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| Faculty members have no relevant commercial relationships to disclose. This presentation does include discussion of the off-label use of clonidine and tizanidine to treat opioid withdrawal symptoms. Clonidine and traindine are not IPCD approved for this use. | 2 |

Hi, this is Dr. Daniel Alford from Boston University School of Medicine and Boston Medical Center, and I'm going to be speaking to you today about a patient-centered approach to opioid tapering.



Our online includes, first, talking about some important definitions, then when to consider an opioid taper, discussing taper with patients, talking about legal and language considerations, talking specifically about withdrawal and management of withdrawal, and then getting into some tapering regimens.



So, let's start with important definitions.



When patients are taking opioids, we need to understand the difference between 'tolerance' and 'physical dependence'. Both tolerance and physical dependence are physiologic adaptations to being chronically on opioids. Remember that tolerance means that you require an increased dose to produce a specific effect. We know that tolerance develops readily for CNS and respiratory depression, less so for constipation, and in terms of tolerance to analgesia, it's a bit controversial in terms of whether or not it exists, but it seems to for some patients and not others. Physical dependence includes signs and symptoms of withdrawal with abrupt opioid discontinuation or cessation, rapid opioid dose reduction, or the administration of an opioid antagonist, resulting in withdrawal symptoms.



Now, let's talk about opioid use disorder based on the DSM-V criteria. You'll see that there are a list of symptoms here, including tolerance and withdrawal. Now, since moving from the DSM-IV to DSM-V, there was an appreciation that if patients are prescribed opioids for pain that they will have tolerance and withdrawal -- that is, physical dependence -- so, those should not be considered part of the diagnosis of an opioid use disorder if someone is taking an opioid as prescribed. But when you look at some of the other symptoms, such as use in larger amounts or duration than intended, a persistent desire to cut down, giving up other interests to use opioids, a great deal of time spent obtaining, using, and recovering from other opioids, and other symptoms, you'll see that some of these may be related to pain and not necessarily an opioid use disorder. That is, there are certainly some patients who are on opioids for longer amounts of time than intended, but every time they come off their opioids, their pain gets worse, or they have this persistent desire to come off the opioids, but again, when they try to do so, their pain gets worse. Some patients spend a lot of time trying to find someone willing to prescribe an opioid for their pain. So, although these are the criteria for an opioid use disorder, it can sometimes be tricky in patients who are on opioids for chronic pain. The other thing to note is that the DSM-V categorizes a 'mild' opioid use disorder in individuals that have two to three criteria, a 'moderate' disorder in people with four to five criteria, and a 'severe' opioid use disorder in individuals that have greater than or equal to six criteria.



The next term is 'addiction', and addiction is not a DSM-V diagnosis, but it's a term that many people use in describing a certain syndrome. As it relates to an opioid use disorder by DSM-V, we're really talking about a moderate to severe opioid use disorder, but the clinical syndrome presents as loss of control -- the patient cannot take the medication or the opioid as prescribed. They keep running out early or showing up in the emergency room. 'Compulsive use' is a preoccupation with the opioid. That is, everything else that you recommend for their pain management, they don't want to hear about it. All they want is more opioid. 'Continued use despite harm' is someone who's having negative consequences from the opioid, like falling asleep in the middle of the day, or slurring their words, or falling, and it's as opposed to what you would expect -- that is, that they would want less -- they actually want more of the opioid. And in some individuals, we'll talk about this continuous urge to take the opioid, and that would be called 'craving'. And all of these behaviors are referred to as 'aberrant medication-taking behaviors', and we're worried about not only the pattern, but the severity as well.



All right. So, now, let's talk about when to consider an opioid taper.



Certainly, you'd want to consider it if somebody is not adequately progressing towards their treatment goals, and this really relies on you having specific treatment goals agreed upon with the patient early on in the treatment plan, and those goals should be specific and measurable so that you can follow them over time.

But also, you'd consider a taper if the person has declining level of function where their pain is just increasing over time, which may be consistent with opioid-induced hyperalgesia, or this paradoxical response that some patients on chronic opioid therapy, their pain actually gets worse. There may also be the patient who has a persistent non-adherence with their treatment plan. There may be side effects or risks that outweigh the benefits of the opioid therapy. There may be some risky behaviors that are indicative or suggestive of opioid misuse -- that is, the person is taking them in a way that was not prescribed -- and it would just be unsafe to continue prescribing the opioid. You may have concerns that the person may be diverting, giving away or selling their opioid, or that they have developed an opioid use disorder or an addiction. There may be patients who are concerned about being on opioids, such as the stigma or the cost associated with them or the physical dependence that's associated with them. And then, finally, some patients on long-term opioids who are stable, and there are no worrisome behaviors, it may be worth a periodic trial of a taper just to assess whether or not they still need the opioid for their pain or not.



Now, let's talk about how to discuss taper with your patients.



The first thing is to be clear in your own mind why you think the taper is indicated. Is it because of a lack of benefit, or is it because you're worried about the person's behaviors -- that is, a loss of control, compulsive use, or continued use despite harm? Center the discussion on health concerns. This is not about whether the patient is good or bad, or whether you trust this patient. It's really about, 'is this patient's health improving on this treatment, or is it getting worse?'. Aim for the patient to understand and agree with your rationale.

Now, oftentimes patients will disagree with the plan for a taper. And why might that be? Well, it might be that they're fearful that their pain is just going to become more severe, or that they're going to go through opioid withdrawal and be uncomfortable, or that some other symptom -- maybe depression or anxiety -- will get worse off the opioid. Maybe they have psychological dependence on the opioid -- that is, in their mind, the only thing that's ever worked for them or ever helped their pain is an opioid, and they feel very attached to it

But they may also have an opioid use disorder or addiction. And again, if you suspect that they have an opioid use disorder or addiction based on loss of control, compulsive use, or continued use despite harm, make sure you refer them to a specialist -- an addiction psychiatrist or an addiction medicine specialist -- because tapering somebody with an opioid use disorder without referring them to addiction treatment can increase the risk of adverse effects. Certainly, someone could be at risk for overdose if they start to use drugs illicitly, and so forth.

| Clearly State the Reasons for the Taper | | |
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| For Example why in the interest of the patient's well being (or public health) it is not appropriate to continue | "I believe it is unsafe for you to continue because" (cite specific examples) | |
| | "I believe the opioids may be increasing your pain." (note increasing doses and increasing pain) | |
| | "We are not achieving the goals we targeted." (note goals) | |
| Avoid | "Guidelines won't let me prescribe." | |
| | "I am not allowed to prescribed these doses." (unless legally prohibited and that is in fact the only reason) | |
| | 12 | |

Clearly state the reasons for the taper, and here are some examples of language you could use. For example, "I believe it is unsafe for you to continue this opioid, because you were unable to maintain control of the use of the opioid, or you take more than has been prescribed over time." So, be specific in your examples as to why you think it's unsafe. You may say, "I believe the opioids may be increasing your pain," -- again, this whole concept of opioid-induced hyperalgesia. "We're not achieving the goals that we agreed upon, that we targeted, and although we had hoped that the opioids would help, they clearly have not, based on my observations over time."

What you want to avoid is language like, "Well, the guidelines won't let me prescribe..." because that's not actually true, or "I'm not allowed to prescribe these doses because of the DEA, or the FDA," and that's also not true either, although some states may have enacted laws or regulations that prohibit certain medications or certain doses, and so you need to be aware of those.



Now, when you're discussing the taper, remind the patient that you believe their pain is real, that you believe their self-report of how severe their pain is and their suffering, and make it clear that you're not abandoning the patient, but you are abandoning an ineffective and/or harmful treatment -- in this case, opioids. Empower the patient with tapering options when possible. So, it may be that your taper's going to be over months, and you can ask the patient to help set the timeline or schedules for a taper, and that improves their sense of self-efficacy. How much are they able to and willing to taper over the next month, or the next two months? Offer continued care, but not continued opioids. Discuss and implement alternative pain management strategies, and make sure you're treating other symptoms that may be exacerbated by being off opioids. Work towards a foundation of self-management. That is, the patient should not be 100 percent reliant upon you to make their pain better, but they need to do something around self-care, pacing their activities during the day, avoiding certain activities that may exacerbate their pain to improve their own self-management, and then include other targeted treatments as indicated.



Remember that we have a whole tool kit of various treatments to help our patients with chronic pain that are both kind of clinical care and self-care, and that our goals are not just to reduce pain, but to restore function, to improve quality of life, and to really cultivate wellbeing, and some of the options include psychobehavioral treatments, cognitive behavioral therapy, meditation, relaxation, procedural treatments including nerve blocks and steroid injections, physical therapy such as exercise, orthotics, acupuncture, and then medications, and it's obviously not just opioids. There are nonsteroidal anti-inflammatory drugs, acetaminophen, anti-convulsants, anti-depressants, and so forth.



So, now, let's talk about legal and language considerations.



What we're really talking about here is termed 'tapering' or 'weaning'. What we're not talking about is detoxification, which is really reserved for withdrawal from intoxicating drugs or medications in the context of addressing addiction, and this really requires appropriate waivers or affiliations.



So, to detox or detoxify a patient due to an opioid addiction using an opioid medication, the provider must have a DEA waiver to prescribe buprenorphine for an opioid use disorder treatment or must be affiliated with a licensed opioid treatment program -- for example, a methadone maintenance treatment program, which is state and federally licensed. To withdraw a patient from opioids prescribed for pain, including individuals that have a co-occurring addiction, you don't need a special DEA waiver, and you don't need to be affiliated with a methadone maintenance treatment program, and you really could use any opiate analgesic for that opioid analgesic taper.





There are some exceptions to the DEA waiver or license requirements around tapering. For example, a patient who's admitted to a general hospital for a diagnosis other than addiction -- maybe it's a medical diagnosis or a surgical diagnosis -- opioid withdrawal can be treated throughout the admission with any opioid, including methadone or buprenorphine. You don't need a DEA waiver. So, an opioid, including methadone or buprenorphine, can be tapered during that inpatient stay if the primary diagnosis for why that patient is in the hospital remains other than addiction. You cannot continue the opioid taper for addiction as an outpatient unless you are waivered to prescribe buprenorphine for an opioid use disorder or affiliated with a licensed methadone treatment program.

Any DEA-registered prescriber may administer, not dispense or prescribe, opioids to prevent withdrawal for three days while arranging for treatment for a patient with an opioid use disorder. Let me explain that. So, if an individual has an opioid use disorder and you're trying to get them into specialty treatment, you can arrange for an opioid to be administered for observed ingestion for three days while you're trying to get them into addiction treatment. So, you cannot write a prescription for a three-day supply, you can't dispense a three-day supply -- that is, give them three days of doses of opioids -- but you can observe them for three days taking a dose, and usually that would be in an emergency room setting.



Now, let's talk about withdrawal and management.





Acute opioid withdrawal: The onset is two to five half-lives with some variability after the last dose of the opioid if the person is physiologically dependent. So, someone who's taking an opioid that's short acting occasionally likely doesn't have physical dependence, but someone who's taking an opioid around the clock on a daily basis likely does have physical dependence. Now, the duration of withdrawal will be longer the longer the opioid half-life, so an individual on an extended-release long-acting opioid is going to have a longer duration of withdrawal. Someone who's on a short-acting immediate-release opioid is going to have a shorter duration.

The common symptoms include CNS arousal -- that's irritability, restlessness, sleeplessness, and pacing -- and also autonomic arousal, sweating, yawning, runny eyes, runny nose, diarrhea, tachycardia, hypertension, and pain. So, whatever pain they have will be worse, and they're going to have muscle aches and bone aches, and joint pain, and stomach cramping, and so forth. It can be extremely uncomfortable, and rarely, though, is it life threatening, although individuals that have gone through opioid withdrawal say that they may not die from it, but they would rather be dead because the symptoms are so severe.

Slide 21



So, how do we manage withdrawal? Well, the taper, if it's gradual, will usually avoid severe acute withdrawal. If an abrupt cessation is necessary, or if withdrawal symptoms are occurring, we need to reassure the patient that these are painful symptoms but will not be long-term harmful, we need to make sure the patient stays hydrated, and we can do symptomatic treatment as indicated. So, for the generalized sympathetic arousal, you can use an alpha-adrenergic agonist like clonidine or tizanidine to treat the withdrawal symptoms. Certainly, joint and muscle pain can be treated with nonsteroidal anti-inflammatory drugs. The diarrhea and cramping, you can use loperamide or anti-spasmodics. Insomnia can be treated with Trazodone or an antihistamine. Anxiety or sleep, certainly you could use a short-term Benzodiazepine with extreme caution, and nausea and vomiting symptoms can also be managed.





It's important to remember that there's also, beyond acute opioid withdrawal, a chronic or post-acute withdrawal syndrome, or called 'protracted withdrawal', and this is a syndrome that can persist for weeks to months, and common complaints, including sleep disturbance, fatigue, anhedonia, irritability, increased pain sensitivity. Patients need to be aware that it's possible, can last weeks to months, but it is self-limited.



What about reemergence of symptoms? So, underlying symptoms that have been attenuated by opioids may reemerge during the taper, and we need to distinguish whether or not those symptoms are due to withdrawal, which are going to be time limited, or whether or not they're going to be chronic. We need to think about alternative approaches to treating those symptoms if they are going to be chronic and persistent. Some of these are going to be short-term symptoms, and some will be longer term, including worsening pain, anxiety, depression, and sleep disturbance.



Now, let's talk about tapering regimens, the goals during taper.



We'd like to avoid or minimize withdrawal and/or rebound pain. We want to maintain patient safety, but we need to work within our system constraints. The first thing to consider is, what is the expected degree of physical dependence? How long has the person been on opioids? Are they taking them around the clock? Or is it an intermittent use, and there is unlikely any physical dependence, and therefore you wouldn't need a taper? What are the patient's preferences and goals, and the reason for the taper? So, if it's misuse and risk, the taper's going to be much more quickly than if it's lack of benefit.



So, what are the options? So, immediate discontinuation -- that is, no taper -- well, certainly, if the person is diverting and doesn't have physical dependence, you don't need to taper. You would be concerned about diversion if the person's urine drug test was negative for the medication you're prescribing or if they were non-adherent with pill counts. You would also do an immediate discontinuation without a taper if the person was high risk -- that is, high risk for an overdose or high risk for a substance use disorder, or they're unable to follow the taper schedule in a safe way. These are people who will likely need referral to specialty addiction treatment to be tapered off their opioid.

You may decide that the taper needs to be rapid using a highly structured taper over two to four weeks, and this would be someone who's high risk, but someone who's able to follow the tapering schedule in a safe way. Or you might decide that the taper can be slow -- that is, over weeks to months -- and that is someone who has lack of benefit and no risk, and there are no acute safety concerns.



It is important to appreciate that there are no validated tapering protocols or published comparisons of speed of tapering patients on long-term opioids for chronic pain, but there is a general approach, which really is more of an art than a science. Again, the speed of taper depends on your level of concern. If it's lack of benefit, you can do it over weeks to months, but if it's apparent harm or risk, you're talking about days to weeks.

The first thing you're going to do is reduce the medication dose to the smallest available dosage unit. Then, when you get to the smallest dose, you can increase the amount of time between doses, and you might end up switching from an extended-release long-acting opioid to a short-acting opioid to get to lower and lower doses. Remember that you can use an alpha-adrenergic agonist, like clonidine or Tizanidine -- that would be off-label use for both of those medications -- to treat withdrawal symptoms. Make sure you're building up alternative pain treatment modalities, as short-term withdrawal from the opioid can lead to transitory increased pain.



Now, there are many ways to taper, and here are some examples for starting points to follow.





For a relatively rapid taper -- that is, over two to four weeks -- you may taper 20 percent of the original dose every two to four days. Then, at 20 to 30 percent of the original dose, recalibrate to a smaller decremental decrease. Consider a second recalibration at the very end. This is an example of someone who's tapered over 22 to 26 days off of high-dose morphine.

Slide 30



A slower taper example -- over three to four months -- would be to taper 10 percent of the total dose per week to start, then recalibrate to smaller decrements once you're at about 20 to 30 percent of the original dose. Consider a second recalibration at the very end. And here again, we give you an example of how you might do that.





So, now, let's talk about what are the endpoints of your taper. A complete taper is your endpoint only if you're worried about the risks of major opioid-associated harm. Other tapers are really trials, and it's not a failure if you don't taper the person completely off opioids if the elective trial of a taper off opioids increases the person's pain and they're unable to tolerate it, or maybe you've completed the taper and the patient states that their pain is worse than it was while they were on opioids, and therefore, it might be indicated to restart the opioid at a lower dose.

Sometimes I'll ask the patient, when they've been tapered off the opioid, "Is your pain better, worse, or the same?" And clearly, if it's better or the same, then we've made some progress, because they're no longer on an opioid and their pain is either better or unchanged, but if their pain is worse, that may be an indication to restart the opioid at a lower dose. But again, the endpoint of a taper is not always to get the person completely off the opioid. However, keep in mind that side effects and analgesia may improve in some patients at a lower opioid dose. If so, that may be the appropriate endpoint -- that is, a lower opioid dose rather than being completely off the opioid.



So, now, let's talk about two tapering case scenarios just to apply what we've talked about.





So, the questions in considering an opioid taper include; is the patient safe? If not, how can we ensure safety? What are the indications for taper of the opioids in the first place? How can we avoid acute withdrawal symptoms or treat them if necessary? What alternatives are available to address pain, including engagement of self-management or self-care and active treatments to address the pain, other than opioids? What other underlying symptoms may need to be addressed, and are there additional expertise or partners needed for optimum care?



Our first case is a 55-year-old male with a history of multiple back surgeries, and he's taking extended-release long-acting oxycodone 60 milligrams twice a day, with short-acting oxycodone 5 milligrams up to three times a day for breakthrough pain. The patient feels that the plan is working well, and he never asks for early refills, there's been no worrisome behaviors, and he's been on this regimen for the past 10 years since his last back surgery. The question is, does he need a taper? Clearly, he's on high-dose opioids for a long period of time, and I would recommend to this patient a trial of a taper -- that is, to at least try to get on a lower opioid dose. It might be that he doesn't require this level of opioid therapy, as his back may have healed over the years. We won't know that unless we try to taper him to a lower dose.

Now, this is going to take some time to convince the patient that a lower dose may do just as well as a higher dose, so that's something that we'll discuss over time. Again, my rationale is, does he really need to be on such high dosages over such a long period of time? The answer may be yes, but we don't know unless we've tried tapering him to a lower dose. How would I taper? I would taper over months, maybe even years.

Again, the goal here, the endgame here, is to try to continue to achieve the same benefits, but maybe with a lower-dose opioid. I'm also going to talk to him about alternative therapies, maybe acupuncture, maybe cognitive behavioral therapy, maybe physical therapy. These are therapies that he may have tried in the past, but they may be worth trying again and really focusing on multimodal care, maybe -- if he can tolerate it -- adding low-dose acetaminophen or a nonsteroidal anti-inflammatory drug to help with synergy along with the oxycodone.



What about a 39-year-old female with hip, knee, and back pain? She was initially started on opioids five years ago after a motor vehicle crash. She would do well for four to six months and then would request a dose increase, and then over the past five years, due to this escalation in doses, she's now on extended-release long-acting morphine 30 milligrams three times a day and oxycodone 5 milligrams four times a day p.r.n. for breakthrough pain. She frequently calls several days to a week early for refills, and today she's asking for an increase in her dose. Does she need a taper?

Well, I certainly get the sense that she's not benefiting, and that there's either tolerance or opioid-induced hyperalgesia causing this worsening pain, requiring higher and higher doses, and I'd really be reluctant to give her a higher dose, and I'm really going to pay close attention to adverse effects and any negative consequences from her opioid use. And, is she achieving functional goals? Is she working? Is she able to function on these medications? But the answer is, if she's not benefiting or if I suspect that there's some risk, then I would say a taper is absolutely indicated, and my rationale, again, will be based on whether or not I think it's lack of benefit and/or risk or harm.

Again, my taper's going to depend. It's going to depend on whether or not if it's lack of benefit, I can do it over weeks to months. If it's because I think there's harm or risk, it's going to be days to weeks. But in this patient, I'm really going to start to focus on non-opioid treatments, including non-pharmacotherapies, physical therapy, relaxation, meditation, acupuncture, and so forth, because I think all too often, we've become opiate-centric -- that is, focusing solely on opioids to treat chronic pain over many years -- when we now know that these other modalities can help. Not only can they help the person's pain and function, but they can help us treat patients like this with lower doses of medications, including opioids.



So, in summary, be clear about clinical indications for the opioid taper. If opioid use disorder is suspected, refer for evaluation and addiction specialty care. Engage the patient regarding the tapering plan. Provide alternative pain and symptom treatment, including engagement in chronic pain self-management. Adjust the taper, including the doses and intervals, as indicated based on the patient's symptoms, and ultimately, the patient's wellbeing should inform the endpoint of the taper.

So, I hope you have found this module helpful in thinking about tapering opioids in a patient-centric manner. Thank you for your attention.