

Dr. Taylor: Hello and welcome, friends and colleagues. You're listening to the first episode of ASAM Practice Pearls, an exciting new podcast series from the American Society of Addiction Medicine.

In this series, we'll explore key topics and best practices for addressing substance use disorders and advancing addiction medicine. I'm your host, Dr. Stephen Taylor, and I'm excited to be joined today by our esteemed expert, Dr. Stephanie Weiss. Dr. Weiss, please introduce yourself.

Dr. Weiss: Thank you so much for having me on. I am a research staff physician at the National Institute on Drug Abuse and the Intramural Research Program in Baltimore, Maryland, and I'm so happy to be here to talk to you guys about one of the trials we're doing on the use of semaglutide for alcohol use disorder.

Dr. Taylor: And thank you, Dr. Weiss. We are super excited to have you join us to talk about this very timely, and very interesting topic. Because we're talking about, in general, this whole topic of the potential of GLP-1 receptor agonists and their possible use in addiction treatment, alcohol use disorder, and perhaps other addiction treatments as well. So, welcome! Thank you so much for joining us. It's going to be a fun discussion.

So, let me just start out by pointing out that just in October, NPR had an episode in which they discussed an article that had just been published a couple of days before in the journal *Addiction*, talking about a study that was looking at over 500,000 people and it was just looking at chart records. Of course, it was a cohort study, but what they looked at was people who had a prescription for a GLP-1 receptor agonist versus a group that did not have such a prescription. And what they found was that the group that had prescriptions for the GLP-1s were less likely to experience alcohol intoxication and less likely to experience opioid overdoses. And so, fascinating study that really will raise your eyebrows.

And then, the next month, another study came out in *JAMA Psychiatry*, and that one looked at a Swedish population, looking at their health records, and they found similarly that there were lower numbers of alcohol hospitalizations among that Swedish population. And, interestingly enough, the GLP-1s seemed to do better, in that regard, than our FDA-approved medicines like naltrexone and acamprosate.

So, with that backdrop, for you to be doing this research on this topic is so timely and so fascinating. So, I'm gonna ask you to just please tell us about the work that you're doing.

But first, explain the science behind GLP-1 receptor agonists like semaglutide. How do they work? Why are they considered promising for treating alcohol use disorder?

Dr. Weiss: Absolutely. So, unfortunately, we don't have a simple answer for how they work, but we do know that they do several different things, and some of which are probably important just to take a step back.

So, the drugs like semaglutide and the other GLP-1 receptor agonists—GLP-1 stands for glucagon-like peptide 1s, and then if you add an R, it's because it's a receptor. And so, semaglutide is one of those. We can't use the actual hormone. These are all in incretin hormones, and there's several of the others like GIP (Glucose-Dependent Insulinotropic Peptide).

So, these are what are called incretin, and they get released in the GI tract in response to glucose in people eating food. And so, what's great about these drugs is that they do lower people's blood sugar, but not just willy-nilly. They do it in response to food being present.

And so, it's much safer than, for example, than giving insulin or a drug like a sulfonylurea that lowers glucose regardless of what the patient's baseline glucose is. Now, they are peptides, and so because of that, they end up getting cleaved, and they have a very short half-life, and so because of that, we can't actually use GLP-1 and other incretins themselves. That's why we have to make these longer-lasting analogs, like semaglutide. And so, in terms of how they work, there are receptors for these hormones, like GLP-1, all over the body in many different organs. And so, the ones that we're most interested in for our purposes are primarily in the GI tract, including the pancreas, and then also in the central nervous system.

So, for the two main indications that are FDA-approved for drugs like semaglutide are for type two diabetes and also for obesity. So, for the diabetes, we primarily are concerned with their effect on the pancreas. And we know that they affect insulin secretion and just some of the other actions, including glucagon release of the pancreas—they decrease glucagon release. And so, that's probably how they primarily help with diabetes. They do have GI side effects like they make people feel fuller, there's slower transit through the GI tract. So, people might have some nausea or even vomiting from them.

So, the question is then, maybe that's why they're eating less. And there probably is some contribution from that, but we actually think the primary effect for obesity and analogously probably for substance use disorders and potentially even behavioral addictions is centrally acting—so the central nervous system in the brain and specifically in the mesolimbic dopamine systems—potentially affecting their appetite and satiety and affecting the reward pathways, essentially. And that's probably more important.

Dr. Taylor: That is great. Thank you for that explanation. That's good to get that background. But you also are currently conducting a research study in this area because, of course, you're at NIDA. That's what you do.

If you would, please tell us about that study. What are some of the key insights or takeaways so far, if there's anything that's unexpected, just tell us a little bit about the work that you're doing.

Dr. Weiss: Yeah, so we are specifically studying the use of semaglutide, which is one of the GLP-1 receptor agonists that's currently on the market. It's approved for both diabetes and for obesity. And we are now looking at it as a possible treatment for alcohol use disorder.

Most of the data so far are coming from preclinical studies. So, primarily in rodents, there are a couple of monkey studies now as well. And so, we do have some anecdotal evidence. There's been some very creative studies coming out recently where people have looked at what random people are posting on sites like Reddit and looking at social media posts and so forth and seeing what people say and analyzing that.

And then some of the studies, like you mentioned, where they're either giant cohorts or—so Sweden, you mentioned the Swedish study. They have a wonderful registry because everybody is covered under their healthcare system. So, they are actually able to look at all their patients in the country, which is pretty neat and, obviously, not something we could emulate in this country. Unfortunately, it's, it's not a randomized controlled trial, even though large numbers.

And same with the other study you mentioned that was done with Cerner data—so, Cerner being one of the electronic medical records that's currently on the market. So, even so, though, with all those advantages and benefits, they still don't substitute though for randomized controlled trials, which is where we come in and some of the other groups that are currently studying these agents.

So, our trial is called STAR. It stands for Semaglutide Therapy for Alcohol Reduction. It's actually two harmonized trials. So, harmonized is different than a multi-center trial. It means that we have similar protocols, but they're not exactly the same. So, we're not the ones in Tulsa, which is our sister trial. We're the ones in Baltimore. And basically, what we're doing is, it's a randomized, double-blinded placebo-controlled trial. We dose these folks for 20 weeks. They do have to have an alcohol use disorder and in certain baseline levels of drinking and binge drinking. And so we then randomize them to either get semaglutide for the 20 weeks or a placebo. The placebo is just saline or salt water. And they are also getting educational modules at the same time called Take Control, which was formulated by our sister institute by NIAAA.

And then, after the 20 weeks of dosing, there is a seven-week follow-up period. And so, we are interested in several things, primarily safety, because this is an early phase—it's a phase one and two trial. So, we're looking at safety and tolerability. So, how many adverse events people have, how many of these folks we can get up to the maximum dose of semaglutide, which is 2.4 milligrams. And then we're also interested in the early efficacy. So, our primary outcome is actually a 28-day timeline follow-

back and the change in self-reported drinks per week from the baseline to the end of the study. But we have several other secondary outcomes as well. So, we're interested in the number of heavy drinking days.

We're interested in any changes in the WHO drinking risk levels. We are interested in biomarkers like PEF or phosphatidyl ethanol. And then we also have several study tasks that we are looking at. So, one of them is a virtual buffet where the patient puts on a virtual reality headset, and we're able to look at things like which foods they select, how many calories they [get], and even how long they spend looking at certain foods.

And then, we also do a cue-reactivity task. So, we do this in two ways. One, we have a room—I call it the mock bar. It's a room that actually looks like a bar. And the patient tells us ahead of time what their alcoholic drink of choice is. And we actually go out and buy it. And they're sitting here in this room that looks like a bar and we let them open the drink, and smell it, and pour it into a glass. They can't actually drink it. And then, we give them an alcohol urge questionnaire. And we say to them, "How bad do you wish you could have a drink right now?" With the idea being that as people go on higher doses of semaglutide, we should see a decrease in their craving for alcohol. So, it's a little bit mean because we're doing this, again, with people who have alcohol use disorder, but actually, most of them tolerate it pretty well.

So, we're doing functional MRI on these folks, too. We do that at the beginning, halfway through, and at the end. And there's actually a cue-reactivity test that gets done there, too. So, they can't actually drink alcohol or have alcohol while they're in the MRI. They're in that MRI for about two to three hours total, doing various tasks. One of the tasks they're doing is that they are looking at pictures of alcoholic beverages, non-alcoholic beverages, food, things that are neither drinks nor food, and then, again, measuring their craving based on those things. And then they're doing some cognitive exercises, too, which is trying to get at some of it.

So, you may be aware that semaglutide and other GLP-1 receptor agonists are also being studied for diseases like Alzheimer's and Parkinson's, too. There's some cognitive effects, too.

Dr. Taylor: Fascinating. So, it makes sense that you're doing such a comprehensive study and looking at so many different things. And that actually brings my next question, which is that there also seems to be some promising data on the use of GLP-1s for nicotine/tobacco disorder.

Dr. Weiss: Yes.

Dr. Taylor: In addition to alcohol use disorder. So, what are your thoughts on that?

Dr. Weiss: Yeah. So, we joke sometimes about how a semaglutide may be good for whatever ails you because it seems like there's so many different directions that

people can potentially go. So, yes, absolutely, and we are not doing a trial ourselves, but colleagues of ours are doing trials looking at not only tobacco use disorder but even other substance use disorders as well—so, cannabis and stimulants. And there have been preclinical studies done on this. So, absolutely, yes, it seems like these pathways are connected, and just as it does not only affect food intake, it does not seem to be specific just for alcohol as opposed to other SUDs. And it's not necessarily the case that it had to be that way because if you think about it, alcohol is really the only drug that has caloric value, right? All the rest of our drugs really do not have any calories to them. So, alcohol is a little bit unique that way.

Dr. Taylor: It is interesting that it started with alcohol, but then you've got to really look at all of these other drugs as well. Again, looking at the NPR story talking about people with a prescription for a GLP-1 receptor agonist were less likely to experience an opioid overdose.

So, I have to imagine opioids are going to be yet another target at some point; at least certainly, it's an interesting additional drug to look at for these compounds. But there's another question that I have, and that is when you integrate new treatments into addiction care, that comes with challenges, and I'm curious to know from you, what are the hurdles that you anticipate with GLP-1 receptor agonists? Things like, could it be cost? Could it be access? Maybe even equity?

Dr. Weiss: Yes, is the answer to that. All of the above. In all seriousness, I kind of look at this as going one of two ways. One of which is that the drugs just don't work even though we have preclinical data and we have retrospective and cohort data and social media data, even suggesting that they do anecdotal data, that maybe we do these—our trial, and there's about half a dozen of them going on right now for alcohol use disorder specifically. And maybe they just don't work, and that would, obviously, be very disappointing. So, that would be a challenge because then we're back to the drawing board.

But on the other hand, let's say they do work, and they work beyond our wildest dreams. And now we have this amazing drug that is really helpful for alcohol use disorder and maybe other substance use disorders. And then the question is well, how do we make sure that it's available for everyone?

So, you may be aware that there have been some issues recently with semaglutide and other similar drugs having shortages where people aren't able to get them. And now people are attempting to supply them through compounding pharmacies, which has its own set of problems.

So, my background is actually in medical toxicology. So, we're interested in how all the different things that can go wrong with drugs, like nobody ever wants the toxicologist at their party because we're always the ones thinking about how everything can go wrong with people's drug and medication use. But in all seriousness, there have been people who've had some issues with compounding

pharmacies where there's dosing errors, there's contaminants. So, these are not being followed by the FDA the same way that you would from a drug manufacturer. So, that's one potential problem. And then, even though, let's say, the supply chain was perfect, and there was no problem there. Now you have a case of these very expensive drugs, and they can cost up to a thousand dollars out of pocket per month for people, which many of us, I think, would struggle to afford. And even if you have insurance, the insurance may not want to cover it.

So, we tend to see people with diabetes don't have as much problem getting their GLP-1 receptor agonists covered compared to folks with obesity. And there's just this idea that sometimes, I think, that even though there is, obviously, a lifestyle component to both diabetes and obesity, there's more stigma with obesity, no question. And so, my fear is that we will see a similar kind of thing with addiction with any alcohol use disorder or any other substance use disorder, in the sense that there's this idea that people have done it to themselves, and so, the insurance companies will not want to pay for the medication.

Dr. Taylor: Yeah, I would argue there's an even greater stigma with respect to addiction. And people who have substance use disorders than even with obesity, frankly.

Dr. Weiss: Yeah, there's significant stigma for both, yeah, for obesity, definitely, and also for addiction, no question. Yeah.

Dr. Taylor: Yeah, so that's gonna be a real concern. And yet, there are a significant number of people who have both, right, who have obesity and who have diabetes and who also have a substance use disorder. And so, I guess that brings to mind my next question, which is what are some practical steps that addiction care providers could take to adopt these treatments to adopt some of the GLP-1 receptor agonists? And what are some unanswered questions that we have still? And I'm sure there are many.

Dr. Weiss: Yeah. So, that's a great question because these sound great, right? And like you mentioned, those recent articles that came out that are retrospective and cohorts, and there's all the anecdotal evidence now.

And so, everybody's super excited, and we're super excited too. We really are hoping hard that this is going to work. And, unfortunately though, we still don't have the data.

The first randomized control trial, which was done by one of our colleagues down at UNC, should be published any time now. He's done his analysis. They're getting ready to publish. So, these data are coming. So, hang on. But unfortunately, we just don't know yet what we don't know. And, of course, we always want to start by not doing harm as clinicians. And we know that these hormones like GLP-1 are very complex. Their systems are complicated. There are receptors all over the body. And we just don't know what we don't know sometimes.

We don't know what the long-term effects like, for example, if we start adolescents on these drugs, you know, 50, 60 years from now, they're taking them for a lifetime. We don't know how long people would even have to take them. Potentially, they could have to take them for a lifetime.

You know, nobody expects someone with diabetes to go off their medication or blood pressure and so forth. And so, it's entirely conceivable that people with addiction could likewise need to stay on these drugs for many years or potentially even their entire life, or the effects will wear off.

So, what I would say is we should have some humility. We should have some caution. If you have patients who have comorbid conditions for which these drugs are FDA-approved, meaning, right now, that would be diabetes type 2 or obesity, and they also have an alcohol use disorder, then it makes total sense to consider trying one of these drugs. But that doesn't mean for folks who just have alcohol use disorder and don't have one of those two comorbidities that you can't do anything. There are treatments, right? We do have FDA-approved treatments, and particularly naltrexone and acamprosate, that are widely underutilized.

And so, what I would say is, don't just feel like it has to be GLP-1 receptor agonists or nothing. You know, there are other things that, in the meantime, while we're waiting for the evidence that we need so that we can make sure we're doing more good than harm with GLP-1 receptor agonists in this patient population, there are other things we can do for these patients.

Dr. Taylor: No, absolutely. Absolutely. There was a financial official back in the government several decades ago who warned against irrational exuberance, and that is something for us to be careful about when it comes to the GLP-1 receptor agonists. We really still need to be thinking if you have a patient with alcohol use disorder and that patient does not have coexisting obesity or diabetes. Really, the treatments of choice, which, as you point out, are very underutilized from a pharmacological perspective, are naltrexone and acamprosate.

But is there anything else that you want our listeners to know about the GLP-1 receptor agonists? Again, these are very exciting times. What else can you share with our audience?

Dr. Weiss: So, like I said, the first trials are, the very first one is done. There's at least four others that are currently in the works. So, this is specifically just for semaglutide. I'm not aware of anyone testing terzepatide, which is the other popular [one]—it's actually a GLP and GIP receptor agonist—but there are preclinical data and also retrospective in social media anecdotal data for that drug as well. So, there will be data coming.

Like I said, hang in there. The calvary's coming, we are going to have these data in the next year or two. And I think we're going to have a very good sense and hopefully be

able to do that. I'm excited. Also, it's a hot area of addiction medicine for a reason because we all feel so hopeful. And, at the moment, we have so few different classes of options—classes of drugs to use for these—and for some of them, like stimulant use disorders, we really have nothing at the moment in terms of pharmacological treatment.

So, I really feel very optimistic and would say to everyone listening, please do feel optimistic, don't be irrationally exuberant. Good way of putting it.

Dr. Taylor: Absolutely. So, Dr. Stephanie Weiss, thank you. Thank you. Thank you so much for sharing your wisdom with us, getting us a little bit of insight into the research that you're actively working on, and just letting us pick your brain today. You know, you are on the forefront of this. You're going to be sharing your data sometime soon and publishing it. And I'm excited to see that as well. And our audience is really lucky to have you as our inaugural ASAM Practice Pearls guest; thank you so much for joining us and sharing your transformative insights on the use of semaglutide in addiction treatment.

For more information on semaglutide's use in addiction medicine, be sure to attend ASAM's session on GLP-1 receptor agonists at the annual conference this April in Denver. Dr. Weiss will be presenting there. So, if you want to hear more of her wisdom, you can do it in person at our conference. You ought to be there. So, register now to secure your spot and gain valuable insights from leading experts like Dr. Stephanie Weiss.

Also, don't forget to subscribe and share this episode with colleagues who may find this information helpful. We'd also love to hear your thoughts. What challenges or benefits do you anticipate in integrating semaglutide into addiction care? Let us know in the comments.

Thanks for listening, everybody. We'll see you next time on ASAM Practice Pearls.