Kendal Williams, MD (Host): Welcome everyone to the Penn Primary Care Podcast. I'm your host, Dr. Kendal Williams. So, we're all prescribing them, maybe multiple times a day. We're managing all kinds of issues with them, probably also multiple times a day. And it's time that we start to talk about them in this format. And that, of course, is the GLP-1 agonist drugs, and beyond that, the newer drugs as well. So we're talking about Ozempic, Wegovy, tirzepatide, and it's brand names that we'll talk about.

So in order to do that, I invited back on the podcast, Dr. Anastassia Amaro, who was by the way, terrific in our first podcast on obesity. And I really recommend you listen to that, in addition to, I hope you listen to the rest of this. But Dr. Amaro really went over the basics of obesity and talked about all the latest trends in that area. But we're back here to talk about a specific class of drugs that are really having a dramatic impact on the management of obesity, and all of us are doing it every day. So Dr. Amaro is the Medical Director of the Penn Metabolic Medicine, the Obesity Center at Penn.

She's an Associate Professor of Medicine at Penn. Anastassia, thank you so much for coming again.

Anastassia Amaro, MD: Thank you, Kendal. My pleasure. Thank you for inviting me.

Host: At our first podcast, we were joined by Rani Nandawada, who is unfortunately unable to join us tonight and really wanted to have Rani's beautiful voice in the program, but weren't able to do that, wasn't able to pull it together. But Anastassia, I'm sure your life is similar to ours, probably in a much greater magnified version.

You are prescribing these drugs every day and managing all of the things that come with prescribing in terms of not just patient symptoms and their effects, but also the whole insurance world and so forth, right?

Anastassia Amaro, MD: Absolutely. Absolutely. And, more recently here at Penn, at UPHS, at the level of UPHS, we've been partnering with pharmacies to get prior authorizations carried out.

Host: Let me just go over the drugs we're going to talk about. So, there is obviously earlier GLP-1s, but sort of the I think the obesity, the use of these for obesity really got going in earnest in 2021 with Ozempic. Of course, Ozempic was approved for diabetes and was semaglutide, approved in 2017.

In 2021, it was then approved by the FDA, more specifically for obesity, and renamed Wegovy with some dosing and other changes that we can talk about. And then more recently we've seen the emergence of tirzepatide, which came out in 2022, I believe, as Mounjaro for diabetes. And then just, last month or the month before, came out now as with a special approval for obesity now is Zepbound.

Anastassia Amaro, MD: October 2023. Yes. Time flies.

Host: It does fly. Yeah, it really does. So these are the drugs we're talking about and we'll drill down on each of them as we go forward here. But I actually wanted to start with some of the physiology for, because this is new physiology for those of us who trained in, went to medical school in my era, this is a new hormonal system to talk about. So let's talk about just GLP-1s, or the glucagon-like polypeptide hormone. What does it do in the human body? This ia an agonist. Semaglutide is an agonist, and like drugs, are agonists of this hormone, so what does it do in the body?

Anastassia Amaro, MD: Absolutely. So glucagon-like peptide is a peptide naturally occurring in the body, produced by L cells in jejunal mucosa. It has multiple receptors in the body. We started learning about GLP-1 agonism in the beta cell, in the islets, pancreas first, and that's how it was developed into a diabetes medication.

Since that time, multiple receptors has been in multiple organs; in the adipose tissue, in certain areas of hypothalamus, in the gut as well. So when treating obesity, we are benefiting from the effects of GLP-1 on beta cell by modulating insulin release in response to nutrient ingestion.

We also benefit by the action of GLP-1 on hypothalamus and sort of re, I would say, normalizing some of the conversation between the brain and the gut. Also by slowing gastric emptying and making food sit in the stomach a little longer. So these three main mechanisms do lead to improved satiation, improved satiety, and reduced hunger.

Host: When I explain these to patients, I tell them that this drug mimics a hormone that your stomach makes to tell your brain that you're full.

Anastassia Amaro, MD: I like that. Mm, mm.

Host: I suppose that's as simple as could be. But it also short changes the hormone to some degree, because as you noted, it really does have effects on

the pancreas, on the fats, on the adipose tissue, as you noted, I think even on bone.

I'm not sure that we really fully understand all of those aspects in terms of what is exactly happening. I suppose other than the early satiety, which is obvious, that people just don't have the hunger that they expressed before or felt before; we don't fully understand exactly how it's working.

Anastassia Amaro, MD: We don't. And I think we actually may learn more about it through analyzing in detail, data from SELECT trial from the five year trial of cardiovascular outcomes. Because we honestly don't even know if the we do. So SELECT trial was first presented at the American Heart Association meeting here in Philadelphia in November of 2023, and it demonstrated quite reliably, 20% risk reduction, in three point, mace, which included non-fatal heart attack, stroke and cardiac death, I believe. But to me, it would be interesting to go back and look if this effect is truly weight dependent or there is a weight independent effect of GLP-1 receptor agonists, possibly on cardiovascular system.

Host: So, I want to go into that trial a little bit more in a bit, but I, let's just, because we're going to talk about tirzepatide, so, semaglutide, Ozempic, Wegovy, is purely working on the GLP-1 system. Tirzepatide came out and was also not only a GLP-1 agonist, but was also affecting gastric inhibitory polypeptide, or GIP, I don't, I don't know if that's how you refer to it. I've

Anastassia Amaro, MD: It is a glucose dependent insulinotropic polypeptide. It's GIP, so it's glucose dependent insulinotropic.

Host: Yeah, so I'd initially written that down because that's what the thing said, and then it was described again in a different article I read, and the way I what seemed to translate better into GIP, and I decided that was probably the accurate one. But the accurate one is what you said, right?

Anastassia Amaro, MD: Well, I want to believe that.

Host: Okay, so let's talk about what that does. So it acts in a very similar way to GLP, right?

Anastassia Amaro, MD: It is, produced a little higher up in duodenum by K cells of duodenum mucosa. It does have affinity towards beta cells in the islands of the pancreas as well. And then, I believe we know much less about GIP than we know about GLP-1, and we don't even know GLP-1, that well. We do know

that GIP binds to adipose cells, so there is a big body of research about what GIP might be doing with biology of adipose tissue.

We do know actually, it was shown here at Penn by Matt Hayes, that it's, GIP does have an effect on the hypothalamus, and that effect is to some degree maybe anti emetic. that helps me understand why, I think I receive much fewer phone calls about nausea from patients who are taking tirzepatide than from people who are taking semaglutide.

And then we also know that GIP promotes insulin sensitivity at various tissue levels, at the adipose tissue level and probably at the muscle tissue level. So it facilitates glucose transport, insulin dependent glucose transport into the cell.

Host: So in reading about that, I had a question, and I don't know if you know the answer to this, but that would seem to, because, you know, insulin is an anabolic hormone, more glucose in cells means more fat storage, that that actually may induce weight gain, but apparently that's not the case. Maybe I'm not just understanding the physiology well enough.

Anastassia Amaro, MD: I think there is a very interesting debate, so you, I don't know if you're going to be surprised by that, so we determined that tirzepatide is a combination of GLP-1 receptor agonism and GIP agonism, right, so we refer to them as dual agonists, medications that combine those two actions.

However, there is another product in research right now, that combines GLP-1 receptor agonism and GIP antagonism, resulting in very successful weight loss. At this point, it's an academic exercise, I think, trying to understand, and explain what we actually see in the research lab and bring theory to explain what we actually see, to explain the practice.

And, one of the explanations that I was somewhat able to comprehend is that actually we're dealing with it's the antagonism that's beneficial to weight management. And the GIP agonism as part of tirazepatide works by almost like saturating this mechanism to the point that the signal that it becomes impermeable for the signal.

So it actually is the antagonism that leads to help with weight management, but more to come. I don't think this has yet been resolved, but a fact that we have two molecules in, we will have them in the market currently in research space. One is already available; GLP-1 GIP agonist, dual agonist, and another one in clinical studies, GLP-1 agonist and GIP antagonist.

Host: So, I don't want to spend too much time on the pathophysiology or the physiology or pharmacology here, but I just found it interesting. So, you know, we have Januvia, which is the sitagliptin, which increases the or actually blocks the DPP-4 system, which leads to the breakdown of GLP.

So you're basically, you know, using these drugs to increase the GLP by reducing its breakdown, a mechanism that's true of many drugs that we use in medicine, you know, inhibiting the breakdown leads to increased levels and so forth. And those are the gliptins. They do not seem to result in weight loss the way these drugs do.

But the other thing I found interesting about GLP-1s is that, you know, they're actually very transient hormones, and one of the issues that I had was in using it as a pharmacological product is that it didn't last long, and so they were able to finally get it out of the Gila monster, you know, the reptile, out of the saliva, a version of it, if you will, that was not broken down by DPP-4, and that sort of became the, uh, like it became exenatide or Byetta and then eventually led to all of these other developments in that space. I just thought that history was kind of interesting.

Anastassia Amaro, MD: Absolutely, yes. The half life of naturally occurring GLP-1 molecule in the body is about two minutes. So, by using DPP-4 inhibitors, we inhibit the breakup, but you are absolutely right; DPP-4 inhibitors do not result in weight management, weight loss. It's possible that we are achieving really supra physiologic concentrations with injectable GLP-1 receptor agonists.

And not always can we measure it in the blood. It's probably, I wish we had ways to measure the action of a drug or a molecule at the level of receptor. I think it's going there right away.

Host: And the last thing I found interesting on this space is just that patients with obesity seem to have diminished levels of natural GLP-1. So by giving it to patients, we're actually sort of bringing them more up into a normal range, or that was an observation at least.

Anastassia Amaro, MD: There are some contradicting observations in different trials, but I think what has been repetitively demonstrated that people with obesity have somewhat higher levels of GLP-1, but they are not fluctuating, they are not going up and down as expected in normal physiology.

And that's very similar to what we're seeing with insulin levels in people with insulin resistance. You have elevated levels of insulin, but then you don't have enough capacity, beta cell capacity, to go up in early postprandial state, and then you never come down because you're so resistant, and so the levels are kind of hovering in the middle.

And when we add exogenous GLP-1 receptor agonists, we sort of reintroduce normal physiologic pattern of going up and coming down, definitely for insulin and for GLP-1s to some degree.

Host: I'm probably more interested than our audience in all of this stuff, so I'm going to leave it for now and but I think, you know, as we think through these drugs, and talk to our patients about it, I did want to go over that so that we, you know, at least have some facility in being able to discuss how it's working in the body.

Let's talk about these drugs and let's just deal with semaglutide first because historically that came before. So as I mentioned, it was approved in 2017 for diabetes. In 2021, it came out as Wegovy after the approval to treat obesity. The trials that have really sort of told us that this drug is worthwhile are the STEP trials.

There's been several of them. You know, the big thing to me is just that, you know, they consistently showed about a 15 percent drop in weight, which is significant, and you had said this before on our previous podcast, it's well known, if you get a 5 to 10 percent drop in weight, you can have, you know, meaningful effects on diabetes and blood pressure and so forth.

So a 15 percent drop is a meaningful amount. All patients in these trials were also encouraged. They were given dietary advice. They were encouraged to do exercise, at least 150 minutes of moderate exercise a week. and, you know, they showed us that these drugs were effective. But the STEP trials much better than I do. But I wanted to do that little intro to them.

Anastassia Amaro, MD: Thank you. That's absolutely accurate. I probably would like to emphasize, or just once again, to mention the nomenclature and names because it's becoming more and more important, to actually prescribe an accurate brand name for a condition. So semaglutide exists in two commercial names. One is Ozempic, which is approved and covered by majority of commercial plans and Medicaid and Medicare for diabetes. And, Wegovy is marketed for obesity. Both are semaglutide, of course, and dose regimen is very,

not identical, but very close. Semaglutide, by the name of Ozempic, goes up to 2 milligrams, per week total, and Wegovy goes up to 2.4 milligrams per week.

Host: They're different in also in how they're, patients experience them, right? So, I was confused about this. I actually went down to our pharmacy at Radnor where I practice and I said, can you explain to me, you know, when I'm ordering this, what are patients actually getting? So, Ozempic comes as a pen, which has four doses in it. So a month supply for a weekly dose of an injectable. And it, you have an ability to toggle between, I actually don't know how high it goes on the initial pen, but I think it's .25 and .5. Do you need to order a different pen if you want to go to the higher doses?

Anastassia Amaro, MD: Yes, absolutely. So it's actually three pens exist. So first pen it goes up to 0.25 and 0.5 total. Both doses are marked on the dial. So people can dial 0.25 and we usually recommend that they do so for the first two to four weeks and then the same pen they can dial up to 0.5. So if they're using 0.5 a week, one pen will last them four weeks. You're absolutely right. The next pen, so if you passed 0.5, if you're increasing the dose past 0.5 milligrams per week, you go into the next pen. The next pen will be Ozempic 1.0. That pen only has one markup of 1.0, the top dose. You can still inject less, but you would need to use what we call click method.

So total number of clicks, I think somewhere in the vicinity of 70, I want to say then. So half of that would be half the dose. If you need to do that, let's say, you know, that's the only, pen available considering the shortages that we've been having. So you can prescribe whichever pen is available and it kind of count clicks and come up with the right amount.

Ozempic is excellent and very convenient this way because it's a, it is dose adjustable pen. And then there is a, the third pen, Ozempic 2. It goes up to 2 milligrams. So again, it's only marked at 2.0. Everything else are just clicks. You can count them and, inject as little or as much as you need.

Host: So I had a patient who's an orthopedic surgeon. For issues of availability, I think primarily, he ended up needing the 2.0 cause, or that was the only option to him. He hadn't started it, but he said he wanted to try it, and I said, you know, that's really not a good idea, you're going to get really nauseated. But when he got the pen, he realized that he could do this click method, and he could start at the .25, and then this pen would actually, if he got more needles, would actually last him a long time. So I think he ended up paying out of pocket for it. Drug costs about $1,000, but he was making it use of it for, I don't know, three, four months or something like that. Is that right?

Anastassia Amaro, MD: That's absolutely right. I'm glad you said all this. It's all against FDA label, but we do that, we do that. It's, it's the same semaglutide, and that's how you make it affordable to some people who can do it.

Host: So I guess if you, let's say you start, you're at 0.5 and you have a two milligram pen, you know, you're going to be able to get eight doses out of that or, or more, right?

Anastassia Amaro, MD: Probably, yeah, so I think at some point, you probably will be nervous about keeping the same open pen for longer than, what, 60 days, 90 days. What's your comfort level when formally it says, do not keep past 28. But, at least it's a clear pen, you can see if the solution is still clear, you're probably safe.

Host: So that's very interesting. And these are kind of little practical things that we struggle with in our area here. Before we get to more practical issues of prescription and getting it authorized and available and so forth, I just want to talk about the trial you mentioned earlier, and that was the SELECT trial.

Because I think that's the other big thing that's out there. It's not just the weightloss trials that showed 15 percent reduction, but the SELECT trial, which looked at over 17,000 non, non-diabetics, so these were obese patients, not diabetic patients, who got semaglutide at 2.4, which would be the highest Wegovy dose.

And then in that, they saw a 20 percent reduction in absolute risk of cardiac events, at roughly three years period. That was a big deal. Not sure the full impact of that study has been felt in our community yet. But the fact that we can prescribe something to patients at risk for cardiac events that would reduce it by 20%, I mean, I don't know, I think statins are about 30 to 40%. So I mean, this is a pretty big deal.

Anastassia Amaro, MD: I think it is a huge deal. I probably would like to point out the inclusion criteria, the patient population that was included, so we don't extrapolate it to everybody. So age, it was 45 plus. BMI 27 plus and people would have to have a high burden of cardiovascular risk factors or actually, established cardiovascular disease such as primary cardiac infarction, stroke, or peripheral arterial disease with claudication. Prior revascularization or amputations. So those are inclusions. We're still talking about sicker individuals. It will be hard to extrapolate this to a healthy 28 year old, with um, BMI of 35 without metabolic complications.

Host: But I think you'll see in this same area that what we've seen with the SGLT-2s, that insurance companies are going to be pressured to approve this drug if it becomes sort of a cardiac drug.

Anastassia Amaro, MD: Absolutely. That's the way to get people on those medications. Absolutely. That's going to be our way. And I, I know for a fact discussions along those lines are happening right now, you know, with the major prescription benefit managers.

Host: So let's go back and talk about Wegovy because that is a little different in how it's dispensed. The folks at the pharmacy told me that if I order 0.5 Wegovy, people get four distinct syringes, not a pen that you can toggle between different doses. You know, you get four and that's your month's supply, and then you have to come back.

So when you order Wegovy, if you want to start at the 0.25 dose, you have to write a prescription for 0.25. You get four syringes, and then you have to write another prescription per 0.5 when they go up to that dose, and so forth. And it goes like that, up to 2.4, right?

Anastassia Amaro, MD: Yes. It's a labor intensive, sort of exercise and a lot of plastic waste, so people receive, four humongous pens, which is, one use only. It's use it or lose it. It's all or nothing. You cannot adjust. So, I do understand how they came to this decision, sort of from a marketing standpoint and it was a business decision, but they also say the company Novo Nordisk, they also felt that was the most convenient way and it's, it was best liked by potential users. You don't even see the needle. You don't touch the needle, you don't manipulate the needle, so it's easy.

Host: You know, I wanted to ask you about dosing because, you know, I have patients who have had a lot of success at the lower doses. I've had patients that go to 0.25. They're losing weight at a pace they're happy with and they never go up to the 0.5 dose. But when I look at the trials, you know, a lot of these were done that, you know, we talked about the SELECT trial. It was at 2.4 milligrams and so forth. I'm just curious in your experience, what you're seeing in terms of the dose finding exercise of where people are having success.

Anastassia Amaro, MD: I absolutely agree with you, Kendal. I have people in the maintenance phase on very different doses. If someone is sensitive enough to start losing weight on the first on the lowest or the next dose, there is no reason to speed up their titration. So save it for a later day when they stop losing or they start regaining or they start struggling despite injecting the medication.

That's my approach. So we, rather than targeting a dose, we're targeting weight loss velocity, if you wish, as long as people are losing one to two pounds a week, that's a good weight loss. That in most likely with one to two pound weight per week, they are losing mostly adipose tissue and less so muscle.

If you're losing more than two pounds a week, you're probably losing muscle. So people who do that need counseling on resistance training. Well, everybody does, but especially people who are losing weight rapidly.

Host: Let's talk about what patients experience and why they're losing weight, because most of the patients that have, and I always ask patients, you know, if they've had success, well, you know, what has, why are you losing weight? And invariably they tell me, I'm not hungry. Food has no attraction. Two patients really stick out in my mind.

One who said, I have to remind myself to eat, and I'm just not really hungry. And then the, the, the other one said, similar to something I think you alluded to, that before I was always thinking about food, I was always thinking about what my next meal would be. My mental life centered around food and that whole dialogue is gone. Is that what you're experiencing as well?

Anastassia Amaro, MD: Absolutely, yes. And it could, it really can take different spins in different people's lives. So some finally feel relieved of that pressure of thinking about a food or pressure of trying not to think about the food when the food is in their mind. And others, actually, may not like it as much because they may be losing their social life over it. They, they are not interested in going out. They're not interested in hosting parties. So yeah, it's, it's individual. We need to talk to people. We need to talk to people and we may need to adjust their expectations or dose of the medication based on their individual goals.

Host: How about side effects? You know, almost all of them were gastrointestinal in the studies, nausea and diarrhea and constipation I saw.

Anastassia Amaro, MD: That's absolutely true, definitely in the studies. But I think what we've been seeing in the last year or so when the medication sort of left that research space with selected and still quite homogeneous patient population and entered the real life clinical space where people with multiple different diseases that were excluded from the studies to begin with, or patients with organ transplantation, patients with different cancer diagnoses. So we start seeing side effects that didn't even give us a signal in randomized controlled clinical trials. So for example, those interesting side effects that I've seen

recently. One is allodynia. So people develop that unpleasant, painful paresthesia type of skin sensation, specifically on semaglutide. I have not encountered it yet on tirzepatide, but semaglutide, yes. At least two cases are in front of my eyes. One responded to dose reduction and another one held it for a little bit, and then I think we switched to tirzepatide, and I'm yet to see how that goes. So, and we will probably see more. There is also fatigue, definitely fatigue.

Host: Fatigue is so hard in medicine. I always tell my patients fatigue is not a medical problem. It's almost never a medical problem, but, and that's why it's so, it's non-specific. And folks, their dietary patterns are changed, so teasing that out, the degree to which the drug is challenging. When they first came out, we were concerned about pancreatitis, both inducing pancreatitis and being a problem for patients who have had pancreatitis, also some gallstone issues. That seems to be less of a concern as it's evolved, but can you comment on that?

Anastassia Amaro, MD: Gallstones. I think gallstones I do continue seeing relatively, I think, increased risk of having a gallbladder attack or needing cholecystectomy while taking the medication. So I do think we're provoking those attacks in people who are predisposed. Whether it's a direct effect of GLP-1 receptor agonist on yet another receptor somewhere near a gallbladder, I don't know.

I doubt it. The thought process was that any rapid weight loss could provoke a gallbladder attack. And I think that's what we're seeing, so most successful patients probably, I shouldn't generalize, you know, I, but I do think people who start losing weight rapidly, are probably more prone to developing a gallbladder attack if they had a predisposition to it.

As far as pancreatitis, I don't see an increased incidence of pancreatitis in patients taking GLP-1 receptor agonists. It is still my question and I do get a careful history of what happened to their pancreas and gallbladder before prescribing. And someone who, let's say, had a bout of pancreatitis related to gallstones many years ago and since then had a cholecystectomy and gallstones are gone and never had another bout, I would prescribe it. It would not be a contraindication in my mind.

Host: So let's talk about tirzepatide because that's the newer one. Came out in 2022, I believe, as Mounjaro as a diabetes drug. Also, a weekly injection. I know these are different companies, but it was kind of nice of them to do it, these two drugs in a similar way, so that when we got used to giving them, we, it was sort of the same system, at least. You know, starts at 2.5 milligrams, I

believe. And I think the high dose is 15. I don't have as much experience with Mounjaro. The trial that changed things is a trial of over 2,000 patients, and found that there was really a 20 percent reduction in weight at the highest doses, at 15 milligrams, lower doses were achieving things, reduction similar to semaglutide. But tirzepatide appears to be somewhat more potent for weight loss than semaglutide. And you alluded to the fact it may be better tolerated.

Anastassia Amaro, MD: True, and we still do not have an explanation. If we do believe that tirzepatide is a little more potent. We still don't understand precisely why. In the studies, there was an estimated approximately 350 calories decrease in consumption, food consumption by patients in both trials, actually, in both semaglutide and tirzepatide groups.

So pretty much people receiving semaglutide and tirzepatide without additional counseling, intuitively, reduce their caloric intake by about 350 calories, and yet, on average, it looks like people on tirzepatide lose a little more than people on semaglutide. Do we have an explanation? We don't. Could it be something related to adipose tissue biology and some signals coming out of there? Maybe, but we don't yet know.

Host: So that turning off of the desire to eat that we see with semaglutide is also there in tirzepatide, but it may be that tirzepatide has a little bit more of a boosting independent effect over and above its ability to just turn off your calorie needs.

Anastassia Amaro, MD: Maybe. Maybe.

Host: So I'm less familiar with prescribing this, but, I believe it's dispensed similar to Wegovy as individual syringes. Is that right?

Anastassia Amaro, MD: So, tirzepatide exists in two commercial forms. Mounjaro is for diabetes and Zepbound is for obesity. Mounjaro and Zepbound have absolutely identical dose regimen. Unlike Ozempic and Wegovy, where you still have slightly different final dose, like highest dose, Zepbound and Mounjaro have exactly the same step titration and lowest and highest dose from 2.5 up to 15. And they are prescribed the same way, four pens at a time, or 2 mls, I think. You need to change your prescription on a monthly basis if you're up titrating, or you could do it slower. I do find that people, actually start losing weight on the lowest dose, and there was no hurry in titrating it up.

Host: So even at the 2.5 milligram dose, you're seeing people losing weight and just staying there.

Anastassia Amaro, MD: Some do, yeah.

Host: That's great. So, you know, looking at the wholesale cost of, of all of these drugs, you know, the four brand names and two generics; you know, it appears to be they're all hanging around the thousand dollars, if bought without insurance support. And some people choose to do that. And, you know, there's little things that maybe we could do in terms of especially that trick with giving the Ozempic two milligram pen and sort of extending it and figuring out how many clicks you get for each dose, and doing it that way.

But other, you know, other than that, you're left with paying quite a hundred, at least hundreds of dollars per month for these medications. So, ideally you want to get insurance approval. To me, that seems pretty variable. You know, Penn Insurance is actually pretty good about it. The rest of the products are, the rest of the companies are all over the place. Is that what you're experiencing?

Anastassia Amaro, MD: Yes, absolutely. And I think 2024 will be a battlefield, between customers, demand is high, prescribers and third party payers. I do think that it may not be sustainable to make this medication available to everyone who needs it, you know. We are expecting the rates of obesity to be around 50 percent by 2030.

So 50 percent of adults in the U.S. may potentially be candidates for these medications. So who's going to pay the cost, pay the price? I don't know. But what I know right now, the insurers and prescription benefit managers, PBMs are doing, they are trying to offer it because the demand is huge. But they try to offer it with certain, they call them guardrails, with certain restrictions, and they are trying to either cut off healthier individuals. So let's say even though in patients with BMI of 27 and 1 complication or 30 plus, regardless of complications, were included in clinical trials, and that's how it is approved by FDA; an individual plan may have a cutoff of BMI 35 and comorbidities, or BMI 30 and 2 comorbidities, or not one. So they are trying to save on sort of healthier patient population. Another, hiccup is what if people already did something to lower their BMI and they had obesity by definition, by BMI definition, six months ago, and now their BMI is 29.

So that's another situation where some plans are better than others. Some plans do recognize that and as long as you mentioned in prior authorization, you mentioned the original BMI, they go by it and continue the medication for healthy weight maintenance. Others give you a really difficult time continuing this patient on a medication.

Host: So these are situations where you're, you're having to get approval again a second time and they've already lost a fair amount of weight and now you're trying to get it back again.

Anastassia Amaro, MD: Or people, this is the first time for a person who just got a job with this insurance plan, for example, but who had been already on a medication before or did a good job losing weight on their own and need to continue.

Host: One of the things I thought as I was reading about this is that I wonder if employers are going to ask, maybe put it in as a perk that they'll simply, rather than having the health insurance company they contract with pay for it, they're actually going to sort of offer to pay for it for their employees. Uh, it's not an overwhelming cost and depending on how long you may have your employees, if you can offer this benefit and say, you know, if you stay on a losing path, it may reduce sick days, you know, and some other issues that may make it affordable even to just pay out of pocket by employers. It's just a crazy idea I had, but

Anastassia Amaro, MD: But about employers yeah, I think this is a good idea. I wouldn't be surprised if, some already look into that, to eliminate one more chain.

Host: And employers are going to have a lot of say about what the insurance companies do, especially the bigger ones. If they feel like it's really beneficial to their employees, they, they're going to be pushing. Okay. So, but that's, those are sort of global health policy issues and not necessarily what the average primary care physician is going to experience.

Let's talk about what happens, you have a patient, you said that healthy weight loss is one to two pounds per week, they're losing weight, they get to their goal weight, or well, let's talk about they don't get to their goal weight, they plateau. What do you do then?

Anastassia Amaro, MD: Well, it depends where they plateau. If they plateau at 10 percent weight loss or more, that may be the goal. The BMI may not be at any kind of ideal body weight, which we don't even know anymore, I think, what that is. But if they've lost at least 10 percent of weight and plateaued, you kind of, you reconvene and see if you, if you've really achieving what you, you've tried to achieve.

Have you achieved any improvement in blood pressure control, diabetes control, pre diabetes is resolved, triglycerides are down, fat in the liver is down. Then at that point, your strategy may be to sort of redefine the goals of care. It may be weight maintenance at this point.

So we do know that yo-yo dieting or yo-yo weight changes up and down are not good for cardiovascular health. It's probably related to changes in body composition. Every time we regain and lose, we may, may be losing sort of more muscle and regaining more fat, although many will argue with me, so we need more data about that.

But nevertheless, we do know that going up and down, up and down almost eliminates cardiovascular benefit. So we do need to help our patients maintain reduced weight. Whatever reduction there was, if it's 10 percent or more at this point, I'd say that's what you want to maintain for as long as possible. So I wouldn't call the medication failed if they are still able to maintain 10 or more percent weight loss. But if they start struggling and regaining while taking the medication, then I think that's time to sort of reassess. Are you going to be switching medications? Are you going to be looking more precisely into what they're doing, physical activity wise and lifestyle wise and other medications that have been prescribed in the meantime or other diagnoses they have received? So that's the point where you definitely want to reconvene.

Host: So it's interesting, because one might think that you would just want to increase the dose. But Lasix is a drug, for instance, has this threshold effect, you know, once you find an effective dose, it's really not helpful to keep going up, because, you know, you found the dose that is going to induce diuresis.

I'm curious, do you let's say somebody lose, they're on Wegovy, they hit one milligram, they're losing at one to two a month. They're on it for a year and a half, they lose 20, 25 pounds, and they've lost over 10 percent of their body weight, they're doing well, and then they say, can I increase the dose? What would you say to that person?

Anastassia Amaro, MD: Again, it depends where the plateau is. If the plateau is in the sort of normal or close to normal BMI range, then we may discuss whether it's necessary. If the plateau is still above 30, you know, of course, let's keep going. Let's keep going. We're going to go slowly, but yes, there is a, uh. What would preclude me from recommending the dose increase is the burden of side effects, honestly. So if they don't experience the side effects, let's titrate to the highest approved dose. Nothing precludes us.

Host: Let's talk about weight maintenance. When I first heard about the rebound effects, my first thought was, well everybody, every diet that has ever been done has rebound effects. When I was looking into this today in prep for the podcast, I saw a statistic that folks were losing weight, but then gaining back 11.9 percent of what they had originally lost, which is lot less than they had lost in the first place. So if somebody loses say 15 percent and they only gained 11 percent of that total back, you know, they're not, they've still lost quite a bit of weight. So, what kinds of weight gains are we seeing when patients go off the medication is my question.

Anastassia Amaro, MD: It varies. It varies. We can see full weight regain of the entire weight that they lost on the medication. And it can happen probably not very rapidly. It's still going to be some legacy, but it may happen. On the other hand, I do see patients who were able, I believe those are the patients whose, sort of physiology allowed them to use the time on the medication to optimize their lifestyle and to train their hypothalamus to new set points, to new portion sizes, to new dietary choices that when they go off the medication for one reason or another, and it could be coverage is over and they have to do it on their own now.

They may have that legacy quite prolonged. They may regain maybe a third of what they've lost, but they may have months and years of still reduced weight. And I think that's where we're moving with positioning the role of lifestyle modification, where in the past it was, um, you, you have to fail weight loss attempts on your own before being eligible to the medication.

While it still holds true for many insurers, we do understand with this second generation weight loss medications, we can start with the medication right away and counsel the person into optimizing lifestyle while on the medication, to actually to get to the target, not only to the target weight, but to the target body composition and metabolic state.

Host: So when you're talking to patients about these medications, you're really sort of looking at this comprehensively. Because, you know, as I noted in the trials, you know, these folks were also given dietary counseling. They were also given exercise goals and so forth. So you're really incorporating a lifestyle change in that, knowing that eventually you would like to get them off the medication and then hopefully they'll be able to maintain that, right?

Anastassia Amaro, MD: Right. And that, eventually is different for everyone. So when they, when people ask me, how long do I need to stay on the medication? My answer has become, as long as it makes sense. If it makes sense

to, if the medication allows you to maintain lower weight, it's worth being on it. If you take medication and you haven't developed side effects and it's doing something, it's worth being on it.

If you're struggling with regain while on the medication or if you developed, you started developing side effects, which can be developing even a year or two into it, not necessarily right away, then we may have to decrease the dose, discontinue or switch.

Host: Actually, I want to highlight that because I, I didn't know that. So if you get patients, through an initial phase where they may be nauseated they accustomed themselves and they're fine, you're saying even after being on it months, they can actually develop more gastrointestinal effects.

Anastassia Amaro, MD: I do believe so. I'm seeing this, you know, it's possible that those are coincidental cases with something else, sort of, developing in their bodies, but I think it's the medication. So, I see people who've been successfully losing and maintaining lower weight on semaglutide for a couple years and then they come in with the terrible nausea and almost like gastroparesis type of clinical picture and it's hard to attribute it to anything else but the medication.

So maybe we will see more of that in the sort of real life experience. All the clinical trials, the original clinical trials, step trials, they were up to two years in duration. And now in clinical practice, we follow people for four, five, six, seven years on those drugs. So I think we will see more of it.

Host: So the final question I want to ask you, you know, really actually has to do with these lifestyle aspects and, you had mentioned that if you lose more than one to two pounds per week, then you can be losing muscle and that you're advising patients on resistance training and so forth. You know, I understand from our conversations that that actually is, it's kind of a hot issue right now.

Anastassia Amaro, MD: Absolutely true. And I think, so there are, I would probably single out a couple of scenarios or patient populations where we as clinicians should be particularly vigilant. One is elderly patients, our senior patients. We know from research prior to GLP-1 receptor agonists that managing weight in patients over 65 is more challenging in that they do lose more muscle when they lose weight.

So, ideally, geriatric population needs to be approached with resistance training counseling right away along with any modality, any weight loss modality. So

now we have patients who are over 65 receiving GLP-1 receptor agonists and losing weight rapidly. We shouldn't be forgetting that they may be losing the wrong kind of weight.

Again, I don't want to discount the importance of weight management in patients over 65, but I think we need to do better job counseling them about resistance training and lean mass maintenance. We may not need to escalate their doses based on what the study says. We may need to to use individualized approach.

So that's one patient population. And another patient population is probably people who are losing weight really rapidly. So that rapid weight loss. That's why I like bringing people back for even inpatient visits, because, you know, telemedicine, I may not even realize, how much muscle they have lost. And they, so I think people losing weight rapidly need to have a sit down conversation about their protein intake and resistance training.

Host: Are there specific dietary aspects other than Mediterranean diet, trying to develop good habits, making sure that people who may be eating reduced calories get, you know, the broad range of nutrients that we need as humans, but you mentioned protein. Are you, are you encouraging a higher protein diet, in patients that are not just losing weight rapidly, but even the general patients?

Anastassia Amaro, MD: Probably not general, but if they're losing weight rapidly and they're planning or starting to do resistance training, then probably yes, slightly, you know, higher than usual. But in general, I am asking people about their diets along the way and making sure they do have, sort of good amount of protein, some 80 to 100 grams of protein a day on average, I would say.

In addition to protein, yes, Mediterranean, low glycemic index, high fiber intake of vegetables, fruit, really, there is no single study and there have been lots of like billions of dollars invested in diet research that shows over and over again that we are not quite ready to recommend a patient specific diet.

It does come to caloric intake and as far as composition, it really comes down to protein, fiber, low glycemic index sort of being important in weight management and insulin resistance management.

Host: I'm a vegetarian, almost entirely, and, occasionally when I'm at the deli at Radnor and there's nothing else to eat, I'll have the tuna. But that is, I try to make that as rare as possible. But in making that transition over the age of 40,

by the way, I had to learn to love some foods that I didn't particularly like before.

But lentils are probably my favorite food now. And I, it's one of the great foods of humanity. You know, that you really appreciate just how wonderful that is. And, you know, getting 80 grams of protein a day as a vegetarian is actually a little bit of a challenge. You have to, yeah, you have to make sure you get something with every meal.

Anastassia, it's late. Really appreciate your time. I know for those of us listening, Anastasisa's had a full day of clinic today and you know, we record these late and I really appreciate you coming on to talk about something that we're dealing with all the time and just going into the weeds on this.

Anastassia Amaro, MD: Thank you, Kendal. Yeah, it was a pleasure talking with you. I like all the questions that you asked.

Host: Great. I should plug the Obesity and Metabolic Center, Anastassia's work on hopefully some of what we do here in terms of the podcast will help folks, who may have trouble getting their patients in or whatever, do the work that they're doing, in our own practices. So thank you all for joining the Penn Primary Care Podcast. We'll see you again next time.