ASAM Practice Pearls Transcript

Individualizing Buprenorphine: *Low-dose Induction to Long-acting Injectables*

Dr. Stephen Taylor: Hello, and welcome to ASAM Practice Pearls, where we turn clinical expertise into everyday addiction care one conversation at a time. I'm your host, Dr. Stephen Taylor, and today we have with us Dr. Steven Holt, whom you may remember from the special series on Advances in Buprenorphine from season one.

Dr. Holt has an incredible wealth of experience with treating patients with buprenorphine, and I'm going to invite him right now to share an example of one of those patients with us. Dr. Holt, if you would, please.

Dr. Stephen Holt: Sure. Hey, Dr. Taylor. What an honor and a privilege to be here with you. I'll start off with a quick case.

So a 35-year-old patient of mine from our addiction recovery clinic here at Yale New Haven, who essentially had a history of snorting fentanyl, illicit fentanyl use for a number of years now, also intermittently using benzodiazepines that he buys on the street. And he has been very erratic with coming to clinic. He'll come for a few weeks. He'll get sublingual buprenorphine and seemingly do well for it, and then he might disappear for a while. Some inconsistencies in some of the reporting of when he runs out of buprenorphine, you know, how much fentanyl he's using from one week to the next. And it was making the whole treatment team just somewhat not at ease with thinking about fluctuating levels of buprenorphine from one week to the next.

Not a lot of clarity about whether or not he was taking the buprenorphine that we were prescribing consistently or not. And just a lot of concern about his safety, knowing that fluctuating buprenorphine levels while there's different amounts of fentanyl being snorted at different times really creates a recipe for disaster and certainly a recipe for clinician anxiety.

And so, that's kind of the situation that I think we were presented with that leads us to, I think, part of our conversation today.

Dr. Stephen Taylor: Well, yeah, absolutely. A patient like that, you're absolutely right, raises clinician anxiety levels because it raises the risk to our patients. And so, that's a great lead-in story for us to address the topic today, which is on individualizing buprenorphine treatment with low-dose induction and long-acting injectables.

I'm going to go ahead with our first question. When a clinician is treating a patient with OUD and initiating buprenorphine, how do they decide between traditional induction and low-dose induction?

Dr. Stephen Holt: Great question. So this is something which has evolved so much since I first started prescribing buprenorphine in 2005. And back then, everybody was talking about in-office inductions, right? You had to actually do an induction in the office, which today is, like, just outlandish that that was something we thought was so important. And then the big novelty was home inductions. Wow, we can send people home with buprenorphine and expect things to go well.

But that, of course, was when there was only heroin out there, and you could wait 12 hours after your last heroin use, certainly 24 hours, and then you could immediately start buprenorphine, sublingual buprenorphine, once they've had a little bit of withdrawals, you know, we had a cutoff on the COW scale as to how much withdrawal you wanted your patient to be in before they started.

And then, of course, the game changed 2015, give or take, plus geographic variation, that's when fentanyl started to really take over the market. And certainly, that's the case today, where we don't even see much heroin anymore.

So, with fentanyl and its really long half-life, the evolution in how to transition people from an illicit opioid or from methadone, for that matter, over to buprenorphine has significantly changed, such that now we're talking about this sort of classic buprenorphine induction, you know, home induction, what have you, which requires a person to be in a certain amount of withdrawal symptoms versus these low-dose inductions. And there's different versions of this now, and there's constantly this sort of evolution of different approaches to low-dose or high-dose inductions, for that matter.

So, I think for me, when I'm deciding which patient would be best for which approach. If you've got folks who are just on short-acting opioids that have predictable pharmacokinetics, or I suppose if they are using heroin, you could use your typical old school approach. Just have them go into a little bit of withdrawal, you know, they'll experience moderate symptoms for a couple hours, and then, you know, launch them with sublingual buprenorphine.

But for folks who are on a stable amount of a predictable long-acting opioid, methadone, things like that, a low-dose induction with sublingual bupe seems to be the best approach.

But, like, the patient I'm describing, with erratic use of buprenorphine, erratic use of fentanyl, there would be a lot to support the idea of either a direct-to-inject kind of approach or a high-dose induction with sublingual buprenorphine.

Dr. Stephen Taylor: Let's go with that because that patient sounds painfully familiar to me and probably to a lot of our listeners, that the person who's involved in erratic use of the substance that they are addicted to and erratic use of the buprenorphine which we're prescribing them, and you got to figure out how to get that patient stable, prevent withdrawal, and try to get them in a place where they are able to really benefit.

You're thinking maybe a higher dose induction or straight to LAI use. How do you do that? What's the approach?

Dr. Stephen Holt: Yeah. I'll talk about the direct-to-inject approach first, and I will give the disclaimer that that's the approach that I have least used, and not because I don't think it's a great approach, but simply because there's a pragmatic challenge with the direct-to-inject approach in the outpatient setting. And there's two ways to equip your office with long-acting injectables, and that's the specialty pharmacy purchasing long-acting injectable bupe that's already got the patient's name on it. Like, literally, the specialty pharmacy gets your prescription, sends you this dose. It's got the patient's name on it. Their insurance has already been billed. It shows up in your office a couple of days later after you wrote the prescription, and you can administer it. That's the specialty pharmacy approach.

But the ideal approach really is this buy-and-bill approach, where you have a collection of doses of varying types in your office, ready to go at a moment's notice. I don't have that. It requires a little bit more logistical oversight, and there's a lot more rules and regulations, and also risk taken on by the clinic to buy these, like, $1,000 doses. To buy a whole bunch of them and have them in your office, and hope that you'll use all of them. That buy-and-bill approach is just not something that I have at the FQHC where I work.

So, the direct-to-inject approach is just one that I would love to do, but it's a little tricky because when a patient comes in, like the one I just described, or maybe a patient I don't know very well who's having their first appointment with me, there's no way that I'm going to have a dose ready to go when they come and see me. I can have it for them maybe in a couple of days, but I don't have it right then.

In contrast, in the emergency department, where some of my colleagues here at Yale, Gail D'Onofrio and others, they're the ones who really first described, or at least that I'm aware of, the first sort of large case series or large trial involving a direct-to-inject

approach. In the emergency department, you can have a direct-to-inject approach. You have kind of a buy-and-bill program. Your pharmacy and therapeutics committee has already bought a whole bunch of different medicines, and they're all available in your hospital pharmacy, so you can do this.

So that's, I think, the ideal approach is to do a direct-to-inject. And the reason that that's so fruitful is when you administer a seven-day buprenorphine shot, whether it's an eight, a 16, or 24 milligram dose, it has a slow rise to its peak. Like, it takes about 24 hours to hit a peak. And during that time, there's this very gradual minute-by-minute changeover where one mu-opioid receptor that was bound to fentanyl is now getting replaced by buprenorphine, and it's this slow, gradual ramp-up. As opposed to if I hit somebody with obviously sublingual buprenorphine, 16 milligrams, it's like maximum effect within maybe 30 minutes, which would completely displace all that fentanyl. The slow rise for long-acting injectable bupe, specifically seven-day buprenorphine shots, really has been a game changer for folks in the emergency department settings.

I don't know what your practice has been, Steve. Do you have access to these seven-day injectables? Do you have a buy-and-bill system, or what's your scenario?

Dr. Stephen Taylor: I was going to say that that's the issue for many of our listeners is that we practice in settings where buy-and-bill is a risk, and it's prohibitively difficult.

From my own practice and in my own situation, we do have the ability to do buy-and-bill, but we have to be very judicious about when we do it for the reasons you've already described.

Dr. Stephen Holt: Yeah, especially with so many doses, you know, and you have to decide which doses are most appropriate. And honestly, once you've given somebody a seven-day, there's no reason to ever use them again. Like, who wants to come in every seven days for them? So, we're immediately transitioning to 30-day shots. So, it is an inherent risk.

Accepting that I just practically at the moment can't do buy-and-bill, there are those situations, and this is a guy for whom I might tell the patient, "I'd love to have you come back next week. I will have a seven-day buprenorphine shot for you then. Let's do this transition. Let's get you onto LAIB next Tuesday or something."

But more often, we're doing sublingual low-dose inductions where we're giving somebody 2 milligram films, having them cut them into quarters. So, we do 0.5 milligrams on day one, then BID on day two, and then you go to 1 milligram BID. You

know, basically, the slow ramp-up over six days. I know it's possible to do it much faster. And in the hospital, you know, I've seen many five-day protocols, three-day protocols where you're every four hours dosing or increasing the dose of buprenorphine, and that approach is certainly great in the hospital setting.

For us in the outpatient setting, we keep it a little simpler over six days. But that's our general approach. But all the time that somebody's doing that, they have to continue to use illicit fentanyl, which doesn't feel great, for us as the clinician, to tell somebody, "Whatever you're doing, just continue doing it while this buprenorphine slowly ramps up." But that's the approach we take.

Dr. Stephen Taylor: Yeah. And I think that's the crux of the matter, is how much it is cringe-worthy almost to tell someone, "Keep doing what you're doing for the next seven days," when your whole goal is to get them to stop doing what they're doing. But the reality of it is that is the way we can accomplish low-dose induction.

But it is a patient-specific thing, and it's got to be tailored to each individual. So, if you would just share with our listeners what are the factors that are most important to consider when tailoring the buprenorphine dosage?

Dr. Stephen Holt: I get asked this question when we have a, you know, addiction medicine fellow or our residents in our clinic, and a patient comes in saying they're using X. And somehow me and my fellow seasoned addiction colleagues will say, "Oh, I think this person should be on 16 milligrams of buprenorphine a day." And then the resident will say, "How'd you come up with that?" Sometimes I can't answer, right? It's just like, I don't know, it just feels like 16 is the right dose for this person.

So sometimes it's a little bit difficult to put a pin on it because there's no direct, really reliable dose conversion from bags of fentanyl to buprenorphine for countless reasons. And so, if I'm thinking about long-acting injectable in general, and it's a person who's using bags of fentanyl, I would say anything more than two or three bags of fentanyl a day, I'm going to use the maximum dose of long-acting injectable bupe.

If somebody's only using a bag or two that they space out over the course of a whole day, maybe they don't need the full dose. Sometimes it also depends. Is this a person who's really just trying to stop using, and they just need something to saturate their receptors and allow them to make that transition? Or is it somebody who is experiencing daily cravings, they're in an environment where there's illicit opioids all around them, and they have trouble envisioning a future without opioids? I'm going to use the higher dose for such folks.

And anyone who we do start on a lower dose, maybe it's 96 milligrams or 64 milligrams of LAIB, if after, you know, a few months or even after a month or so, it's clear that the patient's unable to make that transition to stop using opioids or is still struggling with ongoing use, then we just ramp up to the higher doses, and that's fine. But I don't automatically use the highest dose on every patient who is using illicit opioids.

Dr. Stephen Taylor: So, you really do have to take into account to what extent they're using, what they're using, how they're using it, all that has to come into play.

Let's say you've got this patient finally stabilized on sublingual buprenorphine or a topical or a buccal buprenorphine. What makes them a good candidate for transitioning to the LAI formulation?

Dr. Stephen Holt: Yeah. I think almost everybody's a good candidate at this point. I guess I think of patients like the one I described who are erratic. Everyone feels anxious. It's not clear what's happening with their buprenorphine levels. They're fluctuating. That's a no-brainer. LAIB makes sense.

The second one is the person who's unhoused. They're having trouble keeping track of their sublingual films. Maybe they lose them. They don't have a safe place to store them. They keep losing them on the bus. You're getting all these early refill requests. It's just impractical for them to have their medication. Maybe they're on TID dosing or something, which is just also impractical for a lot of folks. So, the logistical factors around the patient make it wonderful to transition them to a once-monthly injection.

The third group is just patient preference. I mean, if you just want to be on it because you don't like the sublingual films, maybe the taste makes you a little queasy, whatever it is, that's a no-brainer. And so, we offer it to every patient that we have.

The fourth group is folks who you have questions about what's happening when you prescribe them bupe. There's just something that doesn't smell right. Let's say you're giving them two films a day, and they insist that they want four films a day. The urine results aren't really quite consistent with the buprenorphine amounts that you're prescribing, and somebody's tampering with urines, whatever it is. And everybody would just feel much more assured if I'm actually administering this monthly shot. I was there when it went in. I know it's in, and I don't even have to check buprenorphine levels anymore.

Dr. Stephen Taylor: So, once you've got that determination and you know that's the person that needs to be on an LAI, and they're interested in starting it, which is the other

part of that equation, then how do you initiate? Do you have a formula? Do you have a general approach or not?

Dr. Stephen Holt: Yeah. So once somebody's been stabilized on sublingual bupe, which we're assuming that's where we are, then you can simply follow the guidance on the packaging based on if somebody's on eight milligrams a day of sublingual buprenorphine, then you would put them on the 64 milligram LAIB. If they're on 24 milligrams of sublingual bupe, then go straight to the 128, etc.

I'd say one of the big decisions is the Brixadi versus Sublocade question. I always feel obliged to say it. I have no financial disclosures with either of these manufacturers, but we are talking about choosing between the two of them.

So, for me, from a pain perspective and a dosing flexibility perspective, my default is going to be Brixadi, whether it's the 64, the 96, or the 128. I just find that having a 23-gauge needle with .35 cc's and many dosing options, that's what makes Brixadi great compared with the 19-gauge needle, much more thick, viscous stuff. And the experience that I've had with countless patients that say when they get Sublocade, it hurts for most patients.

So Sublocade, I think, is great in the sense of it leads to higher serum buprenorphine levels when you're using maximum doses. And so, there's a lot to be said for completely saturating every mu-opioid receptor in those folks who are still struggling to use. You know, they're on max dose, let's say Brixadi 128, and they're still using five bags of fentanyl a day, still feel like they're getting an effect, still having intense cravings. That's the person I'm going to put on Sublocade because when you're on Sublocade 300 milligrams for a couple of months, your serum buprenorphine levels are so high that I'm confident that nothing can penetrate it.

So, for me, those are the variables that lead me towards Brixadi versus Sublocade. And of course, I just talk to the patient about it too, right? I mean, if the patient wants to have all their mu-opioid receptors completely saturated and really is anxious about their ongoing use, let's go the Sublocade route. If they're anxious about a bigger needle and having some pain at the injection site, we'll go the Brixadi route.

Dr. Stephen Taylor: And of course, you know, I think a lot of our listeners are maybe a little surprised to hear this discussion with all the brand names, but in fact, at this point in history, is there a generic or non-brand-name LAI formulation out there, or are we only choosing between these two name-brand formulations?

Dr. Stephen Holt: Yeah, thanks for asking. I don't imagine that there will be a generic injectable for many years to come. Even though I'm sure there'd be a huge market because all of the drugs we just named are, you know, 1,000 bucks a piece depending upon where they're coming from. But yeah, we don't have a generic version.

And the generic, or the non-branded name for Brixadi, is a slew of like letters and numbers or something. I forget what it is, but it's not something one would use in common practice.

Dr. Stephen Taylor: That explains, just for our listeners, why there's so much of a use of name brands in discussing these products. It literally would become prohibitively difficult to even understand what you're saying if you were not using these name brands.

So, all right, you just gave an example that predicted my very next question. How do you manage that patient who's on an LAI, who has ongoing opioid use or is experiencing breakthrough cravings or withdrawal symptoms before their next dose, even though they are on an LAI?

Dr. Stephen Holt: Yeah. Interestingly, I remember having this concern when we first started ramping up our use of LAIB. A patient who I would've been seeing on a weekly basis and giving them seven-day supplies of buprenorphine because I wanted to keep them close and making sure they were still engaged, now all of a sudden, I'm giving them a 30-day shot, and maybe they just disappear for 30 days. There's the potential that they're less engaged in care.

My anxiety is alleviated, like I know they're safe for 30 days, but in some ways, they're coming in 12 times a year. And that's it. And that's not going to really remedy the complex issue that you and I know is addiction.

Nonetheless, I encourage those folks to come in far more often than is needed for the purposes of pharmacotherapy. I want them to engage in behavioral support. For folks who are continuing to use illicit opioids, this is never my default, but it certainly is often the case that we are providing additional sublingual films to folks to sort of handle those day-to-day cravings.

You know, there's something about the ritual of taking something which we rob them of. As soon as they get an injectable, and we're like, "Okay, I know you were taking buprenorphine three times a day," or "You were using fentanyl 10 times a day," but there's no ritual. There's nothing. You're taking nothing on a daily basis, and that can be

pretty jarring for folks who were accustomed to that daily habit, even if it's a habit they may not have wanted to maintain.

So, providing sublingual films is reasonable. Ramping up to the maximum dose of whatever LAIB you're on, and as I said, I oftentimes will switch over to 300s of Sublocade if folks are still struggling. And doing your best to address all the other things that could be going on.

I've had so many patients who report that they're withdrawing from their buprenorphine dosing, and then you really talk to them and tease it out. The symptoms aren't really consistent with withdrawal. It doesn't really add up. And so, they're just self-medicating with buprenorphine films. Well, maybe we could come up with some other way to handle those anxieties. And maybe even patient education is helpful. Like when you tell me that you just don't feel right and you're taking three films a day of buprenorphine on top of your 300 milligrams of LAIB, let's tease this apart. What actually is going on here?

Dr. Stephen Taylor: Yeah, I think that's right, to go back to the basics and get a history of what's really going on, and is that in fact withdrawal, and that's the great point.

And then the other great point that I want to highlight that you pointed out is that we sometimes lose sight of this when we're talking about treating OUD with MOUD of various forms. But the reality of it is that's not the totality of treatment for addiction. Never has been, never will be. You got to also address some of the psychosocial and behavioral interventions. And particularly for folks who are not being adequately covered on their MOUD, that becomes even more important. And you touched on that. I just feel like that's worth highlighting as well.

And let's go one step further. Not only are some of these folks using additional opioids over and above the LAI that they're taking and that's been administered to them, but they're also using other substances. You'll get folks that are coming in, and they've got a positive result for cocaine or a positive result for methamphetamine. Again, do you have a particular recommendation other than what we've already discussed for those folks?

Dr. Stephen Holt: Yeah, or alcohol for that matter, as well, on top of things. So when folks have multiple substance use disorders, the patient I just described also had a benzo use disorder. You know, I've got, as I'm sure you do as well, several patients who both have opioid, alcohol, cocaine, benzo use disorder, all of the above. I feel that you can't tackle any of those until you've stabilized the opioids, and that's the beauty of the long-acting injectable. It's you've now put one addiction to rest for a time so you can start to really focus on those other things.

And so, if it's AUD, let's talk about trying to do an ambulatory managed alcohol withdrawal or protocol with a benzo or with gabapentin or what have you. Let's look at our options to manage your cocaine use disorder. Do you have contingency management available? Do we have access to using modafinil or topiramate or one of the various medications that have some evidence to support them? And then, you know, are we going to work on a benzodiazepine protracted taper plan to get them on something that's stable?

But, in some ways, it's great that if the patient has another condition that you're managing, that I guess convinces the patient that they should come in every week. You know, let's really try and tackle this. Let's get you into group visits if we have them or something else that's more intensive than just seeing you every 30 days, which, as I said, rarely feels adequate for folks who are in the throes of addiction.

Dr. Stephen Taylor: Indeed. Yeah. We have to remember that addiction is not a drug-specific disease. And to your point, once a month, it rarely feels like it's adequate to take care of this population. I think you're 100% correct. And so, it's important to address that.

So, we're at the point now where I got to ask you to zero in on the main practice pearls that you would like our listeners to take away from this episode. What are the most important pearls that you want to emphasize?

Dr. Stephen Holt: I would say one of the key points is, if you've never administered long-acting injectable bupe and you're afraid to sort of make that transition, just do it once.

It reminds me of when I was trying to get folks, just, you know, they were afraid to start prescribing sublingual buprenorphine. You don't have to start to manage a panel of 1,000 patients with sublingual buprenorphine right out the gate. Just take one, just a single patient, and realize how amazing it is and how transformative it is to start managing folks with sublingual bupe.

Same thing for long-acting injectable. Don't turn your practice into an LAIB clinic overnight. Just pick one patient for whom you think it's worth trying to navigate the system. Like, this particular patient is perfect. They've been on TID bupe for a while. They're stable, let's say, and they just are tired of the films. Maybe you're worried even about, like, the you know, long-term dental enamel problems with taking sublingual buprenorphine for five years. And you check in with the patient. They're like, "Yeah, that sounds like a cool thing." Let's find a specialty pharmacy in your area and just make that

connection just once. You'll very quickly start to see how useful it is, and it's not that hard to do.

Dr. Stephen Taylor: So the journey of a thousand miles starts with a single step. What's your next recommendation?

Dr. Stephen Holt: Sure. Yeah. The concept of the direct-to-inject, which again, as I said, I've only done it a handful of times in my office. But it's a great way to overcome those innumerable barriers for folks who are erratically using illicit fentanyl. And even the complexity of a low-dose induction, I mean, it may seem simple to us because we've been doing it for a while, but it's really not simple to have this, like, roadmap of day-to-day changes and how much buprenorphine you're taking. Boy, a seven-day shot of buprenorphine can really make things super simple for folks. So direct-to-inject is a great approach. I wish we did it more often in our own practice.

My last one's simple, just that long-acting injectables are really something to offer to every patient. No one is too stable or too unstable. It's a great intervention to incorporate into your toolbox.

Dr. Stephen Taylor: That's actually a great thing to remember that I'm not sure a lot of people realize. There isn't a patient for whom an offer of an LAI is a bad idea. That's great.

Well, listen, I have thoroughly enjoyed this conversation with my namesake, Dr. Steven Holt from Yale University, a brilliant doctor treating folks with OUD with buprenorphine and a real expert in this field.

For more information on long-acting injectables, please check out the recorded session from ASAM's 57th Annual Conference, Enhancing Access with Direct-to-Inject Buprenorphine: Evidence and Implementation, which covers direct-to-inject extended-release buprenorphine, including evidence, diverse healthcare settings, and practice-specific planning strategies.

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