

WEBINAR VIDEO TRANSCRIPT

Opioid Addiction Treatment ECHO

Medication treatment of OUD, including use of evidence-based treatment guidelines for OUD

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NARRATOR: Okay, so, as you know these are fairly short talks. So I'm gonna move kind of quickly, but we'll have some time for questions at the end. I'm gonna talk about the medications that are approved for treatment of opioid use disorder, and I have no financial conflicts of interest to disclose.

So, as you probably know by now opioids bind to several different types of receptors that are widely distributed throughout the body. So, we're really aware of the ones that are in the brain and spinal cord, but opioids also have a big impact on the GI tract and several other body systems and that's responsible for things such as opioid associated constipation. There are a number of different types of opioid receptors that are named with Greek letters. The mu opioid receptor is the main one that we're interested in because it causes both the euphoria or high associated with opioids and also is responsible for slowing down breathing, and you know, ultimately causing overdose if too high doses are taken. There's also kappa, delta, a number of other opioid receptors that have various different effects. A few other areas that are controlled by opioid receptors include obviously pain, some aspects of heart rate, and blood pressure as well.

This slide is meant to demonstrate some of what goes on in addiction to opioids and then what happens when someone gets onto medication treatment. So, initially when someone is using opioids for purposes of becoming intoxicated they're in a cycle, a rapid cycle cycling in between feeling normal and feeling intoxicated, and most people in this phase of addiction are trying to recreate the way they felt the first few times they used opioids, but tolerance is developing as they continue to use it. So they need higher and higher doses in order to achieve the same or close to the same feeling of intoxication. As people continue using and full fledged addiction starts to take hold then they get into another phase of opioid use disorder in which they report that they feel much less pleasure or euphoria if I'm using the opioids and instead are using largely to try to avoid withdrawal. So, they're cycling between feeling normal and feeling bad. So quite a different set of motivators there to avoid feeling sick, and you may well have had a patient who has said to you, doc, I don't use to get high anymore, I don't feel high, I just use in order to not get sick, and that's a really common experience among people with opioid use disorder.

When someone goes on medication treatment one of the big benefits is they stop going through these intense cycles of up and down or high and normal or normal and withdrawal and instead they have a steady level of opioids in their system and in their brain so that their moods can stabilize and their whole experience of life can stabilize and in that situation they're able to go back to participating in

normal activities, working on understanding the issues that may be triggering them, or setting them up for relapse, et cetera. So, the idea is to stabilize those new opioid receptors with a steady, low, non-intoxicating dose of the opioid agonist and help the person return to more normal life.

The goals of medications for opioid use disorder are certainly first to alleviate physical withdrawal and craving, and also to blunt the euphoric effect of other opioids. So, if someone does slip up and use they don't have nearly as reinforcing and positive an effect. Another goal is to reduce or eliminate risky substance use and to normalize the brain physiology, and the only three medications that are approved for treatment of opioid use disorder are methadone, which fully activates the mu opioid receptor, buprenorphine, which partially activates the mu opioid receptor, and naltrexone, which blocks the mu opioid receptor and prevents other opioids from attaching to it. Substance use disorder is incredibly costly and study after study has shown that paying for treatment yields tremendous returns for society in terms of reduced crime and criminal justice costs as well as many dollars saved in healthcare and not to mention many lives saved. For instance, the average cost of one year of methadone treatment is \$4700 per person, whereas one year of incarceration is at least \$24,000 per person.

So how about methadone? Methadone is a full activator of the mu opioid receptor and it's very long acting. This means that you don't change the dose every day, that if the patient comes in after a couple of days of a steady dose and says, doc, I'm still not feeling well, you might have the urge to increase that dose, but the problem is that they don't reach a steady state with that methadone until about five days out. So you don't wanna be titrating very frequently or you'll end up with an overdose situation.

One of the most important things to understand about methadone for treatment of opioid use disorder is that the federal government says it can only be dispensed in a federally operated opioid treatment program. It is illegal to prescribe methadone for addiction in general practice, and this is really important to note. So, it's legal to prescribe for pain, but illegal to prescribe for treatment of opioid use disorder in the office setting. Some of the benefits of methadone treatment are that people are taking their medication in a daily, observed dose. This means we know exactly how much they're getting into their body and we know that they're taking it every day. It's a very structured environment and it's required by federal regulations to be multidisciplinary. So, patients in an OTP are assigned a counselor and are required to attend some number of counseling sessions per month.

Methadone is also high potency. So people who have been using very large amounts of opioids can still have their disease controlled with methadone. It's been super well studied. We've been using methadone for more than 60 years at this point. So, we know that methadone has been proven to improve survival, increase employment. It decreases infection with hepatitis and HIV, decreases crime in communities where methadone OTPs are implemented, and it's highly cost effective. So, in spite of the bad rap that methadone gets in a lot of settings it is extremely effective. And in studies of treatment for opioid use disorder methadone typically shows the best treatment retention compared with the other medications that are available.

Limitations are that it still carries a risk of overdose and it has lots of interactions with other medications. So, if you're in outpatient practice and you know that your patient is being treated with methadone you'll want to look up interactions for pretty much any medication that you prescribe to

make sure that you're not gonna either be causing that patient to experience methadone withdrawal or methadone overdose, as well as to assess whether you need to change the dose of the other medication that you're prescribing. You have to titrate up slowly in order to stabilize the dose, and opioid treatment programs are not available in all parts of the country. Particularly in rural areas patients may not have access.

Methadone has traditionally been thought to have a significant risk of heart rhythm abnormality, something called Torsades de Pointes, which can cause a fatal arrhythmia. A recent study has called that into question and says that actually methadone doesn't cause any more of that than other opioids including buprenorphine. But several other studies in the past have found an increased risk. So it's prudent to keep an eye on that. Stigma is also a big issue, that methadone is still highly stigmatized.

So, if you put all this together and think about whether methadone is a good bet for your patient it helps to recognize that methadone is so effective and so important that the WHO lists it as one of the 100 essential medications that should be available worldwide. It has all of these proven benefits shown in the upper half of this graph, and the things that are in the lower part of the slide are myths to one extent or another and most important to point out is that methadone clearly improves pregnancy outcomes for women who have opioid use disorder. So, occasionally I still hear a healthcare provider or a counselor urging a pregnant mom to just stop using opioids and that could be a fatal mistake. So, a much, much more evidence based recommendation would be to encourage that mom and help that mom to get on medication treatment for her opioid use disorder.

How about buprenorphine? So, this is probably the medication we talk about the most in this Echo series, and that's because it's a highly effective medication for treatment of opioid use disorder that can be used in the outpatient setting. Unlike methadone, it's only a partial activator of the mu opioid receptor, and this probably explains why it is vastly more difficult to overdose with buprenorphine than with methadone. However, even though it only partly turns on that receptor it holds onto it like crazy and that's called receptor affinity. So buprenorphine will hold on and not let other drugs like heroin come along and knock it off of that mu opioid receptor and that helps to have a blocking effect to discourage the use of opioids because people don't feel as intoxicated if they use them while they're on buprenorphine.

Buprenorphine is typically combined with naloxone such as the brand name Suboxone and the reason for that is because when naloxone is taken under the tongue it's not absorbed and essentially it just disappears without having an impact. But if it's injected or snorted it causes withdrawal which is unpleasant, and so this discourages people from using it for purposes of becoming intoxicated when it's typically injected or snorted. Buprenorphine's been available since about 2003 in the form of sublingual tablets and then dissolvable films that are taken under the tongue.

More recently an implant was released, and quite recently there's a new long acting injectable, brand name Sublocade, that last for a month or more after injection and really offers some pretty exciting opportunities for using this medication in a way that avoids diversion we think, and hopefully will increase adherence. There are some restrictions on who can prescribe buprenorphine as you probably all know. Physicians who have a DATA-2000 waiver are allowed to and that requires an eight hour

training course and then as of 2017 nurse practitioners and physician assistants who have completed 24 hours of approved training are eligible for the buprenorphine waiver.

Some of the benefits of buprenorphine are the much lower risk of overdose and sedation and minimal if any effects on the heart rhythm. There are also very minimal interactions with other medications, but a couple that we do worry about are benzodiazepines and the substance alcohol. When combined with those or other strong sedatives overdose can occur. Another nice thing about buprenorphine is because it can be prescribed in the primary care setting or the outpatient mental health setting that reduces stigma and allows for the treatment to be integrated into primary care.

That's really desirable because we would like our patients to have access to medical and behavioral care as well as prevention. Buprenorphine is also a super useful tool when a patient's being treated with opioids for chronic pain and runs into problems with that, starts developing an opioid use disorder. We also know that home induction is safe and effective. It used to be kind of scary to have to have patients come into the office in withdrawal. Turns out that people with opioid use disorder are better at starting themselves on buprenorphine than we are, and so home induction works great.

Buprenorphine is also highly effective for pain. It's an excellent analgesic, but if you're using it for pain you wanna give the same total dose but divide it up three or four times a day so that the person's not taking it as a daily or twice a day dose, but instead they're taking the same amount but divided up typically four times a day because the analgesic effect of buprenorphine is much shorter than the duration of the withdrawal prevention properties of the buprenorphine. What are the limitations of buprenorphine? Risk of diversion, possibly lower retention rates in some studies compared to methadone, and limited access due to reluctance to prescribe.

Studies still show that most counties in the United States don't have a supply of buprenorphine waived providers or providers who are willing to prescribe buprenorphine that meets the need. A couple of other barriers in primary care include the urgency of scheduling, the need for that induction visit and frequent early follow up, although as I mentioned home induction is increasingly becoming the standard of care, and then urine testing and the logistics of prescribing, as well as the need to link patients to psychosocial services. We used to worry quite a bit about DEA regulators visiting. They have cut way back on that and having survived a couple of those myself they're not as bad as we thought anyway, and nobody gets handcuffed and taken to prison. It's more just they wanna look at your records and they pat you on the back and off they go. So, overall this type of treatment is really a highly gratifying thing to engage in in primary care practice and is a huge service for the communities that we live in.

Why is overdose potential low with buprenorphine? It probably has to do with this partial activator effect that there's a ceiling to the amount of respiratory suppression that occurs with buprenorphine. Once you get up above a dose of about 32 milligrams there's no increase in that respiratory suppression. So whether you take 32 milligrams or 64 milligrams there's no increase in the slowing of breathing. So, people don't die from respiratory suppression.

Many studies have looked at the benefits of buprenorphine. This one I still think is really powerful from the Lancet in 2003 in Sweden where these researchers randomized a small group of young people

addicted to heroin to get intensive counseling, individual counseling and group therapy several times a week by master's level trained therapists and then half the group got buprenorphine 16 milligrams every day for a year and the other half got tablets that contained a brief taper of buprenorphine followed by a placebo. At the end of 50 days you can see in that right hand column all of the patients who were on the placebo had dropped out, and as compared with the buprenorphine group of whom 70% were still retained at one year. Most of them had urine drug screens that were negative for all other substances. Notably, 20% of the group who received placebo died in that single year that they were being studied, really emphasizing the lethal nature of this disease.

This slide shows a number of studies that have come out since then, showing typical retention rates in treatment. These are mostly outpatient primary care practices. The second one on there by Alford and Labelle was remarkable in that half the patients in that study were homeless and they still achieved a rate of retention of 81% at one year out. So it's clear that with really good support in the practice, support for the patients you can achieve pretty outstanding results with this medication. But it's also important to note that if you do this treatment there are gonna be some patients who are gonna disappear and drop out of treatment, no matter how good you are at offering the treatment and it's important not to take that personally.

This study shows overdose rates in Baltimore. The red line showing overdose rates falling as that dotted line along the bottom started to rise and that dotted line along the bottom shows availability of buprenorphine in Baltimore. So, they had a big public health campaign to increase access to buprenorphine treatment and they saw a really remarkable fall in overdose deaths. This same pattern has been seen in other municipalities that introduced buprenorphine in a big way, including in Paris years ago when France made buprenorphine widely available. They went from having 560 overdose deaths to a few years later having less than 50 when they introduced widespread access to buprenorphine.

What about the new long acting buprenorphine? So, this medication called Sublocade has to be obtained through a specialty pharmacy who delivers it to your practice for that patient. The patient has to be stabilized for seven days on sublingual buprenorphine and then it's recommended that you start with a 300 milligram injection dose. This is injected subcutaneously and you do the injection in the office. You don't give it to the patient to take home because it would be very dangerous if the patient injected it intravenously as it causes an immediate kind of clot, lump to form, and they could have an embolism or other really bad consequence. So, it's dangerous to send a patient home with it, but if it's injected subcutaneously in the office it's quite safe. We're still gathering data about this. A study was published last week actually showing that it's at least equally effective to sublingual buprenorphine but this study was interesting from a couple of years ago where they started people on Sublocade and then they gave them hydromorphone doses.

So a very potent opioid, and they gave them increasing doses of hydromorphone to see how much the person liked the hydromorphone. These were no treatment seeking adults who had opioid use disorder and they were trying to see how well does the Sublocade do at blocking the effects of other opioids, and it was quite interesting that after they had had two total doses of Sublocade they had very minimal response even to the very high doses of hydromorphone. So, this shows they got the injection at

number one on that X axis and another dose at number four and then they didn't get any subsequent doses of the Sublocade for the next eight weeks and yet the effect of the Sublocade persisted in blocking the pleasurable effect of hydromorphone all the way out to 12 weeks. So, this suggests that even when patients don't return for an injection on time they still have a blocking dose of that hydromorphone in their body. We're hopeful that this may help to decrease diversion of Suboxone which has been as you all know a significant issue.

How about naltrexone? So, naltrexone is the newer kid on the block for treatment of opioid use disorder. It is an antagonist. It binds very tightly to that mu opioid receptor and won't let anything else attach. If you give it to somebody who is opioid dependent they will have spectacular withdrawal and will no longer be your friend. It's very important to avoid giving it to someone who has opioids in their body. It was available and still is available as a pill, an oral dose, but that is basically completely ineffective for treatment of opioid use disorder. So, we don't recommend that. However, the extended release injectable form Vivitrol given as a 380 milligram intramuscular monthly injection is effective and we've been getting increasing amounts of data recently showing how effective it is. One nice thing about it is you don't have to have any special setup or license to prescribe it other than a regular medical license.

There are some issues around insurance coverage for it. It's not 100% covered yet and there's a special injection technique that the injector has to learn in order to inject it safely. A couple of studies published this last year gave us a lot more confidence in this medication being effective. A study in Scandinavia by Tanum randomized patients with opioid use disorder who had gone through detox. They then randomized them to start on injectable naltrexone and they found that naltrexone was non inferior to buprenorphine in terms of retention, urine drug screen results, and use of heroin.

A study that was done here in which actually our colleagues here at the University of New Mexico were one of the study sites that was by Lee and published in the Lancet shortly after that other study last year was larger and here they actually randomized patients at the time of admission into a detox setting but they were either going to use buprenorphine or they were gonna get the naltrexone injection and here what they found was many more patients assigned to naltrexone were likely to leave during the first couple of weeks of treatment. This was because the patients who were going onto naltrexone had to go through withdrawal before they started the naltrexone and they were uncomfortable and decided to leave, whereas the buprenorphine treated patients didn't really have to withdraw, were started on buprenorphine, and were doing well. So, 94% of the patients assigned to buprenorphine were successfully inducted and stabilized versus 74% of the naltrexone patients. However, once patients got started on naltrexone they did as well as the buprenorphine treated group. All of this underlines the fact that it's a whole lot easier to start people on naltrexone if they are already detoxed, quote unquote.

So, if they're in a setting of inpatient, of rehab, or of incarceration as long as you're fairly confident they haven't had access to opioids that's where people can effectively be started on naltrexone. Some people do this in the office setting but it's pretty hard to convince patients who are opioid dependent to stay off of opioids for long enough to do this induction. You would wanna start with an oral test dose with such a patient to make sure, absolutely sure, that they don't have any opioid in their body. Special caution, methadone only shows up in the urine drug screen for about three days after it's been taken but its

effect is much longer. So, a patient who took methadone last week will have a negative urine drug screen but will still get very sick if you start them on naltrexone. So that's a super important question to ask and ask again with a patient if you're considering inducing them on naltrexone.

Benefits of naltrexone are that it does not create opioid dependence, so someone can stop it and not develop withdrawal. It's also effective for treatment of alcohol use disorder as you know, so it's particularly nice to use in the setting of opioid and alcohol use disorder combined. It does not cause any respiratory depression or sedation and it's not a controlled substance, so there are no restrictions on prescribing. Retention appears to be similar to buprenorphine if successful initiation is achieved. We still don't have anything like the same kind of long term outcome studies for naltrexone that we had for buprenorphine or certainly for methadone, but what we're learning is encouraging in terms of the benefits.

Notably one limitation of naltrexone is that if someone's taking naltrexone opioids are ineffective for pain. So, someone who is in a, you know, a crash injury trauma kind of situation, it's really hard to control their pain. So other approaches like regional anesthesia plus non opioid medications are what you definitely need to turn to.

Always important to mention overdose prevention when we're talking about medications and opioid use disorder. Naloxone which is a short acting cousin of naltrexone is our friend Narcan which reverses opioid overdose and overdose education and naloxone dispensing are effective harm reduction strategies and are really effective at keeping your patient alive while you work with them. So, they should be widely distributed and used in all kinds of settings where people may be at higher risk of opioid use disorder but there's also a pretty good argument to be made for dispensing naltrexone to anybody who's being prescribed opioids for any length of time.

There are some emerging models of treatment for medication, medication treatment for opioid use disorder. The Massachusetts Nurse Care Model we'll hear about later in this series, but here nurses are actually the main actors in treatment of opioid use disorder. They manage the care of patients with OUD and the prescribers are in a more limited role where they're largely just reviewing what the nurse is doing and signing the prescriptions. This allows more patients to be followed and followed effectively. This is the model that was used in that Alford paper that I showed you that had such excellent retention rates.

And then the Vermont Hub and Spoke model is one in which addiction specialists actually start patients on buprenorphine and then refer them out to primary care practices as they're stabilized. So, in summary maintenance medications are an essential, very important component of evidence based treatment for opioid use disorder and the strongest long term data at this point support methadone and buprenorphine, but naltrexone is also highly effective. Important to note that it's easiest to initiate in an inpatient setting and can only be initiated in patients who are not currently physically dependent on opioids. Primary care teams play an incredibly important role in treatment of opioid use disorder and prevention of overdose and we're really grateful for the great work that you all are doing. So, tons of references if you care to peruse any of those and my email address in case you wanna get in touch with me to--