In contrast, when we are treating both opioid use disorder and pain, it needs to be dosed three times a day. So, divided doses in order to achieve that analgesic benefit.

Methadone, in contrast, is really complex, and sometimes I consider this the most complex of the opioids. The problem is that it's potentially the most dangerous, but it also has some excellent added utility. Unfortunately, it has a long, variable, and unpredictable half-life; so the analgesic half-life of the

drug is about six to eight hours. We usually have to dose it TID, but the serum half-life is somewhere between 20 and as many as 120 hours. It also carries the risk of QTc prolongation, and thus the risk of torsades de pointes. Now, it's only available in 5 mg and 10 mg tablets, which can lead to a large pill burden for patients on higher doses. But there are some possible advantages. In addition to its opioid receptor effect, it also has an NMDA receptor antagonism effect, and so there is potentially less risk for analgesic tolerance, and sometimes better efficacy in neuropathic pain. It has no active metabolites, and those small, inexpensive dosage units might allow for easier titration.

Let's turn our attention briefly to the dual mechanism opioids. And some of you might be surprised that we're including these as opioids, but they do bind the μ-receptor. So, I'm talking about tramadol and tapentadol, which also are norepinephrine and serotonin reuptake inhibitors. Tramadol is a weak μ-opioid receptor agonist. It has a minimal norepinephrine effect, but a very prominent serotonin effect. Along the same spectrum, tapentadol has a stronger μ-opioid receptor agonist effect, and a more prominent norepinephrinergic effect, and a more minimal serotonin effect. So, when the pharmacists call, and they alert you to patients that are taking other serotonergic or norepinephrinergic drugs, we should thank them kindly and appreciate that tramadol and tapentadol increase seizure risk. They do carry risks of physical dependence. We should be concerned about and screen our patients for risk of serotonin syndrome. And they are, indeed, controlled substances with addiction potential.

We might consider the use of abuse-deterrent or resistant formulations, and this is accomplished in a number of different ways. So, through the formulation with physical barriers, like making medications crush resistant, or containing gelling agents. They could have a sequestered antagonist. Sometimes they can be co-formulated with aversive components, or they could administer a pro-drug, so that changing the route of administration is more challenging or impossible.

We could change the route of administration. It's certainly more difficult, for example, for most patients to abuse a transdermal formulation. And we can reduce drug rewards. But at the end of the day, while these may decrease medication diversion, and they may decrease street price, they don't prevent taking many intact tablets, and they can be expensive, and some insurers do not cover them. Currently, there are no 100% proven misuse-resistant opioids. You can find an updated list of abuse-deterrent, extended-release, or long-acting opioids at www.fda.gov/drugs/drugsafety.

John Emery: Dr. Alford, can we talk a bit more about other things to consider when you are thinking about prescribing an opioid?

Dr. Alford: Yeah. So, I think just thinking about opioid choice, and summarizing what we've learned, we need to consider the duration and onset of action. Remember, if the patient's pattern of pain is intermittent, then we're going to use short-acting. If it's constant, and they have tolerance, we could use a long-acting. But also, the patient's prior experience. Remember there are different effects and side effects, and we remember that we learned about the μ-opioid receptor polymorphisms, and the differences in opioid metabolism.

The patient's level of opioid tolerance: We always want to assess that before starting an extended-release, long-acting formulation. What other drugs, the patient is taking, their age, and other diseases, the route of administration, and then, finally, probably equally important to everything I just said, is insurance issues and cost. We certainly don't want our patients going to the pharmacy, and being turned away, because their insurer does not cover the formulation that we prescribed.

I want to talk about another important concept, and that's called rational polypharmacy, and I think a lot of us were taught that polypharmacy is something to avoid, but when it comes to chronic pain, polypharmacy can actually be helpful, because each one has mechanism-specific treatment targets. For instance, we talked about the descending inhibitory pathway, which shuts down the pain signal, and certainly there are different medications that enhance that, including tricyclic antidepressants, SNRIs. But also, we can target central sensitization at the spinal cord level with tricyclic antidepressants, and the gabapentinoids. And then, peripherally, we can target the pain signal, using NSAIDs, opioids, tricyclic antidepressants, and lidocaine.

But the other piece to remember is that we want to exploit synergism with this polypharmacy, and these are two studies looking at treating neuropathic pain with multiple medications. If you look at the left, this study compared placebo versus gabapentin versus morphine versus the combination for treating painful diabetic neuropathy. And what you can see is that placebo did better than baseline; gabapentin did better than placebo; morphine did better than gabapentin, but look at what group did the best: The combination group. And that's not even the most interesting part of the story, because with better pain control, they were able to achieve that with lower doses of both medications, and therefore, fewer adverse effects. A word of caution: That co-prescribing gabapentinoids and opioids has been associated with a dose-dependent increased risk of opioid-related deaths. So, although it could be beneficial, we need to do it with care. The graph on the right is a similar study, this time looking at morphine versus nortriptyline versus the combination. And again, you can see that the combination group did the best.

[Music Plays]

Dr. Alford: Okay. Here's what I suggest we do moving forward: Since you have severe pain all day, and you're tolerating the oxycodone four times per day, but you told me you experience really severe pain right before the next dose, I'm going to switch you to a long-acting version of the same medication, which you'll only have to take twice a day. And that should stabilize your blood levels and should prevent the severe pain you've been experiencing right before your next dose. And with the longer-acting medication, and more stable blood levels, I want to see if we can get good pain control on an actually decreased total daily dose of the oxycodone, and see how that works. It's important that these long-acting medications are not broken or crushed, so please don't do that, because that could be extremely dangerous, and I'm also going to continue the acetaminophen, and I'm also going to increase your gabapentin, because that is going to help the oxycodone work better. I'm also going to refer you to physical therapy to help work on that hip.

Michelle Jones: Hang on a sec. I don't really understand how getting a lower amount of pain medication is going to help my pain. Dr. Robertson never recommended these kinds of changes.

Dr. Alford: Yeah. I understand your concerns, but I hope that you can trust that I'm making this change to ultimately improve your pain control. Because we know that opioids carry serious risks, I'm going to walk you through the office policies around how we'll monitor you for safety. This is our standard office procedure for all patients on opioids, so let's go over an agreement, which is going to outline my responsibilities and yours, and then, if you agree, we'll both sign it, and then I'll have the nurse out front get you the next appointment, and an appointment with physical therapy.

Michelle Jones: Okay. That's a lot of stuff to do, but I trust that you really are trying to help me.

[Music Plays]

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 discussed strategies for Michelle's weight loss.

Dr. Bial, can you give us some detail about the monitoring and documentation strategies you and Dr. Alford would put into place in order to try to keep your patients on chronic opioid therapy safe?

Dr. Bial: So, I think we're talking about universal precautions. That ideally we should be always undertaking careful documentation, because predicting opioid risk and misuse is imprecise, and so, consistent application of precautions reduces stigma, as well as standardizes care.

So, some of those precautions might include assessing and documenting the pain diagnosis, as well as an assessment of the patient's opioid misuse risk. And then, we want to prescribe opioids always, initially, as well as over time, as a test or trial, and then that therapy should be continued, modified, or discontinued, based upon ongoing evaluation of the balance of risk versus benefit. So, depending on the patient's level of risk, maybe every one to three months. We always want to state in our prescription, as well as how we educate our patients, the maximum number of tablets to be taken per day. Patient Prescriber Agreements should be written at a fifth-grade level, and without any coercive language. And then, finally, carefully we want to monitor for adherence, misuse, and diversion, and document our monitoring strategies. And this is consistent with the CDC Recommendation Number 7, which states simply that we should evaluate benefits and risks one to four weeks of starting opioids, or after dose escalation, and then regularly.

So, what's in a Patient Provider Agreement? I think that there are two broad categories that should always be covered, and those are Informed Consent, and then, the Plan of Care.

So, turning our attention first to Informed Consent, we want to set realistic goals. We want to make sure that patients understand that we are not seeking to wholly eliminate their pain, but that we want to reduce their pain and improve their level of function. And as such, we want to set what we call "SMART" goals. So, SMART is an acronym for S being Specific; M being Measurable; A being Action-oriented; R being Realistic, and T being Time-sensitive. So, SMART goals, and we should document them in a way that is specific to each patient.

We also want to make sure that the patient is given Informed Consent about potential risks, reviewing adverse effects, and drug interactions, the risk of over-sedation and impairment, especially during dose adjustments, or dose initiation, the risks of misuse, overdose, death, as well as the risk of neonatal withdrawal, hyperalgesia, and victimization by others.

The second portion of a Patient Provider Agreement should include the Plan of Care. We should set expectations that our patients engage in other treatments, as directed, so we're avoiding monotherapy. We want to review strategies for safer medication use, such as taking medications as directed, don't double dose if the prior dose is missed, safe storage and disposal, and of course, no sharing.

We should review the expectations for no illicit drug use, and to avoid, or minimize sedatives. Patients need to report all other medications, as well as medication side effects, and for patients of reproductive age, reviewing pregnancy plans, so discussing birth control, monitoring for pregnancy, discussing

neonatal opioid withdrawal syndrome, and we should discuss that all opioids will transfer into human milk to some degree.

We also want to consider monitoring strategies, and a commonly undertaken one is urine drug testing. On the one hand, this is useful, because it provides information about therapeutic adherence, and information on use or non-use of illicit drugs. So, we don't need to be sneaky about it. We want to discuss urine drug testing very openly with our patients. And I might ask, "If I send your urine right now, what will I find in it?" Along with sending a urine sample, we should document the time of the patient's last medication use and a list of what those medications are, but we should recognize that it's only one medical datapoint, and it needs to be integrated with all the others. We can't discriminate elective substance use from substance use disorder or diversion, and the concentrations cannot determine how much opioid is actually being taken. Dedicated deceivers can and will beat the system. And these strategies are consistent with CDC's Recommendation number 10, simply that we want to use strategies to mitigate risk, including toxicology testing.

So, urine drug testing are typically urine drug screens that are immunoassays. Now, the advantage of this approach is that they're quick, they're inexpensive, and they're point-of-care testing. But you need to know what's included in your testing panel. And there are risks, both of false negatives, and of false positives due to cut-offs, as well as cross-reactions. But unexpected findings can be verified with more definitive testing, so this is GC-MS or LC-MS testing. The advantage here is that testing is very specific, because it's identifying specific molecules, but it's time-consuming, and it's more expensive, and ultimately, you need to understand that opioid metabolism slide that we reviewed before in order to interpret these results. For example, hydrocodone can be metabolized to hydromorphone, or that oxycodone is metabolized to oxymorphone. And at the end of the day, if you receive spurious results, contact your lab toxicologist for questions regarding those unexpected findings.

Another monitoring strategy commonly used is medication counts and Prescription Drug Monitoring Program queries. So, let's talk first about medication counts. They give us information about medication adherence, at least insofar as what's still in the bottle, and sometimes this can be useful for gleaning information for diversion. So, ideally, we want to prescribe 28-day prescriptions, rather than 30 for our patients, because this helps prevent running out on the weekends, as well as medication hoarding, that if a patient has a few extra tablets every month, that they build up over time.

Many states also require the querying of the Prescription Drug Monitoring Program. This can provide information about harmful polypharmacy, or about multiple provider use, but neither is 100 percent effective, and there's insufficient evidence that PDMPs either increase or decrease nonfatal or fatal overdoses. It's also important to recognize that some states allow delegating access to others, and have interstate data sharing, which can be very helpful, but that methadone that is dispensed at Addiction Treatment Programs is not included.

So, we want to titrate our minimum level of monitoring, based on the patient's risks, and I'd like to refer you to the TOPCARE Program. So, this is Transforming Opioid Prescribing in Primary Care, and you can find more at www.opioidresources.org. One example would be through the use of the ORT, the DIRE, or the SOAPP that we could group patients into low, moderate, or high risk, and that we should adjust the number of visits per year, for example, four for low, or six for high, as well as the number of urine drug screens, pill counts, and PDMP queries to two to six visits annually. But state laws might mandate level of monitoring, and monitoring should be more intensive during the first six months of opioid therapy, and I would advocate, also, any time of a dose adjustment.

So, what do we need to document during an office visit? A commonly used acronym here is the Six A's. So, they are Analgesia, Activities, Adverse Effects, Aberrant behaviors, Affect, and Adherence. And I would encourage you to document this every time. A national study demonstrated that approximately 30 percent of charts had no pain diagnosis at a visit when an opioid was prescribed. Other things you may want to document include subjective reports. So, from the patient, co-care providers, caregivers, and reliable family members but we want to beware of family members with secondary gain for giving inaccurate information in one direction or another. We want to include objective information, so observations of the patient, their PEG score, results of urine drug screenings, pill counts, and the PDMP query, and I'm a big fan of taking a 24-hour inventory to get a better understanding of how the patient is using their medications in real life. So, for example asking, "Tell me how you're taking your medications," or "Do you miss doses on some days?" or "On average, how many doses do you take per day?"

So, what's the clinician's role? We always want to refer back to that risk-benefit framework. We recognize that we are there as healthcare providers, and that we're not the police or a judge, that we're assessing the treatment, and not the patient.

We want to discuss monitoring in an open way, using a consistent approach. So, harkening back to those universal precautions. But we want to apply that approach individually to match each patient's risk. We want to review with the patient the personal, as well as public and community health risks of opioids. We want to discuss agreements, pill counts and drug tests, as ways that we're helping to protect the patient from being harmed by medications, and we want to discuss openly our responsibility to look for and manage early signs of harm.

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

Dr. Alford: So, there's this concept called "opioid stewardship," which is really a way of organizing your clinical practice to prescribe opioids safely, correctly, and under the right circumstances. So, what's included in opioid stewardship? Well, first you want to develop a leadership team who can establish accountability. And that leadership team can work to develop office controlled substance policies and procedures, and these policies and procedures should be evaluated, monitored, and improved over time. Next, you want to educate patients and prescribers around these policies and procedures, and you also want to use information technology, including a patient registry, which allows practice managers to track office-wide adherence to guideline-based practices. You want to utilize the entire healthcare team, and that includes nurses, pharmacists, psychologists, medical assistants, and front-desk staff. And you certainly want to have developed a list of referral and support resources around pain, mental health and addiction. You don't want to wait until the patient is there desperately looking for maybe addiction treatment to start looking for those resources. So, those should be available to you. If you want to learn more about optimizing office systems, I would encourage you to go to SCOPE of Pain, and click on Supplemental Training.

I think an important partner in safer opioid prescribing is your community pharmacist. First of all, you need to recognize that a pharmacist has to ensure that the prescriptions are for a legitimate medical purpose, and keep in mind that they're doing this without access to the medical record. They can help with medication choices, doses, and substitutions. And they do interact with patients. They can educate on risks, proper use, storage and disposal, drug takeback programs, and the proper use of

naloxone. They also check the Prescription Drug Monitoring Program and can monitor for worrisome behaviors. They can identify potential drug-drug interactions, and they can assist you with formularies and prior authorization issues.

We can help our community pharmacist by including the diagnosis or indication for the prescription on the prescription. We can also list parameters for when the script should be filled, and we should really maintain open lines of communication, and sometimes this requires giving them a direct phone line, so they don't have to go through the usual phone channels.

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, discontinuing opioids, and managing opioid use disorder.

Michelle did well on her pain treatment plan, including opioid therapy for her painful diabetic neuropathy and chronic hip pain for 11 months. Then, Dr. Alford was notified that Michelle was seen in the Emergency Room of a local hospital, requesting an early refill of her oxycodone after running out early. The ED physician noted that she was in moderate to severe opioid withdrawal and gave her a prescription for enough oxycodone pills to last until her next appointment with Dr. Alford in one week.

[Music Plays]

Dr. Alford: Hi, Michelle. I have to tell you, I was really surprised when I got a call from the Emergency Room doctor about your visit last week when you requested an early refill of your oxycodone. Can you tell me about it?

Michelle Jones: Yeah. Well, my foot pain has been so much worse. I just…I decided to start taking an extra pill in the afternoon and I ran out. I think I've really gotten used to this dose, and it doesn't work the way it used to. [Sighs] But I've got my husband telling me that I'm addicted, and I'm really 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 really think I need a higher dose.

[Music Plays]

John Emery: Dr. Alford, what do you think is happening with Michelle, and how will you respond to her worrisome behavior and request for a higher opioid dose?

Dr. Alford: So, I think the first thing to do is to take a deep breath, and kind of think about this from a differential diagnosis perspective. What's causing this new worrisome medication taking behavior, which by the way, could be quite dangerous.

Is she substance seeking? That is, has she developed an opioid use disorder? Is she self-treating some other symptom? We know that opioids make people feel better. Is she treating an anxiety or insomnia? Or is there some diversion going on, that is she's sharing or selling the opioids? Or does she have pain relief seeking? Maybe her disease has progressed. Maybe her neuropathy is worse. Maybe she has some new painful condition. Maybe her pain is poorly opioid responsive. Maybe she's developed opioid analgesic tolerance. Maybe she's developed withdrawal-mediated pain, or maybe she's developed this opioid-induced hyperalgesia, which I'm going to talk more about in a little bit.

Let me just mention something about withdrawal mediated pain, and that is, remember that when patients are on around-the-clock opioids, they're going to become physically dependent, and there may be times during the day where their opioid level drops, where they start to feel some withdrawal, and the withdrawal is going to be experienced as worsening pain. They then take their opioid, which treats their withdrawal, but they actually feel better. And so, are they treating their pain or withdrawal? And I think that's one of the rationales for using a long-acting opioid in someone who's on around-the-clock opioids: to try to avoid that up and down potential for withdrawal-mediated pain.

Sometimes our patients have many of the above, which includes pain-relief seeking and substance seeking, happening simultaneously. So maybe their pain is worsening; maybe they have developed an opioid use disorder; and maybe their diverting some of their opioid for income.

So, let me just take a moment here and talk about how do you diagnose an opioid use disorder? Well, you're going to go to the DSM-5, and there are 11 criteria. The first two are tolerance and withdrawal, and you should already be saying to yourself, "Well, I thought those were expected outcomes." And they are, and therefore, you cannot use those two criteria if a patient is prescribed opioids under medical supervision.

So, that leaves you with nine other symptoms to make the diagnosis. First are three that are classified under loss of control or compulsive use, using larger amounts over longer periods of time, inability to cut back, increased time spent obtaining, using, recovering. And then there are a bunch of criteria that signify continued use, despite negative consequences. That is they're taking this medication, but things are getting worse, whether it be at home, at work, and using in physically hazardous situations.

And then, finally, are they craving, or have a compulsion to use? You only need two of these nine criteria to have a mild OUD, and six or more to have severe OUD. Keep in mind that the DSM-5 criteria for diagnosing an opioid use disorder has been extensively validated for illicit opioid drugs, but has not been so for opioids prescribed for pain. So, it is a little bit challenging. However, this is the gold standard.

How do we discuss possible opioid use disorder with our patients? Well, first, you want to give specific and timely feedback about those behaviors that raise your concern, such as, "You're showing me that you've lost control of this prescription. You run out early." Or there's compulsion. That is, "Everything else that I recommend to you for your pain, you don't want to hear about it. You just want more opioid." Or "It seems that things are getting worse for you, but yet you want more of the opioid, despite this harm." Remember that patients may suffer from both chronic pain and OUD. Sometimes we need to agree to disagree with the patient. Benefits can no longer outweigh the risks, if you think the person has an OUD, and you can say something like, "I cannot responsibly continue to prescribe opioids, as I feel they would cause you more harm than good." And always, always, always offer a referral to addiction treatment, even if the patient isn't ready at that time to accept that referral.

I alluded to this concept of opioid-induced hyperalgesia. And it's a paradoxical enhanced pain sensitivity in patients who are on chronic opioids for more than one month. Unfortunately, the underlying pathophysiology and its true incidence is unknown, and there are no official criteria or guidelines for diagnosing it. But clinically what do we see? We see the pain is generalized; it's diffuse; it's ill-defined, and it's not necessarily located at the source of the original pain. An increased dose may improve the analgesia, but only temporarily. It's also uncertain whether tapering or opioid rotation to an alternative opioid is more effective.

So, I don't worry about opioid-induced hyperalgesia in a patient who's on chronic opioid therapy and doing well. I only worry about it when someone isn't doing well, and I think of it in the differential diagnosis of why aren't they doing well? And maybe they've developed hyperalgesia, and maybe the best course of action is to taper.

What about lack or loss of benefit? Remember, this patient was doing well, and then they increased their dose. So, what are the next steps? Well, first you want to reassess the factors that are affecting their pain. You want to re-attempt to treat the underlying disease and comorbidities that may be making their pain worse and consider to add or increase a non-opioid or non-pharmacological treatment, or add breakthrough medications, or switch to a different opioid – sometimes referred to as "opioid rotation" – and avoid dose escalation to high-dose opioids.

So, let's talk about breakthrough medication. Now, remember in this case, we didn't assume the patient would need breakthrough medications, but if they do, your first choice is a non-opioid. Just because she's on a long-acting opioid for her chronic pain doesn't mean she needs a short-acting opioid for breakthrough medication, so I would start with an NSAID or acetaminophen. But if that doesn't work, you certainly could use an immediate-release/short-acting opioid, either the same molecule or a different molecule, or you could try one of the dual-mechanism opioids, tapentadol or tramadol.

If you're going to switch to a different opioid, you might consider this to, 1) restore analgesic efficacy; 2) limit some adverse effects the patient may be having; and thirdly, to decrease the overall dosage, or the MME. Now, this concept of opioid rotation or switching to one opioid to another is based on large intra-individual variation and response to different opioids, those different variants of the μ-opioid receptor we talked about, and it has limited evidence, as most trials were retrospective and studied small numbers of patients. But I do find this helpful in some circumstances.

So, if you're going to switch from one opioid to another, you're going to go to an opioid conversion table, or an equianalgesic table. You need to know that these are derived from relative potency ratios, using single-dose analgesic studies in opioid-naïve patients. They're based on limited doses, or ranges of doses, and therefore, they don't really reflect the clinical realities of chronic opioid administration in our patients. They're often not reliable due to individual pharmacogenetic differences, and unfortunately, most tables do not adjust for incomplete cross-tolerance. What is incomplete cross-tolerance? Well, remember that if you have a patient on a specific opioid – in this case oxycodone – and they've developed complete tolerance to the sedating and respiratory depressant effects, and you give them the exact equal analgesic dose of a different opioid, say morphine, there is no guarantee that they will have complete tolerance to the respiratory and sedating effects, and therefore, we need to adjust, that is to decrease the equal analgesic dose.

So, that may all seem confusing, and so I'm going to give you an example, again, using our case study of Michelle Jones. And one site that I like to go to is called Global RPH.com, and let's go through an opioid rotation. Now, remember our patient's on long-acting oxycodone, 15 mg bid, or 30 mg of oxycodone per day, and that's the equivalent of 45 MME.

Now, I'm going to put in the calculator her oxycodone dose, her total dose, 30 mg, and if she was on a breakthrough opioid, I'd put that in, as well, but she's not. And now, we can reduce for incomplete cross-tolerance, and it's such an inexact science that the recommendation is to always decrease by 25 to 75 or 50 percent, so it's pretty inexact, but here I'm going to decrease by a third, and put her on

morphine, and say, "Okay, calculate," and see what it comes out, 30 mg. So, now, I'm going to convert her to long-acting morphine, 15 mg bid, and that's the equivalent of 30 MME. So, you can see that I've decreased her overall morphine dose.

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 home exercise that she learned at physical therapy, and joined a monthly chronic pain support group. Her individual PEG scores remained 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 scenario 1b, after being switched 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 of a dose increase of the morphine, she demanded that she be changed back to oxycodone. 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 she is now smoking marijuana to help her pain. Dr. Bial, what do we know about marijuana and pain? And what should be the next steps for her apparent lack of benefit from opioid analgesics?

Dr. Bial: Yeah. These are really common and really complicated questions. So, thinking first about cannabis and pain, we know that cannabis is actually multiple potential drugs, so whole plant cannabis contains greater than 60 pharmacologically active cannabinoids as yet recognized, including cannabidiol or CBD, as well as the psychoactive substance THC, or tetrahydrocannabinol. THC, itself, is a Schedule I controlled substance, meaning that it is implied to have no currently accepted medical use.

But endocannabinoid receptors are found in high concentrations in the brain and the spinal cord, and there is moderate quality evidence that cannabinoids can be effective for short-term treatment, so one to six months of chronic pain, particularly neuropathic pain and fibromyalgia pain.

But there may be other alternatives that are, at least statistically speaking, more effective. So, for example, for 30 percent pain reduction, the number needed to treat was 24, compared to 4 to 10 for tricyclic antidepressants, opioids, gabapentinoids, and SNRIs. Treatment studies of musculoskeletal pain and the use of cannabis are inconclusive. Now, while side effects are mild, generally speaking, compared to opioids, it can cause dizziness, sedation, and impaired coordination, and we believe that long-term use in younger individuals can result in cannabis use disorder, as well as cognitive impairment.

So, our patient, Michelle, is exhibiting a continued lack of benefit, and again, we need to remember that not all chronic pain is opioid-responsive, and that more opioid is not necessarily better. More opioid may increase the risk of adverse effects, and some chronic pain, which is very surprising, and sometimes

very hard to achieve that leap of faith with our patients, but to recognize that some chronic pain paradoxically improves, sometimes quite dramatically, after an opioid taper.

So, how do we talk about continued lack of benefit with our patients? I think first and foremost, we want to preserve that trust, so we want to stress how much you believe and empathize with the patient's pain severity, and its impact on the patient's life. It's okay to express frustration about the lack of a good pill to fix it.

We want to focus on the patient's strengths, so recognizing in ways that are specific to the patient all of the excellent ways that we can have a growth mindset, and then encourage therapies for how to cope with pain, rather than erase it. Show continued commitment to caring about the patient and the patient's pain, even without the opioids, and schedule very close follow-ups during and after a taper.

When we're discontinuing opioids, we must remember that you're not abandoning the patient, you are abandoning the opioid. You don't have to prove addiction or diversion, only to assess and reassess that risk to benefit ratio that we keep describing. And if the patient is unable to take opioids safely or is non-adherent with monitoring, then discontinuing opioids is appropriate, even if the patient is deriving benefit.

You need to determine how urgent that discontinuation should be, based on the severity of the risks and the harms, and always, always document your rationale for discontinuing opioids, and determine if the opioid needs to be tapered due to physical dependence.

So, there are risks associated with discontinuation of opioids, and we should recognize that tapering, or discontinuing should not be considered a harm reduction strategy for patients who are receiving stable, long-term opioid therapy without evidence of misuse. We worry about this in patients who are not doing well. There are risks of discontinuation. Observational studies have identified harms, namely suicide and overdose, associated with opioid tapering and discontinuation. In a comparative effectiveness study of almost 200,000 individuals that were on stable, long-term opioid therapy, they found that opioid tapering was associated with a small, absolute increase in opioid overdose or suicide, compared with maintaining their stable opioid dosages.

So, harkening back to that risk-benefit framework, we want to consider in a way that is individualized to the patient, the benefits in terms of their pain, function, quality of life or maybe the absence of those benefits against the risks and harm, such as misuse, addiction, overdose, or just the adverse side effects of the drug.

It can be very useful to avoid the pitfalls that I'm sure we've all seen. The patient describes, "I really, really need the opioids," or "Don't you trust me? I thought we had a good relationship. I thought you cared about me." The ultimatum, "If you don't give them to me, I will drink or use drugs or hurt myself," and the bargaining: "Can you just give me enough to find a new doctor?" And our response needs to be a careful and considered mantra, "I cannot continue to prescribe a medication that is not helping you or is hurting you or both."

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 non-opioid pain treatments, including cognitive behavioral therapy, Michelle keeps on insisting that she needs a higher oxycodone dose.

[Music Plays]

Dr. Alford: Oh, Michelle, so it seems that we're not going to agree on the treatment plan moving forward, and I want to make sure you know and understand why I'm suggesting this change. So, can you tell me in your own words why I'm suggesting that you taper your oxycodone, and that we try other treatments for your pain?

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

Dr. Alford: 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 not with opioids.

[Music Plays]

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 plan, including oxycodone for her painful diabetic neuropathy and chronic hip pain for 11 months, but then she started to struggle and became frustrated with the rules and stigma of taking opioids.

[Music Plays]

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

Michelle Jones: This is she. Hi, Dr. Alford, thank you so much for returning my call. The pharmacy won't refill my prescription! They said they can't put it through my insurance. There's new rules or something, I guess. The company just refuses to pay, even though I've been on these meds for a while. I told the pharmacy that I'd pay cash, but they refuse to give it to me.

I'm just so sick of this. Everyone treats me like a criminal, or like I'm a suspect or something, just because I need these meds, even my husband is looking at me funny. I hate being put through the ringer by people in your office. I mean, come on, drug tests? Dr. Robertson never made me do that. These things are ruining my life. I tried just stopping on my own, but oh, my God, I got so sick. I just want to get off them.

Dr. Alford: Well, Michelle, unfortunately, your experience is actually not that uncommon, and I completely understand your frustration, and the insurance company rules don't seem to help at all, and I'm not surprised that you felt sick when you stopped taking the medications, because remember your body is used to these medications, and so they need to be tapered slowly. So, let's talk about how we can taper you off, safely, to minimize any discomfort, and then we'll try you on other treatments for your pain.

[Music Plays]

John Emery: Dr. Bial, what can you tell us about the stigma that Michelle is experiencing, and how do you taper someone off opioids?

Dr. Bial: Yeah. Stigma in the setting of chronic pain and opioid use is a very real problem. And so, stigma is being discredited or undesirable because of an attribute. It's common among people with chronic pain. Individuals who experience pain with less clear pathology certainly report greater feelings of stigma.

Stigma internalized by individuals with pain contributes to poorer pain-related outcomes. There is a known positive correlation between stigma and pain intensity, as well as disability and depression. Patients might believe that they deserve their pain, that they're being punished, and do not deserve to be included in social activities. Opioid-related stigma includes fears about anticipated negative attitudes and judgments from others.

So, in this case, we've made the decision to taper opioids, and when we are tapering opioids, we should remember that there's no validated protocol in patients on opioids for chronic pain. There is very low-quality evidence that suggests several types of opioid tapers might be effective, and that pain, function, and quality of life may improve for some patients with decreased opioid dose.

One study found that 62 percent of patients in a pain clinic who completed a voluntary, patient-centered opioid taper over four months with a greater than 50 percent dose reduction, that neither pain intensity, nor pain interference increased with opioid reduction, and that success was not predicted by starting dose, baseline pain intensity, the number of years prescribed opioids, or any psychosocial variable. Another study of over 100,000 patients on long-term opioids found that annual tapering increased and was more likely in women and those on higher opioid doses. Nineteen percent of those patients had a maximum dose reduction rate exceeding 10 percent per week.

So, to think about a general approach to opioid tapering, you want to set first your speed and your goals. So, if the patient is merely having a lack of benefit, but doesn't have any immediate risk of harm, you could taper slowly over weeks to months, or even a longer period of time. But if there's an apparent harm, or apparent risk, you want to taper more rapidly, days to weeks. And while you are doing that, simultaneously build up alternative pain treatments as short-term withdrawal can lead to transitory increases in pain flares. And I think it's important to educate patients about that.

The first step, then, is to reduce the medication dose, so get the patient down on whatever their current formulation is to the smallest available dosage unit, and then, you might want to increase the amount of time between doses or convert to an immediate-release opioid when you're at the lowest ER available dose. You can also prescribe alpha-2 adrenergic agonists, so things like clonidine to treat withdrawal symptoms.

This is consistent with the CDC Recommendations, which generally you want to decrease the patient's opioid dose by 10 percent per month if they've been on opioids for years, or a decrease as quickly as 10 percent per week, if they've been on opioids for weeks to months. An excellent patient-centered approach to opioid tapering can be found at www.scopeofpain.org.

John Emery: Over six months, Michelle successfully tapered off the oxycodone. Her neuropathic pain was moderately controlled on accommodation of acetaminophen, nortriptyline, gabapentin and capsaicin cream. Michelle joined a monthly chronic pain support group. Her individual PEG scores remain between 4 and 5 on the 10-point scale. She remained employed and remained adherent with treatment and monitoring. She continued with her regularly scheduled follow-up visits.

In the final scenario, we return to Michelle doing well on her pain treatment plan, including oxycodone for her painful diabetic neuropathy, and chronic hip pain for 11 months. But then she started exhibiting some worrisome opioid-taking behavior.

[Music Plays]

Dr. Alford: Michelle, your most recent urine drug test didn't have any oxycodone in it. Did you run out early? Can you tell me about it?

Michelle Jones: I have no idea why the results would come back that way. I've been taking them exactly like you told me to, and I never would give my pain pills to anyone else.

Dr. Alford: Well, unfortunately, I'm not able to do what I normally do, which is a confirmatory test to verify it, but I do want to tell you that I'm worried, and that this is not the first concern I have. Remember that the last couple of appointments, you were supposed to bring in your pill bottles, so I could do a pill count, and you told me you forgot them.

So, as we discussed early on, this puts you at greater risk for harm from these potentially very dangerous medications. And so, I'm going to need to monitor your more closely, including doing urine drug tests more frequently.

[Music Plays]

John Emery: Dr. Alford, how do you talk to patients who you are worried may be diverting some of their opioid pain medications?

Dr. Alford: Well, remember that prescription drug diversion is one form of opioid misuse, and is really defined as either giving, selling, or trading prescription medications, and as we alluded to earlier in the course, surveys indicate that family and friends are the most common source of diverted opioids. So, you want to discuss why you're concerned about diversion. Was it that the patient's drug test was negative for the prescribed opioid, or maybe they're not adherent with pill counts. And then you need to discuss your inability to continue to prescribe opioids if the opioids are being diverted to others.

John Emery: There were no additional unexpected test results. But then, 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 been fired from her job for missing too many deadlines, and that she once fell asleep with a stove burner on. He acknowledges that he has been rationalizing, assuming that it was due to pain, and not the medications.

He reports hearing a staff person in the ED refer to Michelle as an "addict," and a "drug abuser," and is upset by this characterization. Dr. Alford, is Michelle a quote "drug abuser" unquote, and how would your treatment plan change after her opioid overdose, and with this added history that she has been experiencing other negative consequences related to her opioids?

Dr. Alford: Let me start with, "words matter," that is, we should avoid stigmatizing language, and we should opt for non-stigmatizing language. So, let me give you some clearcut examples. So, as opposed to saying someone's an "addict," or a "substance abuser," or an "alcoholic," we should really be talking about a person with a "substance use disorder." As opposed to saying, "substance abuse," we should say, "substance use." Instead of saying the person had a "clean urine," we should say they had an "expected test result," or that the patient is "clean," we should say the patient has a "substance use disorder in remission," or that the patient had a "dirty urine," now we should say that they had an "unexpected test result," and we shouldn't be calling patients "dirty." We should say they have an "active substance use," if they're actively using.

Now, patients may use this stigmatizing language, but we should not. Stigma surrounding substance use disorder is perpetuated by the stigmatizing terminology used in healthcare settings, by the news, and other media, and by society as a whole.

So, in terms of someone who's had an overdose, there are treatment gaps, and a colleague of mine, Marc Larochelle, has done two studies that I think are important to talk about. The first one was that opioids were dispensed to 91 percent of patients after a non-fatal overdose, and that there was a 7 percent repeat overdose after that initial overdose. And at two years, the cumulative incidence of repeated overdoses was 17 percent for patients on high opioid dosages after that index overdose.

So, while you would ask, "Why is the patient still on an opioid?" Maybe there was miscommunication, or a lack of communication, and that the prescriber was not aware of the overdose, but if someone is going to be continued on an opioid after an overdose, it's a very high-risk proposition.

The other study showed that less than a third of opioid overdose survivors received the standard of care treatment, that is, medications for opioid use disorder, or MOUD in the subsequent 12 months. Why is this important? Because receipt of MOUD was associated with decreased all-cause and opioid-related mortality.

So, let's just talk a little bit more about opioid use disorder. We did talk about the DSM-5 criteria, but really, what we're talking about is a chronic, relapsing brain disorder that's characterized by compulsive use despite negative consequences that involves changes to the brain, involving that reward pathway, changes involved in the stress and self-control pathways, changes that persist after stopping the drug. Like other chronic diseases, OUD often involves cycles of relapse and remission, and without treatment, OUD is progressive and could result in disability or premature death.

The good news is we have highly effective medications for OUD or MOUD. These medications can normalize brain changes; they can alleviate the physical withdrawal. They provide something called "opioid blockade," that is if the person uses an illicit opioid on top of this medication, they won't get euphoric, and it alleviates the drug craving, or the urge to use. And our choices include methadone, however, remember when we talk about methadone for treating OUD, we're talking about methadone that's dispensed in a licensed program only. It is illegal for you to prescribe methadone for the treatment of OUD outside of one of these licensed programs.

A second choice would be naltrexone, the opioid antagonist. It comes in an oral form, but also monthly intramuscular injections. And then, finally, buprenorphine, which used to require a training

requirement, but no longer does. Anyone can prescribe buprenorphine for treating OUD now. It comes in submucosal preparations, and weekly and monthly subcutaneous injections.

And the outcomes that we have seen with these medications include increased treatment retention and employment, decreased relapse, decreased HIV and hepatitis C seroconversion, and decreased mortality, specifically for methadone and buprenorphine. And this making medications for OUD available is highlighted in Recommendation 12 of the CDC Guideline.

John Emery: Dr. Alford continues the buprenorphine started in the ED with doses at three times per day rather than once per day in order to treat both her chronic pain and OUD. Months later, because of Michelle's hip pain from her end-stage osteoarthritis is affecting her quality of life. She is scheduled for a right hip arthroplasty. Dr. Alford, now that Michelle is taking buprenorphine, how should her surgical pain and OUD be managed perioperatively?

Dr. Alford: So, that's one of the most common questions that I get asked as an addiction specialist, and the good news is there's growing consensus on how to manage perioperative pain in patients taking medications for OUD or MOUD. And the best available evidence suggests that patients with OUD are often more sensitive to painful stimuli, that is they're more sensitive to pain, and that we should continue their methadone or buprenorphine throughout the perioperative period, that we should treat their pain with analgesics on top of the patient's daily MOUD, and that patients taking MOUD may, actually, need higher doses of opioid analgesics. Finally, we know that ineffective pain management can result in disengagement in care, which is something we obviously want to avoid.

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 taken three times per day, 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 in Part Two of this program?

Dr. Alford: So, in summary, we should employ universal precautions, but individualized care based on that patient's risk, continue or modify opioid treatment, based on clinical indication and response, optimize our office systems to involve the entire healthcare team, including community pharmacists, document benefits, risks, and harms, and the rationale for our plan of care. That worrisome opioid-taking behavior can signify pain-relief or substance-seeking behaviors, or a combination of both, and that decisions to continue, modify, or discontinue opioids should be based on risks and benefits, and should be well-documented. And finally, offer medications for OUD for patients with OUD, and continue maintenance methadone or buprenorphine during the perioperative period.

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

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