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Experts on Call: Connecting Specialists and PCPs to Improve Patient-Centered Obesity Management

Announcer Open:

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Dr. Still:

Hello, and welcome to this presentation, Experts on Call: Connecting Specialists and PCPs to Improve Patient-Centered Obesity Management. This video roundtable is supported by an educational grant from Lilly and provided by Clinical Care Options.

I'm Dr. Christopher Still, Professor of Medicine at the Department of Clinical Sciences at Geisinger Commonwealth School of Medicine. I serve as the Medical Director for the Center for Nutrition and Weight Management, and also the Director for the Center for Obesity and Metabolic Research at Geisinger Health System in Danville, Pennsylvania.

And I'm pleased to be joined with Dr. Robert Kushner. Bob is a Professor, Departments of Medicine and Medical Education at Northwestern University Feinberg School of Medicine. And he serves as the Director of the Center for Lifestyle Medicine at Northwestern Medicine in Chicago, Illinois. Also joining us is Dr. Donna Ryan, Professor Emerita at the Pennington Biomedical Research Center in New Orleans, Louisiana. Welcome, Bob and Donna.

And the correct answer is D, you share decision-making strategies to discuss pharmacotherapy options for weight loss. And we'll come back at the end and discuss these.

And the correct answer is D, subcutaneous semaglutide.

And the best answer is C, a 32-year-old woman with a BMI of 30 and no comorbidities.

And the best answer would be weight loss pharmacotherapy likely will be needed long term to maintain weight loss.

And we'll return to these questions again at the end of the presentation.

Now, let's talk about obesity and treatment in a slight – a quick obesity overview. So, hopefully, if you don't believe it now, everything on the left-hand side should be a myth: that obesity is indeed a choice, it's caused purely by lack of discipline or laziness, eating poorly, lack of intelligence and education. But really the truths are that obesity is a complex disease that has multiple determinants in between endocrine and metabolic physiology, the environment, genetics, behavioral and psychosocial elements. And that the take-home point of this slide is that obesity is a chronic disease similar to heart disease, diabetes, COPD, hypertension, that requires long-term management. And it's just not as simple as decreasing calories and increasing energy expenditure. The principles may be the same, but it's much more complex with regards to metabolic regulation, or what I would say dysregulation, which you'll hear about in a little bit.

The other thing I think is important is stigma among us, healthcare professionals. It's not just the public, its healthcare professionals have anti-obesity attitudes towards patients with overweight and obesity. And in fact, physicians, we are the second most common source of stigma, only behind family, I believe, that has the first. So, many healthcare providers believe that patients are lazy, undisciplined, and unlikely to adhere to anything we recommend anyhow, so why – it's a waste of time, why do we do it?

Even healthcare providers with obesity themselves have anti-obesity attitudes. I struggle with my weight. And I've been doing this for

25-30 years. And I'm embarrassed to say I was traveling and on a plane and on a window seat, and this large gentleman came down the aisle and I thought, 'Oh, I hope he doesn't sit next to me in this middle aisle.' And I felt terrible. But I mean, we all have our own attitudes. And that's okay, if we can appreciate those attitudes, but we can't make – we want to make sure it doesn't interfere with how we talk to our patients. Because words really matter. And I think how we set that tone of how we connect with that patient is really important, and the patients can pick up on it very easily.

So, how do we discuss obesity? How do we have that initial conversation? Oftentimes, it can be very odd awkward, but it really should be patient centered. It should be empathetic, not sympathetic. It should be unbiased, free of judgment, shame, or guilt. It should be really focused on health rather than the weight. Oftentimes, patients that had a bad experience will say, 'Well, my doctor, my healthcare provider said everything was related to my weight. And if I would just lose weight, everything would be better.' To a point, that may be true, but it's how you relay that and how you have that conversation with your patient is really important.

The other thing is what I think is most important of this slide is how we use terminology. We really want to use patient-first language. Patients with obesity or with overweight, they're not obese patients, we don't say patients are cancerous. We say patients have cancer, or affected by obesity, we want to avoid obese or fat.

And morbid obesity really is no longer accepted terms. We may use it for coding and billing purposes, but it really has no appropriate terminology in talking with patients.

And finally, we really want to focus on shared decision-making and providing practical options to assist in weight loss through their weight loss journey.

So, with that, I'm going to turn it over to Bob and Donna and ask how do you initiate conversations with patients regarding the importance of weight loss? You know, we're a little different in that we're a referral for patients that come for weight loss. But you guys have a lot of experience in, and I think, would concur that this is a really important moment and getting it right and talking with our patients. So, Bob, and Donna, what do you think?

Dr. Kushner:

Thanks, Chris. It's a great question to talk about a little bit. And I think there's two major points I want to make. The first is highlighting the whole idea of stigma and shame. And you could assume that most of the patients that come in to see you have a legacy of having healthcare professionals put them on the spot or shame them or call them out with stigma or bias.

For that reason, we often use the 5 A's framework. I think most of the attendees are familiar with it, because it's been used for smoking cessation and for alcohol misuse, where the first day is typically assess. But we've changed the first day in the obesity field to ask, and ask permission. So, it goes something like this, 'Is this a good time to talk about your weight?' Or, 'I see you have diabetes and hypertension, your weight may be affected. What do you think? Can we talk about it?' So, that's one thing is ask.

The other, Chris, is what I bring up with my medical students and residents all the time, particularly when you're seeing a new patient, and that is to incorporate a weight history into the medical history. You could put it in into the social history, you can put it into medical history, wherever it is in part of your medical history framework. But by asking it as part of a history, you've already broached the topic. And as they go through their weight history, of life events, what worked well, what didn't work well, what was their highest weight, what was their lowest weight, you're already talking about weight. And then at that point, you could say, 'You know, I have a lot of other things to cover in the medical history, but is this something you would like to return to when we talk about counseling? Because I think it may have an effect on hypertension we've been treating.' They say yes or no.

So, those are the two recommendations or caveats I'd like to bring to think about how we bring the topic up.

Dr. Ryan:

Yeah, that's a hard act to follow, isn't it? But you know, I'd like to just amplify something that Bob said, and that is the importance of asking. You know, obesity is a chronic disease, and we can't help patients unless we keep them coming back. And the last thing you want to do is have the patient have their feelings hurt and not return because they don't feel comfortable. So, I think asking for permission to raise the topic is important.

Bob also talked about the importance of taking the history about weight. You know, if it's the first time you're meeting a patient, do not assume that this is the patient's highest weight. That patient, even though that patient has obesity, may be significantly reduced already. So, don't have any assumptions about who that patient is or where that patient's coming from.

I think what our patients are looking for in us is helpful with health, and they feel judged about how they look. And so, that's why I don't really like to talk about obesity so much. I hardly ever use the word. It's really more about health. It's that connection between weight and health that I really try to focus on.

I think patients are also looking, even when they're not looking for weight loss, they're looking for competent medical care in people who have larger size. So, it's very important that we keep that in mind too. We need to treat patients' other conditions with other things besides just weight loss.

Dr. Still:

Excellent. The only thing I'll just end with, everything you said, I couldn't have said better, but patients want us to ask. They really want to have that conversation. So, don't think they don't, they do want to have that conversation. And hopefully after today, you'll have more tools in your toolbox to talk about – talk to them about their weight loss journey. So, very good.

Now, I'm going to turn it over to Dr. Ryan, who's going to tell us why it's so difficult to lose weight and keep it off. Donna?

Dr. Ryan:

Thank you, Chris. You know, so this really illustrates the problem with trying to lose weight. Yeah, it's true, you must create an energy deficit in order to lose weight, you must consume fewer calories than you're expending in physical activities and in living. And so, that's what weight loss takes. We usually focus on the dietary side, because it's much more efficient to subtract calories than it is to lose calories by increasing physical activity. It takes too much time to do a whole – the physical activity calorie burning that it would take. But what happens when we start to lose weight? The body has this immediate physiologic adaptation that comes into play. And our metabolic rate decreases. The more weight we lose, the greater the reduction in metabolic rate. This is not just the fact that our bodies are smaller and our metabolism's requirements are lower because of that. It is a reduction in resting metabolic rate, it's an increase in muscle efficiency, and the net result is that you have a handicap, you have what's called metabolic adaptation or adaptive thermogenesis. And that fights against further weight loss.

And at the same time, you've got a double whammy on the appetite side. So, you have measurable increases in hunger and measurable decreases in satiety. So, our hunger hormone, ghrelin, is higher after we lose weight, and it's not suppressed as much around meals as it is before we lose weight. And when we're reduced, the satiety hormones are not as high. So, after we eat, hormones from the small intestine and from the pancreas, go to the brain and tell the brain that food is on the way. And that's what really promotes that full feeling. Well, those hormones are diminished when we are in that reduced weight state. And so, it's these metabolic and biologic adaptations that fight against further weight loss, and really drive weight regain. So, it's not a matter of willpower. It's a matter of biology that is driving these factors.

You know, one of the things I really like about our clinical endocrinology friends, is that they have developed these algorithms for how to approach individuals who have obesity. And so, the very first step in approaching a patient with obesity is to evaluate that patient with, of course, a medical history, physical examination, and clinical laboratory tests. What we're trying to do here is a couple of things. We're trying to stage that patient, we're trying to determine if that patient has excess abnormal body fat that's impairing health. So, we're looking for abnormal laboratory values, abnormal physical findings, such as an increased waist circumference, we're looking for evidence of metabolic syndrome on our laboratory tests that shows that that patient does have excess abnormal body fat that's impairing health.

We're also going to be doing a weight history. And, as Bob talked about earlier, this is the initial point of contact with the patient. One thing that Bob has taught me and that I really like is to ask the patient to graph their weight across their lifespan, because it really allows you to see factors that produced weight increase, and other factors that are associated with weight loss. So, it gives you a lot of information in a graphic picture, and patients like doing it.

After we do that initial evaluation, we want to identify patients for different kinds of treatment. And I want to talk about when we're going to use our medications for chronic weight management. So, we want to identify patients who meet the indication, and that's a BMI of 27 and up with a comorbid condition. So, for individuals who have mild to moderate complications or no complications, we're going to start with lifestyle intervention. But frequently, patients will not have enough weight loss to achieve health benefits with lifestyle intervention alone. And so, if patients have difficulties with lifestyle intervention, we want to add anti-obesity medication. Or if they regain after an initial successful weight loss, we want to add our anti-obesity medication. And if patients have more severe disease, if they have established more serious weight-related complications, like prediabetes, like diabetes, like obstructive sleep apnea, other complications of feeling in function, like GERD, like chronic knee pain, we want to add our anti-obesity medications, because we want to achieve more weight loss so that we can achieve more health benefits. So, that's how we're going to identify our patients who would be candidates for anti-obesity medications.

Look, I wish lifestyle alone would work in every patient, but it doesn't. You know, we know from our many systematic evidence reviews and many studies that if we can give a good enough lifestyle intervention, we can produce on average weight loss of about 5 to 8%. But these interventions are done with about 14 visits in the first 6 months. And that is hard to achieve in a routine medical practice. Yes, we can refer patients to a commercial program in order to get that. And in some community programs that are doing like the DPP lifestyle

intervention, that's available. But even with the very best gold standard lifestyle intervention, there's a subset of patients, probably about 40%, who do not achieve even that moderate weight loss that's associated with health benefit. And weight regain is the real problem. You know, we know that 50 to 80% of weight that's lost is regained within 3 to 5 years of that initial weight loss. So, we need more than lifestyle intervention for many, many patients.

So, Bob and Chris, how do you help patients set realistic expectations for results from lifestyle modification?

Dr. Kushner:

Thanks, Donna, for the question. It's critically important early on that just to reinforce that patients have realistic expectations about lifestyle changes by themselves with or without medications, and including bariatric surgery. Patients often come in thinking of what they weighed in high school, right? It's an ideal – they still use the word ideal body weight, or 'that is my preferred weight' as if they're a thermostat on the wall and we're going to dial in that weight, and they slowly come down to it, and we can guarantee it. And of course, we can't.

So, what I do is tell them that weight is in large part, it's complex, it's due to a lot of factors. You talk about the life events, a weight graph, so the life events of their psychosocial behavioral causes, talk about genetics, and I talk about biology. And so, a lot of it is determined about that. But what we're going to focus on is what you have control over, which is how you live your life, your physical activity, your diet, your sleep, use of substances, stress management, social interactions. And based on that, we will follow you and see where your weight ends up. I sometimes tell them what average weight losses are, but you know, Donna, I shy away from that; no one wants to be average, right? They're going to say, 'What is your best patient, because that's going to be me.' So, I shy away from average weight losses, but I try and often temper down their, I think, unrealistic expectations many times. And I also talk about that long-term use of medication, which actually was one of the questions that Chris asked early on, when it comes to medication, at least.

Dr. Still:

Yeah, I agree. I do tend to give them percentages on average. And I say some people lose a lot more, some people lose a lot less. Because, as Bob said, most people have very unrealistic expectations. So, they come in wanting to do a little bit of diet and exercise and have the efficacy of the gastric bypass or the duodenal switch. So, I do think really setting realistic expectations, as Bob nicely said, is important.

The other thing that I think is important is when they come in to see us, I give them all their options because most people say, 'Oh, I just want to do diet and exercise. Let me see how I do on that.' That's fine, but just so you remember, say they have a BMI of 40, so they would fit the criteria for considering obviously diet and exercise, and anti-obesity medication and bariatric surgery. So, I like to have them, in the beginning, know what their options are. Because if they aren't successful with diet and exercise, they say, 'Oh, I remember there may be some medications,' or 'I heard there may be surgery.' So, and it takes a while for someone to hear about bariatric surgery to actually undergo bariatric surgery. So, if they are a candidate, I like to set the stage of all their treatment options in the beginning.

Dr. Ryan:

Yes, and lifestyle is foundational. I think we would all three agree on that. You know, to me, one of the big advantages of medications is that they work through biology to help patients better adhere to their dietary intentions. So, it's a real window of opportunity to improve the quality of the patient's diet. And I don't want to miss that window.

Okay, Bob, your turn now, can you take it away?

Dr. Kushner:

Thank you, Donna. Well, what we're going to do now is take a deeper dive into pharmacotherapy. That was kind of a setup that Donna just did. And I want to start off with what's the primary purpose of using medications in obesity management. And we put three bullet points here to highlight those aspects.

The first thing to keep in mind is that obesity, we think of it as a disease in part because of appetite dysregulation. And that is they may not be getting the right signals regarding fullness, contentment, hunger, thoughts of food cravings for food, and so forth. And what the medications do is to work internally, the internal environment, the biological environment, to try to regulate appetite more towards a normal sensation or experience, and we call them, that they regulate appetite. So, by taking a medication, and if someone responds, we're going to talk about medications more in just a bit, patients are often likely to feel less hungry, full sooner, more content between meals, less cravings, less thoughts of food, even a change in food preference. That is what medications do. They do not, by themselves, cause instant weight loss. They don't target fat, they don't burn fat, they don't change metabolism, at least in a significant way. What they do is alter appetite. So, that's the first bullet point.

And for medications to work, they have to be translated behaviorally into a healthier diet that's calorie reduced. That's the second bullet point. So, to reemphasize these first two bullet points, medications set the stage by changing and augmenting appetite regulation.

Patients then are taught through lifestyle and guidance to follow a healthier diet lower in calories, and that is how weight loss occurs.

And the third bullet point is that those two facilitate weight loss and improvements in health. And Donna already talked before, as well as Chris, that weight is one of the metrics of health; it isn't the end-all. The goal is not how thin can I help a patient get? It's how healthier can I get them to get, and weight is one of those parameters.

And I want to emphasize also on the bottom is that according to the FDA packaging insert, at least in the United States, it is indicated for an individual who comes with a BMI of 30 or more by itself, or a BMI of 27 or more with the comorbidities like dysglycemia, hyperlipidemia, or elevated blood pressure. A patient does not need to earn the right or prove to you as a prescriber to give them a medication. We would never think about that in diabetes like you have to earn me giving you Metformin or something. So, obesity, we need to think the same way. It's not someone who's failed lifestyle alone; it's someone who needs more aggressive treatment in addition to a lifestyle.

So, we have on this slide are the seven medications that are available in United States. And let me just orient you. On the left are the agents we have starting with phentermine and ending up with semaglutide. The middle column is mechanism of action, which I'm not going to go into great amount of detail here. The third column is the effect, and towards the right is the approval dates. You see it scans from 1959 when phentermine was approved, all the way to just 2 years ago when semaglutide was approved. So, highlights on this slide.

Regarding the effect, all of the medications on here except one, which is orlistat, causes weight loss by appetite regulation. That's why I harped on that in the previous slide. By regulating appetite, people tend to feel less hungry, portion sizes go down, and they lose weight. The only one that is a proof for weight loss because it reduces partial fat absorption is orlistat. Phentermine, the first one on here is a sympathomimetic. It actually has a category of stimulants. We put phentermine on here because it's the most commonly prescribed medication in the United States and it's the only one that's generic and is the cheapest, and that's probably why it's most commonly used.

The other medications, phentermine, topiramate, naltrexone, and bupropion work on appetite regulation for neurotransmitter modulation, either through dopamine or norepinephrine, or GABA, and so forth. Liraglutide was the very first GLP-1 receptor agonist approved. And last year, the second one was approved for weight management, and that is semaglutide, and we'll take a deeper dive into that in just a moment. The last on the list is setmelanotide, which is used specifically for individuals with monogenetic obesity, probably the least commonly used among the attendees of this conference. But if you happen to be a pediatrician or med peds, or potentially some adult patients, you may be thinking about using it.

Last thing I want to mention is many of these drugs are approved for our pediatric population, some of them for 12 years or older, some of them for 16 years or older. And you see setmelanotide is actually approved for those that are 6 years or older with a monogenetic condition.

Now, this slide is very helpful in understanding the average expectation of loss one can expect by different levels of aggressiveness regarding a medication at the top is bariatric surgery. So, what you see here on the very top, the most effective treatment we have for treatment of obesity is bariatric surgery. And we gave an example here of sleeve gastrectomy. Gastric bypass is another one in which individuals over 12-18 months and longer are losing 25% or more of their body weight. Although there may be some weight regain, it is by far the most effective treatment on average. After that are all the medications I had just reviewed with you. And the percentages on here reflect individuals who stay on the medication for at least as long as the trial occurred, which for most of them are a year or longer. So, the average weight loss with the semaglutide was nearly 17%. And right behind that is the phentermine topiramate with a little over 14% weight loss. And the others drop off from there. One note is that phentermine, I already mentioned, is the most commonly used medication, the longest data we have for that is actually 28 weeks.

Now, GLP-1, or glucagon-like peptide-1, really is the direction, or paradigm shift if you will, regarding the treatment of obesity. We're shifting from neuromodulation of receptors, to mimicking more gut hormones that are produced in the body, in this case, GLP-1. And they were first approved for treatment of diabetes. So, if you look towards the right of this slide, GLP-1, or glucagon-like peptide-1, is a satiety hormone, and it's also known as an incretin hormone affecting insulin secretion, reducing glucagon secretion, increasing beta cell survival, effect on muscle sensitivity, as well as slowing gastric emptying. So, this drug at a lower dose is approved for diabetes. But once it gets to reducing food intake or appetite suppression, particularly at higher doses, now you're shifting into an anti-obesity medication that also has effects on the liver regarding reducing fat and gluconeogenesis, as well as other pleomorphic effects, which we'll talk about in just a moment.

Now, the STEP trials were the key pivotal trials of that were used to submit to the FDA for approval of semaglutide in 2021. The STEP 1 trial was the largest, 1,900 individuals. And what we're showing you here is average weight losses in individuals who were randomized

to either placebo or semaglutide with escalating up to the dose at 2.4 mg by weekly self-injection shots. Towards the left, the individuals who were randomized to the trial, towards the right or those that stayed on the drug. And they almost look identical because the numbers of patients who've stayed in a trial for were long, as well as those who's stayed on the drug.

And what you see here very clearly, clinically and statistically significant is those randomized to placebo and received lifestyle counseling, lost on the average of just a little under 3% of their body weight. And that's in contrast to those randomized to semaglutide also with lifestyle counseling, lost 15 to 17% of their body weight, depending upon the intention to treat or those that stayed on the drug.

Now STEP 1 extension trial was done as well, published a little bit later. And this is so informative for us as clinicians when we think about treating patients. So, let me orient you here. Of the 1,900 or so individuals randomized to STEP 1, of little over 300 of them signed up to be observed for another year once the trial ended. So, if you look to the left of the dotted lines, in both of these figures, I already showed you that the individuals on the drug lost about 17% of their body weight versus placebo, which is a little under 3%. Towards the right, again, left of the dotted line, we're taking all those individuals, but I'm not showing them now as the average but categorically. And we know there's a heterogeneity of response in everything that we do. And here we separated out the individuals randomized to drug and how much weight they lost from mechanical point of view. So, some lost less than 5% of body weight, all the way up to more than 20% of their body weight, and that was actually 1/3 of the individuals lost 20% of body weight or more.

But what happens if an individual stops the drug and they're just observed? So, there's no other treatment? Really quite profound. If you look again, towards the left, individuals on average regained 2/3 of the weight that they lost over the subsequent year. And placebo, of course, they regained weight basically back to baseline. And towards the right, same thing happened even if we look at it categorically. Interestingly, those that lost the most amount of body weight, regained the most amount of body weight, although at the end of the year, they still had lost more weight than the others as far as net weight loss is concerned.

Take-home message that's so clinically important: medications need to be taken long term for the drug to work. If you stop the medication, particularly do not render any other treatment, your patient is likely to regain the weight that they've lost. Kind of makes sense if we use to compare to diabetes. If you stop an anti-diabetes medication, you would expect blood sugar to start rising again. Same thing with obesity as a chronic relapsing disease.

Now, regarding use of the medications, this is not a good format to go over every drug and every adverse event and every management strategy, you need to become familiar and competent yourself if you're going to be using these medications.

There are some general tips though and comments I'd like to make regarding phentermine. It's a stimulant medication, so you always want to make sure the heart rate and blood pressure is well controlled, they don't have hyperthyroidism, they don't have an arrhythmia or acute coronary event, you would never ever give a stimulant medication for someone like that. Phentermine topiramate, you want to be careful about kidney oxalate stones, keep the patient well hydrated. Naltrexone bupropion, it can cause constipation and nausea. Probably the most important thing though, is that naltrexone is an opiate blocker, so you would never give this drug and someone is taking an opiate for pain control, because you would block that control. The side effects for the GLP-1 receptor agonist, liraglutide, semaglutide, are essentially identical, and they're all gastrointestinal: nausea, diarrhea, heartburn, potentially vomiting, so you have to be careful with that. Orlistat, also all gastrointestinal, because you're blocking the absorption of fat, so you have a very fatty, oily stool.

Now GLP-1, we've already talked about the benefits of it and how it works. And what I'm highlighting here is that it also causes natriuresis, diuresis, and cardio protection, because we know the GLP-1 receptor agonist, by looking at cardiovascular outcome trials, have reduced cardiac events. So, that's why it's listed as a preferred agent in the diabetes guidelines, for example, and it's currently being looked at in the SELECT trial for individuals without diabetes with results pending.

But on this slide, I'm introducing another incretin hormone, GIP, which stands for glucose-dependent insulinotropic polypeptide, it's the last time I'm going to say that, I'll say GIP instead. And when you add another incretin hormone as a dual agonist, you get augmented effects, not only appetite control with increased weight loss and insulin secretion, but also effects on fat tissue, as well as bone resorption, sort of additive, perhaps even synergistic effects by combining the two incretin hormones in what's called a dual agonist.

So, the dual agonist that's currently on the market is called tirzepatide. It is currently not available for the treatment of obesity. It is however, approved for the treatment of diabetes. And what I'm showing you here are the five SURPASS trials, all in individuals with diabetes from SUPPASS-1 to SURPASS-5, lasting from 40 weeks up to 52 weeks. And unlike the semaglutide trials, these trials looked at three different doses of tirzepatide, 5, 10, and 15. And what you see across the board and all these SURPASS trials, whether they were used de novo, by themselves, or in a background of Metformin or an SGLT2 inhibitor, is there's really a very nice dose response effect. The higher the dose of tirzepatide, the greater the weight loss. It's very clear looking at this, the 15-mg dose causes the most weight loss, and it actually outperforms STEP 2 trial which was looking at semaglutide in individuals with diabetes.

Now, I've already mentioned tirzepatide is currently not approved for individuals with obesity; however, the SURMOUNT-1 trial has been

published. This is looking at the effect of weight loss in individuals without diabetes, who have a BMI of over 30, or 27 or greater with a comorbidity. Again, on the left, you're looking at the dose response, average weight loss of tirzepatide 5, 10, or 15 mg, and it reproduces what we already looked at for patients with diabetes; the greater the dose, the greater the weight loss. Here, you're losing almost 21% of your body weight at the end of the dose escalation and after a year. Towards the right is the tempo, what the graph looks like, again, you see the 15-mg tirzepatide losing 22% of their body weight in those individuals who stayed on the drug.

So, that's a quick overview of pharmacotherapy. I'm going to turn to my co-faculty host, and Chris, I'm going to ask you first, how do you determine which of the obesity medications is best for your patient?

Dr. Still:

Yeah, Bob, excellent review, as always. So, that's a good question. It's a tough question. You know, going back to what we talked about, number one, it should be patient-centered decision-making. But they're coming to us to help that decision. So, the first thing I look at, are there any contraindications? You know, do they have a seizure disorder? Then say, bupropion would not be appropriate because it can decrease the seizure thresholds. So, things like that. If they have high blood pressure or uncontrolled blood pressures, you alluded to phentermine would probably not be the best. So, I look at what are the contraindications.

The second one, you know, for better or for worse, I look at coverage. You know, what is covered for that individual? And then I try to work on their health benefits of what the dual action may help, you know, not only weight loss, but you know, any other medical problems they may have. Prediabetes or diabetes, then obviously the GLP-1s would be a good choice. And that's my thought process, but really, with the patient, you know, they may be needle averse, or nausea averse and, you know, don't want to take a medication that may cause nausea, so we would steer clear of that.

Dr. Ryan:

Yeah, so I'll just add to Chris's, yeah. The very first is contraindications and complications. So, I'd add to Chris that for young women, women of childbearing potential, we do not like to give topiramate, so phentermine and topiramate, we like to have a negative pregnancy test before it starts. And then a monthly pregnancy test. Because the topiramate is associated with cleft palate. So, we don't want to do that.

And then the other thing that I would add is that I think all of these medications that you talked about, Bob, have a place. So, you shouldn't have your favorite medication, you really need to know about all of them, because we have a great variation of weight loss response. And sometimes patients are not going to respond to one, whereas they will to another. So, even poor little orlistat, there are some patients who do very well on orlistat. And look, honestly, that is a very good drug for constipation.

Dr. Kushner:

Right. Good points. I want to highlight some of the things our field suffers from because it's such a nascent and it's such a new field, is we currently have very limited drug-to-drug comparisons, like you see all the time with diabetes and hypertension, all these other chronic relapsing diseases that we treat every day, we don't have that in obesity yet. So, we're really left with what you guys just said is indications, dual indications, contraindications, coverage, needle phobia, oral intake, and so forth. But no head-to-head.

And the last thing I want to emphasize. Donna, what you just said is so true, is that we all think you know the more the merrier, bring them in, you know, have more things in the toolbox. And we all have super-responders to almost every medication. And then we have individuals who don't respond well. And then we move to another medication. So, it's really the art of medicine right now, until we get more data. But that's what we all need to learn.

Dr. Still:

I just want to add one last thing, if I may, Bob. It went to that you pointed out that I think is so important if we're going to consider the GLP-1s that this is not a short-term jumpstart, that we really have to be in it for the long haul. Because, as you pointed out, the weight gain is profound if and when they stop the medication. So, that's another thing that I think factors in, in the decision of are they committed to taking it long term?

Dr. Kushner:

Free of expectations, which is a question you asked us before, are the expectations are you're going to be on this medication, long term for the drug to work. Good point.

Donna, I'm going to hand it back over to you.

Dr. Ryan:

Oh, thank you, Bob. Let's see. Let's talk about a patient, it's what we like to do best. So, here's our patient. She's 40 years old. She's a woman who's coming in for her annual wellness visit in her primary care providers office. She's concerned about her weight. She's

frustrated that she hasn't lost any weight following a lowfat diet over the past 8 weeks, and is looking for assistance. She has hypertension, dyslipidemia, depression, and GERD. She's single. She lives alone. She works from home for a digital and advertising company.

On review of systems, she has daytime somnolence that makes you think of obstructive sleep apnea, early morning headaches, and fatigue. She's on Losartan, that's an ARB, gemfibrozil, fish oil for her dyslipidemia. She's on paroxetine for depression. She's on omeprazole, that's for her GERD. Her blood pressure is higher than we want it to be, 136/92. Her BMI is class 2 obesity, 35. Her waist circumference is too high at 42. She has a normal cardiopulmonary exam, but a Mallampati class 3, which is a narrowing of the airway, which goes along with that obstructive sleep apnea. She's got trace edema bilaterally.

Let's look at her chemistries. Glucose 118, that is too high; A1c 6.2, that is prediabetes; her total bilirubin is normal; albumin okay; ALT is a little high; AST is okay; alk/phosphatase is a little high; total cholesterol higher than we want it to be, 240; and the LDL is 146; the HDL is lower than we want it to be, we'd like it to be 45 and up for women, she is 40; her triglycerides, we want those less than 150, she's 270.

So, here I've got a patient who has metabolic syndrome. She's got evidence of excess abdominal body fat located viscerally. She's got complications of hypertension, dyslipidemia, depression, GERD, probably obstructive sleep apnea, but we haven't diagnosed that. So, a lot going on with this patient. And it's not unusual. Obesity affects every organ system. So, if we look at this patient through this lens, look at how many of these known obesity complications our patient has.

So, I think our traditional approach is we've got great medicines for blood pressure, we got great medicines for lipid abnormalities, let's approach treating the complications because we can do very well with that. But I think the new paradigm would be that if we could treat weight, we could treat all of these complications at one time. So, the options open to us are the foundational lifestyle intervention with diet, physical activity, and the behaviors around diet and physical activity. To that, we can add anti-obesity medications. And then we also have our newer devices and also bariatric surgery. So, that is our general approach to treatment.

The strategy that we're going to use for this patient is we want to improve her health, right? And so, we need – the way I think about this, I think about how much weight loss do I need to get to achieve different health benefits? Well, I know that we can start to see improvements in glycemia with as little as 3% weight loss, that with 10% weight loss, we can get almost all patients with prediabetes, we can prevent that progression to type 2 diabetes. And with people with established type 2 diabetes, we're usually aiming for a bit more, about 15% weight loss. In that moderate weight loss range of 5 to 10%, we can improve dysglycemia, hypertension, and lots of other risk factors. If we want to improve obstructive sleep apnea, we need to exceed 10% weight loss to really have a significant impact on those symptoms. GERD, the same thing, we need to lose more. So, for this patient and looking at this patient, my aim for this patient would be to aim for hopefully 15% weight loss, because I know I want to have an impact on obstructive sleep apnea, on GERD, on all of those markers of dysglycemia and her prediabetes status on improving her dyslipidemia. So, all of these factors, I could improve if I can get 10 to 15% weight loss.

So, how would you treat this patient? I'll start with you, Chris. And then to you, Bob.

Dr. Still:

I think you did a great overview of her case. You know, she definitely has that visceral type of weight distribution, 42 inches of waist circumference, you know, she has that mild abnormalities or LFTs. You brought up the obstructive sleep apnea. The only thing I would point out is in her medications, she, as you noted, she's on paroxetine. So, I think that it's very important for all of us to make sure we take a good medication reconciliation to make sure we are not promoting or prescribing medications that promote weight gain and retard weight loss. And it's estimated that 5 to 10% of the obesity epidemic is iatrogenic what we prescribe. So, I think that I agree with everything you said. In order to get that, you know, 10 to 15%, we really need to pick or have that discussion about pharmacotherapy, anti-obesity pharmacotherapy, I think in this patient to be most successful in the long term.

Dr. Ryan:

Yeah, that would be aligned with the ACE guidelines. Bob?

Dr. Kushner:

Yeah, I'm going to reinforce what Chris said, and Donna, the way that you describe this patient. So, we think of this patient as a high-risk genotype, right? That's kind of the newest area in obesity care now. As we see, you know, if your practice represents the American population, 4 out of 10 of your individuals are going to have obesity, 7 out of 10 are going to have overweight or obesity. So, how does someone who's in a busy practice start to identify which patient you have to be more aggressive with and spend time with? Or refer to a dietician or see an obesity specialist? And that's where phenotypes come in; an individual presents with the characteristics that are high risk for cardiovascular disease or liver disease, and so forth. And this is your prototypic patients. So, I would be spending time with this

patient.

The other thing I want to highlight, Donna, you showed this slide of how much weight loss is needed regarding each of the comorbidities. And that is a great way for us also to change our paradigm to treat to goal. We're all used to treating to goal in diabetes and hyperlipidemia, right, hemoglobin A1c or an LDL cholesterol. We've never done that in obesity. So, we are now thinking if you need to lose 15% to improve her sleep apnea, which I think she has when you do a polysomnogram, then you have to treat to goal. Her likelihood of getting a 15% weight loss and maintaining that, and lifestyle alone is not impossible, but it's a lower likelihood.

So, having a realistic kind of expectation conversation with her is important. Avoiding clinical inertia, right? Where you say, 'Well, let's try lifestyle alone and we'll see you in 3 months. And well, let's give you another 3 months.' We want to be more proactive with our patients. And this is a perfect example of someone you want to be aggressive and proactive using shared decision-making. In other words, what are her personal values and what are her goals?

Dr. Ryan:

And you know, I didn't like her liver function tests, either, you know, so I have an index of suspicion here about fatty liver disease and maybe even early NASH. So, a great discussion, guys. Thank you so much.

But now I'm going to turn this over to Dr. Still.

Dr. Still:

Thank you, Donna. So, as Donna alluded to, in the treatment pyramid, lifestyle modification, pharmacotherapy, devices, and then bariatric surgery. So, I just want to briefly discuss bariatric surgery. It's traditionally indicated for the body mass index of 35 plus a comorbidity such as diabetes, sleep apnea, fatty liver disease, or a body mass index of 40 alone. This patient, as you recall, had a body mass index of 35 with some comorbidities, so she would fit the criteria. So, as I alluded to in the beginning, I would bring up that she meets the criteria. I wouldn't rush her right to bariatric surgery. But as long as she knows that she's a candidate and hears that word, you know, maybe parallel she can do some investigation and education herself on bariatric surgery.

There are new guidelines just because of the efficacy that Bob alluded to briefly on the efficacy of not only weight loss, but the importance of improving comorbid medical problems. And I think we're going to see that in our new generations of medications as well. But the new guidelines recommend individuals with a BMI of 35, regardless of their comorbidity, be considered for bariatric surgery. Up to 85% of patients do well. Like any other treatment, obesity is a chronic and relapsing disease, and you may have patients that have undergone bariatric surgery, even the duodenal switch, that can and do gain back weight afterwards. So, I think early intervention of that weight regain is important. We use a lot of pharmacotherapy in those individuals as well. But the weight loss range, as Bob alluded to, the sleeve, you get about 25 to 27% weight loss, the bypass is about 25 to 35% weight loss. And as Bob alluded to, to date, it is the most effective tool or treatment modality we have for long-term weight loss. But hopefully, stay tuned, that in the future, you know, we may have some anti-obesity medications that will rival the efficacy of bariatric surgery in the not too distant future.

So, with that, I'm going to go through the conclusion. Boy, this went fast. So, obesity, I hope that you are aware or will agree that obesity is a chronic disease and should be treated as such long term, that patients with a body mass index of 27 plus one comorbid medical-related comorbidity or patients with a body mass index of 30 alone should be offered weight loss pharmacotherapy if they qualify and they're interested. Multiple effective agents are available for weight loss, and the selection of individual agents should be based on patient preference and characteristic and shared decision-making. And finally, the GLP-1 receptor agonist and tirzepatide are emerging as effective weight loss therapies. But to date, only liraglutide and subcutaneous semaglutide are approved for patients without type 2 diabetes.

So, the correct answer is D, use shared decision-making strategies to discuss pharmacotherapy options for weight loss. The other answers, the only other one to explain that weight loss is based on decreasing calories and increasing energy expenditure, as you know, it's not as simple as that; it's a foundation of it, but really the best approach is using the shared decision-making strategies.

Dr. Kushner:

Yeah, I'll just add, Chris, a moment is that I agree with completely that D is the best answer. A is not incorrect, but it's not the best answer. You know why? Because they have heard that a million times from healthcare professionals, eat less, move more, what's wrong with you? So, it's not the best answer. That's why D is.

Dr. Still:

And the correct answer is indeed subcutaneous semaglutide. As you recall, it was about 16% weight loss, almost 17% weight loss, and the other ones were effective, but not as effective. So, this question asked, which was likely to be the most effective for this patient.

Dr. Ryan:

I think we would also be a little concerned about blood pressure. We want to make sure that the blood pressure is well controlled before the naltrexone bupropion were prescribed.

Dr. Still:

And the best or the most appropriate is C, a 32-year-old woman with a BMI of 30 and no comorbidities. So, A, their BMI is 26, not 27 with hypertension; B, the man recently initiated lifestyle changes; and D, she prefers a natural weight loss strategy. So, C would be the best for this answer.

And the correct answer is B, weight loss pharmacotherapies likely will be needed long term to maintain weight loss.

The only thing I want to point out, and I don't think we touched on it is D. So, most of the agents, excluding semaglutide, has in their FDA label about a 3 to 5% weight loss, if they haven't achieved a 3 to 5% weight loss after 3 to 4 months on the steady dose of the medication, the medication should be discontinued due to nonresponse, and another medication should be considered. So, but for the other ones, you shouldn't stop after 5 to 10%. And patients who successfully lose weight with lifestyle, will maintain their weight greater than 5 years.

Okay, so thank you for that. So, I would just like to invite you to go online for more Clinical Care Options coverage of obesity management. You can download the slides that we reviewed today. And also, there's a CME/CE certified on-demand case-based simulation that you can take. So, I encourage you all to do that. And in addition, you can practice your skills with a live patient, this is a great opportunity. You just use this QI code, it's 15 minutes with the live patients, they can hone your skills on asking the questions about, you know, do you want to talk about your weight? What have you done in the past? And it's really helpful. They'll talk you through, you know, the right answers and wrong answers, and they'll give you some pointers so you'll be much more comfortable when you're seeing Mr. or Mrs. Jones in your office. And believe it or not, that for a limited time, they're pleased to offer a \$25 certificate for your participation.

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