# SCOPE of PAIN: Safer/Effective Opioid Prescribing Education

Podcast - October 1, 2023

## Episode 4

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**Ilana Hardesty:** Thanks for listening to Boston University Chobanian & Avedisian School of Medicine's Safer and Competent Opioid Prescribing Education: *SCOPE of Pain* Podcast Series. I'm Ilana Hardesty.

This series has eight episodes. If at any point you want more information on receiving credit, please visit our website, scopeofpain.org. There are also resources that accompany this series. All of it can be found at scopeofpain.org.

In this episode, we'll speak again with Dr. Daniel Alford and Dr. Erica Bial. And we'll bring back Kristin Wason, a primary care nurse, and Don, a patient on long term opioid therapy for chronic pain.

Last time we talked in general about the risks associated with opioids. But now it's decision time for our case study Michelle's new clinician. How do you decide whether to continue prescribing opioids for a new patient with chronic pain who's already on short acting opioids, like Michelle?

**Dr. Daniel Alford:** Great question. And I would say when pain is severe; when pain has a significant impact on function and quality of life; and also when the patient has a specific pain type that I think will likely respond to opioids, because we know that not all chronic pain is opioid responsive. For example, fibromyalgia and migraine headaches, not so much. They don't really respond to opioids very well, but certainly chronic pain related to musculoskeletal issues and neuropathic issues can be opioid responsive. In a patient like the one we presented. I'd like to know if they've been tried on non-opioid modalities and how did they work and were they ineffective? And finally, again, for a patient like the one we've described, is there any documented benefit on her current opioids?

So let me just put opioids and chronic pain in perspective. And the first thing I just want to emphasize is that the efficacy of long-term opioid therapy for chronic pain has been inadequately studied. That's the bottom line. And therefore, opioid prescribing needs to be more judicious because we need to remember that opioid misuse can be fatal, including overdose and opioid use disorder; and that opioids for chronic pain are really only indicated after alternative safer options have been found inadequate. And remember that they're only one tool of a multimodal approach for managing severe chronic pain. This is consistent with the CDC guideline, which again, maximize non-pharmacological therapies and non-opioids before considering opioids and only consider opioids if you expect that the benefits, namely pain and functional improvement, outweigh the risks. And before starting opioids, we need to make sure we discuss realistic benefits and known risks. And really, it's important to establish treatment goals and how opioids will be discontinued if the benefits

no longer outweigh the risks. So this is a good time to hear from our patient, Don. Don, how do you conceptualize the risks and benefits of opioid therapy?

**Don (Patient):** It's a diagram of a couch with a semicircle on the wall behind it with a sort of old-fashioned elevator dial pointer. If the pointer is going straight up to the highest point on the semicircle, I would call that sort of the sweet spot for pain medication prescribing its maximum time off the couch. If you go to the left, there's no prescription. You're on the couch because of pain. If you go all the way to the right, then you're taking so much pain medication that you're not getting off the couch. And that's not useful either. And I think that's probably when going into long-term opioid treatment, it should be made really clear to the patient that getting rid of all of their pain is not a realistic expectation. I guess I've become something of an apostle of good enough.

**Ilana Hardesty:** Dr. Bial, how would you assess Michelle for her misuse risk prior to writing any prescription?

**Dr. Erica Bial:** So as we're talking about our specific case and we're talking about a conversation with the patient about the risks of starting opioids, we should also, before prescribing, assess a patient for those misuse risks so that we can have a strong sense going in to this: What are the concerns that we might have in a way that's tailored specifically to our patient? So we use a number of tools for assessing opioid misuse risk. Urine drug testing, right? We should get a urine drug screen before prescribing. We should check a urine drug test to confirm the patient's substance use history. Prescription drug monitoring programs so we can query our particular state's or our region's PDMP to confirm medication and prescriber history. Again, one of many useful data points. One tool in the box that is underutilized is old medical records. So we should, when they're available, review the prior records from the patient's prior prescribers or other providers. And if you can, talk to the prior clinician, those conversations really give us a stronger sense of what's really going on with our patients. So we also have available a number of screening tools. Now there's no gold standard and there's a lack of evidence for the use of these tools, but they might be useful. And of course, using a tool carries no risk at all. So things like the Opioid Risk Tool, the SOAPP (the Screener and Opioid Assessment for Patients with Pain), are a few of the available instruments that we might use to have a standardized way of trying to help screen our patients for opioid misuse risk.

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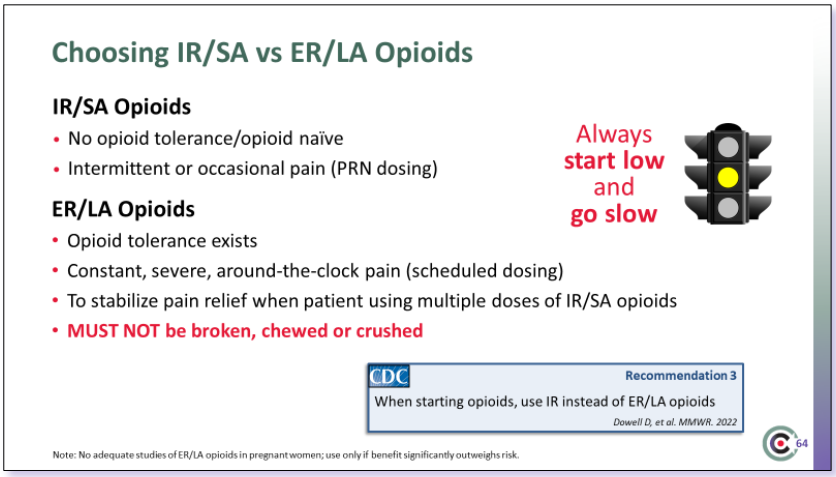
**Ilana Hardesty:** As we return to our clinical case. Keep in mind that Michel came in asking for an opioid prescription today. The state prescription drug monitoring program confirmed that she has been getting oxycodone from only one doctor and one pharmacy, and it was last filled seven weeks ago. The PCP arranges for a follow up appointment in two weeks, prescribes a two-week course of oxycodone ten milligrams, four times per day, and has Michelle leave a urine sample for a drug test. Michelle's problem and medication lists are reconciled, and the PCP reviews her records from her previous doctor. 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.

After the first visit, the new PCP was unable to contact Michelle's previous PCP. Her urine drug test returned positive for oxycodone only, as expected. On her follow up visit two weeks later, Michelle reports a six out of ten on each of the three PEG scales, but notes that her pain is sometimes a nine out of ten immediately before her next oxycodone dose. She denies sedation and she completed her two-week oxycodone prescription on schedule.

Based on this history, should the provider make any changes to Michelle's opioid prescription? Should she be changed to a long acting opioid to avoid the increase in pain she's experiencing before her next dose?

**Dr. Daniel Alford:** So it's important to think about our opioid choices in two buckets: the immediate release/short acting opioids and the extended release/long acting opioids. They're essentially the same molecules. It's just how they are formulated. We're talking about morphine, hydrocodone and hydromorphone. And in one formulation, they're immediate release and another formulation, they're long acting. So I think we need to decide whether the patient would benefit from short acting or long acting.

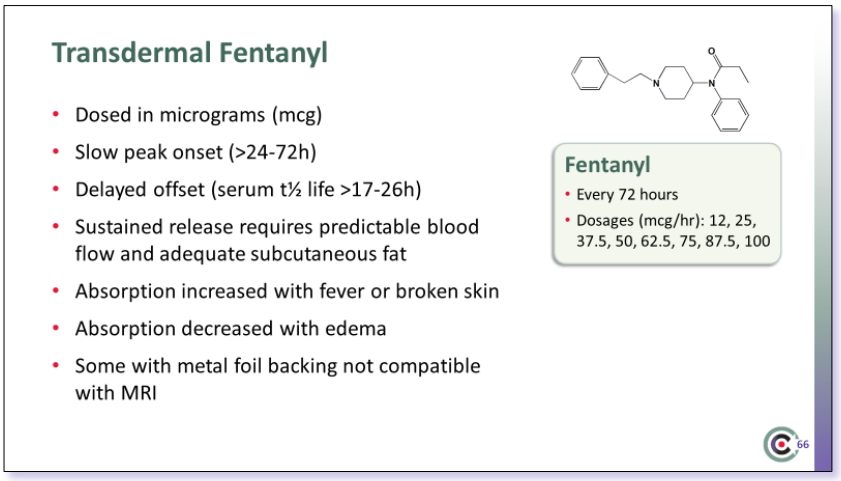



So how do we make those choices? Well, I think about short acting or immediate release opioids in a patient who has no opioid tolerance; that is, they're opioid-naive. And if their pain history tells me that their pain is intermittent or occasional, so they don't need around the clock scheduled pain relief. I would think about extended release/long acting opioids in somebody who already has some opioid tolerance, they are no longer opioid-naïve; that their pain history is telling me that their pain is constant, severe and around the clock, so they would benefit from scheduled dosing. Or if a patient has pain in a way that I want to try to stabilize it by preventing them from needing to use multiple doses of short acting opioids during the day, similar to our patient that we're describing here. It's really important to emphasize at this point that when you prescribe extended release/long acting opioids, our patients must understand that they should not break, chew, or crush these tablets because the long acting nature of these medications is dependent upon an intact tablet. Regardless of whether you use short acting or long acting opioids, it's important to remember to always start low and go slow. Now that may seem pretty simplistic. However, if you think about it, some of our patients are really in a hurry to feel better, and they are in a hurry to increase their dose to feel better. But we need to do it slowly to make sure that they're able to take the medications safely and that we titrate it in a safe way. I will mention that the CDC guideline, one of their recommendations, talks about when you start opioids, always start with an immediate release opioid as opposed to a long acting opioid. Again, that speaks to the never starting a long acting opioid in someone who is opioid-naive.

I think now it's important to talk about what are the uncertainties about using short acting versus long acting. And first of all, there's insufficient evidence to determine whether long acting opioids are more effective or safer than short acting opioids. And there's even debate about whether the bolus dosing of short acting opioids versus the continuous exposure of long acting opioids is more likely to result in things like opioid analgesic tolerance or hyperalgesia, which we'll talk more about, which is kind of an increased pain sensitivity, or addiction. So what do you do? You need to individualize your treatment. That is, to choose the options that best meet your patient's need based on your pain assessment and the risk profile of that particular patient.

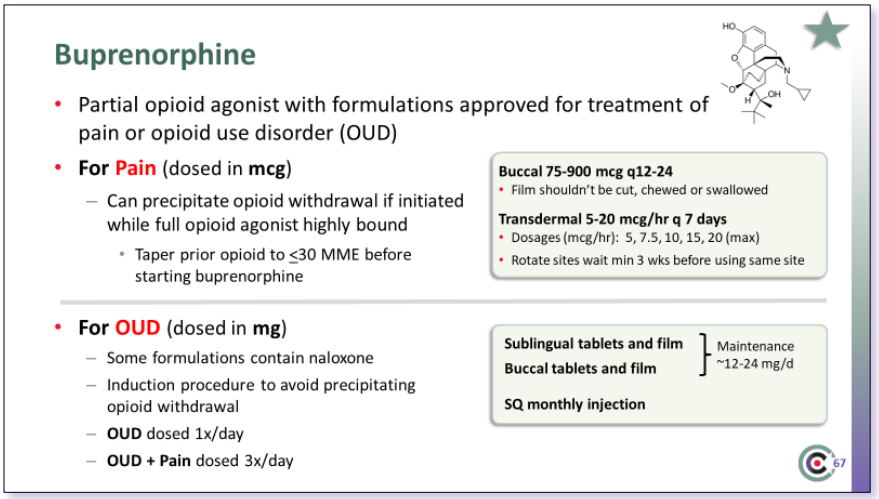
**Dr. Erica Bial:** Yeah, as you're talking about that, I think it's important, of course, that when we start, we want to start low, go slow and always start short acting. But there are some particularly long acting agents that I think are really worthy of conversation.

So the first would be talking about transdermal fentanyl. So fentanyl is an opioid that's getting a lot of press right now in its immediate release format. But we do find that it has a lot of utility in certain circumstances in its long acting format. so transdermally delivered. Remember that fentanyl is dosed in micrograms, an incredibly potent substance. When we're dosing it transdermally, the way that it works is through development of a depot underneath the skin, so in the subcutaneous fat, and so there's a slow peak onset – 24 to 72 hours after a patient applies the fentanyl patch – before they start to achieve a steady state. Similarly, there's a delayed offset, so removal of the patch, the medication will take some time to wear off. The serum half-life is between 17 and 26 hours. So, as I mentioned, because transdermal patches work by forming that subcutaneous fat depot, the medication, sustained release will require predictable blood flow and adequate subcutaneous fat in the region where the patch is applied. So, if your patient is very, very thin and you've applied a transdermal fentanyl patch and they don't seem to be achieving any analgesia, even though it's been enough time and it's properly applied, remember that they might not be adequately absorbing it. Similarly, absorption is increased if there's fever or broken skin and decreased with edema. So conditions that might influence blood flow to and from the area where that subcutaneous fat depot of the medication exists. It's also just a little side tip to remember that some fentanyl patches might have a metal foil backing and it could be incompatible with an MRI. If you choose to use a fentanyl patch, usually it's dosed every 72 hours that the patch would need to be changed.



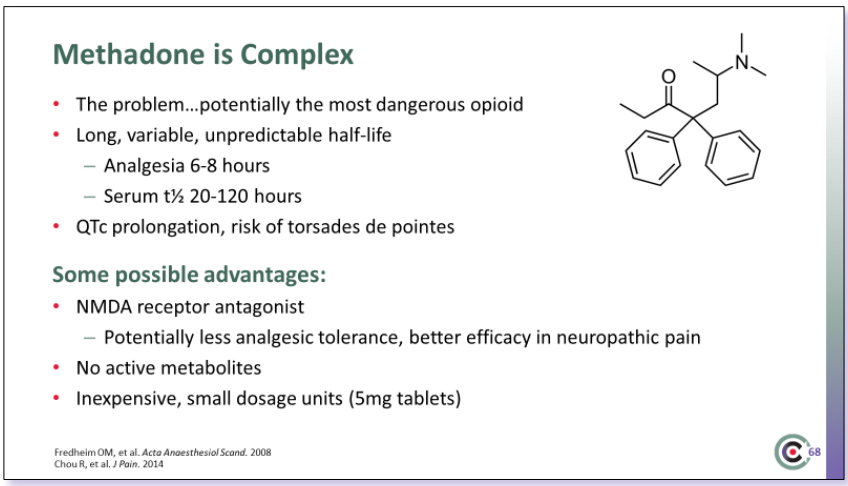

Also, there exists buprenorphine. It's important to remember when we talk about buprenorphine that it is a partial agonist. So it does have formulations, and these are the

immediate release formulations, that are approved for the treatment of pain or opioid use disorder. So when we dose buprenorphine for pain, we dose it in micrograms. So this is available as a transbuccal film or in a long acting format as a transdermal formulation. This can precipitate opioid withdrawal because it is that partial agonist. So if it's initiated while full opioid agonist is highly bound to the patient's mu receptors, the buprenorphine can come along, knock it off the receptor and only provide partial receptor stimulation. So you need to taper prior opioid to fewer than 30 MMEs before starting buprenorphine. In the transdermal patch, there's a very, very broad dose range which can be useful; it gives the clinician a lot of flexibility. But it can be irritating to the skin, so it's important – this is a seven-day patch usually – that we need to rotate sites, and the patient will need to wait a minimum of three weeks before using the same site again to avoid those reactions.




Now, in contrast, when we use buprenorphine for opioid use disorder, we're dosing it in milligrams. Some formulations will contain some sequestered naloxone. And again, there's the importance of an induction procedure to avoid precipitating opioid withdrawal. When we prescribe buprenorphine in opioid use disorder, it's dosed once daily. But remember that when you are treating both conditions – so patients might present both with an opioid use disorder and a painful disease – that you want to dose it three times a day. Interestingly, and more newly developed, buprenorphine is also available as a subcutaneous monthly injection when it's used for OUD.

So methadone, another one of these medications that we think of, particularly in chronic pain, is a really complex molecule. I have never once taken a board exam and not been asked this question. And so I want to take a quick sec and advertise the right answer, which is: the problem with methadone is it's incredibly useful, but it can be the most dangerous opioid. And the reason is – this is the commonly tested question – it causes QTc prolongation, and so it includes a risk of torsades de pointes. So it has a long variable and very unpredictable half-life. Similarly, the analgesia is actually kind of short. So usually when



we're dosing methadone for chronic pain, this is a TID medication. Analgesic half-life of the medication is 6 to 8 hours, but the serum half-life is somewhere between 20 and 120 hours. So highly variable.

But it has some possible advantages, and this is something that is rarely tested but I think is cool to know, it is an NMDA receptor antagonist and so it might yield less analgesic tolerance and better efficacy, particularly in neuropathic pain. It might carry a lower risk of development of opioid induced hyperalgesia, and it has no active metabolites. It's also convenient for dosing. So it's available in some very small dosage units, only five mg tablets. so you get the ability to really kind of dial up and down your dose; and it's inexpensive, making it more readily accessible to many patients.

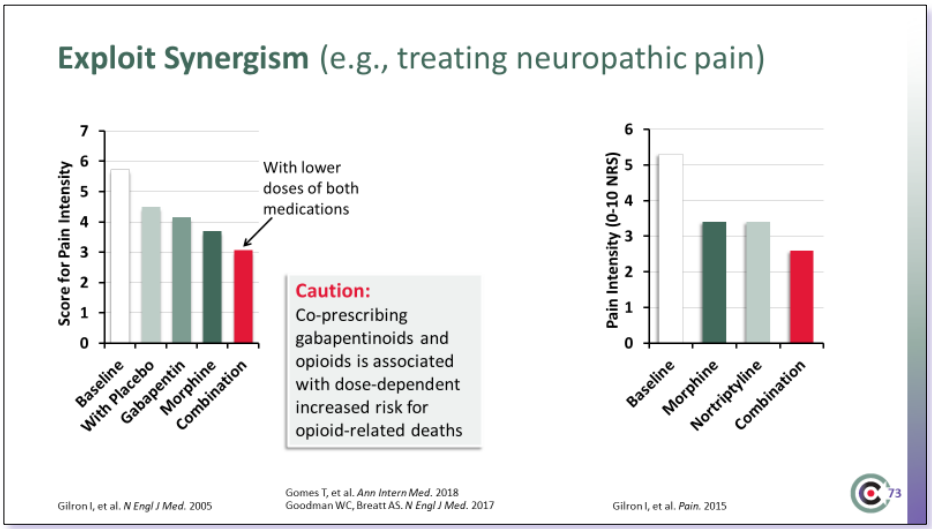
Let's also take a moment and talk about dual mechanism opioids. And some people are surprised to hear that we include these in a conversation about opioids. But these two substances do in fact bind the mu receptor. So we're talking about tramadol and tapentadol. And these are dual mechanism opioids. They also yield norepinephrine and serotonin reuptake inhibition and as a result they carry seizure risk as well as risk of physical dependence, as well as a risk of serotonin syndrome. So when you get that phone call from the pharmacist, when you've prescribe tramadol in a patient who's also on another serotonergic medication, thank the pharmacist for calling and alerting you to that risk of serotonin syndrome and an increased risk of seizure. These are, in fact, controlled substances and they do carry addiction potential. They're subtly different. So tramadol is a weak new opioid receptor agonist. It has a minimal norepinephrinergic effect, but a very prominent serotonergic effect. In contrast, tapentadol is a stronger mu receptor agonist. It has a more prominent norepinephrine effect and a more minimal serotonin effect.

**Ilana Hardesty:** What about the newer abuse resistant opioids? How do they work?

**Dr. Daniel Alford:** So in response to the problem with extended release oxycodone, where people weren't taking it as prescribed; crushing it, they were sniffing it. And that was causing the extended release oxycodone to turn into a short acting oxycodone with a lot of milligrams in that tablet. So what the pharmaceutical companies have done is to create barriers to the crushing or use or misuse of the opioid in that way. So, they've created physical barriers. That is, you cannot crush the tablet or if you do crush it, it turns into a gel. But they've also done creative things like put in a sequestered antagonist; that is, if you don't take it as prescribed, there is an antagonist which might cause withdrawal. They've also put in some aversive components. If you, again, take it incorrectly, you might get some flushing or some other kind of aversive reaction. They've created pro-drugs. So again, if you don't take it as prescribed, you don't get the medication and so forth. Now, we do know from surveillance studies that there is a decrease in diversion and street price of these medications. So, there is some effect in that regard. But even though they can't be altered, it doesn't prevent people from taking too many of the intact tablets, which can be problematic. And they tend to be expensive and some insurers don't cover them. So I think probably the take home message here is that currently there are no 100% proven misuse resistant opioids. So regardless of whether or not you use one of these formulations, you still need to do it cautiously and monitor the patient for safety.

**Ilana Hardesty:** Are there other things to consider when you're thinking about prescribing an opioid?

**Dr. Erica Bial:** I think so. I mean, I think that probably one of the most important things that we can do as health care providers is to think creatively and tailor our treatment approach to the multiple points of potential intervention when we have a patient before us with pain. And we want to think about rational polypharmacy. There are multiple mechanisms-specific treatment targets that we could consider. So rather than monotherapy, imagining all of the points along the pain pathway that we could potentially intervene. So we think about in situations of peripheral nervous system sensitization: so we can intervene with non-steroidal anti-inflammatory medications, tricyclic antidepressants, lidocaine affecting the sodium channels as well as the opioids. We want to also think about intervention at the level of the spinal cord: so modulating central sensitization, our targets here might be the calcium channels or the NMDA receptor. So again, substances like tricyclic antidepressants, the gabapentinoids, as well as the opioids might all have an impact here. And also considering ways in which we can enhance descending inhibition from the brain. So again, use of the tricyclic antidepressants, the SNRIs, as well as medications like tramadol and the opioids, might all play a role in helping us to have a rational polypharmacy approach in addressing the patient's pain at multiple points in the pain pathway.




Additionally, we want to exploit synergism. So a convenient example comes from the treatment of neuropathic pain. And we know, just like when we treat many other diseases, that if we use lower doses of multiple substances addressing the symptom at multiple target points, we might achieve a greater outcome with fewer risks. So for example, there was a study where they evaluated a patient's pain against baseline and against placebo with treatment with gabapentin alone, morphine alone, or with a lower dose combination of both medications. And they found that patients who were receiving combination therapy, even though the doses of the individual substances were lower, that they had greater impacts on scores of their pain intensity. So just a word of caution: that co prescribing gabapentinoids and opioids may be associated with a dose-dependent increased risk, however, for opioid-related death. So on the one hand, we want to respect the risk of using these multiple substances, but also be aware that we may be able to get an equal treatment benefit but with lower doses of either medication.

**Ilana Hardesty:** We've talked a lot about many different opioids in this episode. What's your take away?

**Dr. Daniel Alford:** Some of the things we talked about is to consider the duration and onset of action based on the patient's pain history or the pattern of their pain. Is there pain intermittent? And I might think about a short acting opioid. Or is it constant and around the clock? And I might consider a long acting opioid if they're no longer opioid-naïve. I'm also going to consider the patient's prior experience. Remember, we talked about all of the mu opioid receptor polymorphisms and the differences in how our patients metabolize opioids. So I really want to know, what have they experienced in the past? Have they been on an opioid and how did it work, both in terms of benefits as well as side effects? Again, I want to think about the patient's level of opioid tolerance. I'm always going to assess that before considering a long acting opioid formulation. And I also want to consider other medications they're taking, their age, and other disease, comorbidities. Consider the route of administration. Maybe a patient would benefit from the transdermal formulation as opposed to taking a pill. And then finally, really importantly, is the cost and insurance issue. So is this medication going to be covered by this patient's insurance, or am I going to need to do a prior authorization? So those are some of the things to consider.

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**Ilana Hardesty:** Thank you, Dr. Alford, Dr. Bial, and Don, our patient. The PCP decides to continue Michelle's opioid therapy for her chronic pain, but changes her regimen. Since she tolerates short acting oxycodone, but has significant worsening pain before her next dose, her pain may improve with more stable blood levels, even at a lower overall daily dose. He prescribes extended release oxycodone 15 milligrams two times a day, which is a lower overall opioid dose equal to 45 morphine milligram equivalents or MME instead of the 60 MME she was on. He continues the acetaminophen and gabapentin. Note that the provider did not assume that Michelle would need medication for breakthrough pain when he switched her to long acting opioids. And before ending the appointment, they discussed strategies for weight loss, improved sleep and stress management, and he refers Michelle to physical therapy for her hip pain. The PCP reviews a patient provider agreement with Michelle and they sign it. Over the ensuing months, Michelle reports improved pain control, allowing her to be more active.

How should patients prescribed opioids for chronic pain be monitored? Should we apply these monitoring strategies to all patients or just focus on those who are high risk? That's in our next episode.

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I'm Ilana Hardesty. Thanks for listening.