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What You Need to Know About Weight-Loss Medications

Announcer:
Welcome to CME on ReachMD. This activity, titled “What You Need to Know About Weight-Loss Medications,” is provided by Prova Education.

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Dr. Vega:
In the United States, obesity and overweight are an epidemic, and they are a major health concern worldwide. While lifestyle modifications are a cornerstone of weight management, most patients do not achieve durable results, highlighting a need for pharmacological interventions. So as physicians, where do we stand with our approach to obesity in the primary care setting?

This is CME on ReachMD, and I'm Dr. Chuck Vega.

Dr. Ryan:
And I'm Donna Ryan.

Dr. Vega:
Great. So, Dr. Ryan, let's jump on in here. Can you give us an idea of how we should be approaching obesity in our patients and explain a little of the biology of obesity and weight regulation?

Dr. Ryan:
Well, let's begin by defining obesity. BMI [body mass index] has come under fire lately. And there are a lot of valid arguments that it does not always capture excess abnormal body fat. The definition of obesity is excess abnormal body fat that impairs health. BMI is measuring body size. And on a population basis, it's a very good measure because it's a good correlate of body fat. But in the clinic, we need to use BMI as a screening tool. For individuals with a BMI of 25 to 29.9, that's overweight, and 30 and above, that's an obesity range. But we don't make the clinical diagnosis without evidence of the excess abnormal body fat. Waist circumference, over 35 inches in women and 40 inches in men, tells us that visceral adiposity is likely.

Cardiometabolic risk factors, if abnormal, also point to clinical obesity. So we need to use our clinical judgment to exclude those with large body size like body builders who have an increased BMI, but they do not have clinical obesity. So remember, BMI, we're getting it at every electronic health record visit, it's just a screening tool. After that, we look more closely at the patient and the patient's physical and laboratory values to determine if that patient has evidence of excess abnormal body fat. That's the clinical diagnosis of obesity.

And I think that clinical obesity means that that excess abnormal body fat is really driving risk for type 2 diabetes, for hypertension, for dyslipidemia, for cardiovascular disease, for obstructive sleep apnea, and many more complications.

Why is that? When we exceed our ability to store fat in healthy depots like subcutaneously in the hips and thighs, we start to accrue fat ectopically. And that means in pancreas, in muscle, in liver, around the epicardium—the epicardial adipose tissue—around the kidneys. And that fat has a very adverse profile; it’s lipotoxic. That fat looks different than subcutaneous fat. It's full of macrophages; it’s producing angiotensinogen, other adverse cytokines and lipokines; it's full of macrophages. And so it produces this prothrombotic and

proinflammatory milieu that exists in obesity, and its location is very important too. So for example, the coronary arteries run right through the epicardial adipose tissue and are directly exposed to all of the toxic effects of that abnormal adipose tissue.

Dr. Vega:
Well, that sounds very motivating, in terms of maybe following lifestyle change when we think about the coronary arteries running through increased adipose tissue. It's scary. I would also advocate for the use of waist circumference. Measure tape costs a couple of dollars, and I do use it. I would caution folks: I don't start with measuring waist circumference in every patient. It's only after we'd have a sense of trust, because even getting on the scale for a lot of patients may be fraught. And we want to ask permission before we do that. And then, you know, measuring waist circumference is only when we have a good relationship and patients feel there's trust, because it's a very personal thing for them. But at the same time, I want an objective measurement.

Unfortunately, by that time, a lot of folks come in and they've had that visceral adiposity, and they've had the diagnosis of obesity for some time. So how did it develop in the first place? What are some of those pathophysiological mechanisms? And why is weight loss so darn difficult?

Dr. Ryan:
Yeah. What causes obesity? Well, it's complex. It's genetic susceptibility, first and foremost. You know, these are very common gene variants. And there are many of them, you know, maybe 200 of these common gene variants, but as we accrue them, we're at increased risk when exposed to an environment, and if that environment is obesogenic, and so certainly the food and physical activity environment are important. But medications—the medications we're writing for our mental health needs, antidepressants, antipsychotics can drive weight gain, contraceptives can drive weight regain, but there are many, many factors that can cause the expression of obesity in genetically susceptible individuals.

And once weight is gained, it is difficult to lose. When we lose weight, or try to lose weight, our bodies react by changing the appetite hormone patterns, making us hungrier and less satisfied with foods and more susceptible to rewarding foods. And when we lose weight, our metabolic rate also decreases. So it's a double whammy: we have more appetite, and we have a slower metabolism. And both of those things drive weight regain if we are successful in losing weight. And that's really why losing weight with lifestyle alone is so difficult. Many patients need anti-obesity medications that work through appetite to help them lose enough weight to achieve health benefits and to sustain that weight loss.

You know, Dr. Vega, our knowledge of the gut hormones has increased, and we've been able to design medications around that knowledge. For example, the GLP-1 [glucagon-like peptide-1] receptor agonists are producing some of the most robust weight loss to date.

Dr. Vega:
For those of you who are just tuning in, you're listening to CME on ReachMD. I'm Dr. Chuck Vega, and here with me today is Dr. Donna Ryan. We're discussing everything you need to know about the medical management of our patients with overweight and obesity.

Great points. And yeah, I find that the issue of weight regain and the hormonal changes that occur with weight loss are just, frankly, for many patients directly contradictory to their goals and, in their own way, quite diabolical. But these medications, as you point out, can reverse some of this negative metabolic profile that promotes weight regain, so maybe you could cover some of those medications and go through the anti-obesity drugs with us.

Dr. Ryan:
Yeah, let me give you an overview to start with.

Since 2012, we've had medications approved for chronic weight management. These medications have undergone much more rigorous scrutiny for safety and effectiveness than older medications like phentermine. They are orlistat, a combination naltrexone/bupropion, combination phentermine/topiramate, liraglutide, and semaglutide. Orlistat does not affect appetite. It produces modest weight loss by blocking fat absorption. The others all work through appetite, and naltrexone/bupropion and phentermine/topiramate affect central—in the brain—neurotransmitters, and liraglutide and semaglutide are GLP-1 receptor agonists.

Naltrexone/bupropion and phentermine/topiramate and liraglutide all produce weight losses in the range of 5% to 10%, on average, when they're given at their approved doses along with lifestyle recommendation. The game changer has been semaglutide, 2.4 mg given subcutaneously weekly, after a dose escalation. This is associated with 15% to 17% average weight loss, and that's attracted a lot of attention. We know that 5% to 10% weight loss can improve glycemia and cardiovascular risk factors and bring improvements in how patients feel and function. But more weight loss produces more improvements. And patients are seeing this robust weight loss as highly desirable.

And we're not done yet. The FDA is reviewing a new medication, tirzepatide, which is both a GLP-1 receptor agonist and a GLP/GIP [glucose-dependent insulinotropic polypeptide] receptor agonist. So it's got dual actions on those appetite hormones, and it's producing 15% to 22% average weight loss at its highest dose. You know, that medication is under FDA review. It's not approved yet for weight management, but we're hoping to get it out on the market this year.

Of course, all medications have safety and tolerability issues. All of them require a dose escalation to minimize side effects. Phentermine/topiramate and naltrexone/bupropion are oral. Liraglutide and semaglutide are sub-q injections, daily for liraglutide, and weekly for semaglutide. Tirzepatide will also be a weekly injection.

Let's run through these quickly and go over their contraindications and side effects. Orlistat is taken 3 times a day before meals. You know, if it's blocking fat, it's going to cause some steatorrhea if patients take a meal or a snack that has fat in it, and so that produces the side effects. But it's important to patients who are on this drug for a long time, for more than just a few weeks, take a multivitamin at bedtime. Because if you're not absorbing fat, you're not absorbing those fat-soluble vitamins. Phentermine/topiramate. Well, remember topiramate is associated with fetal cleft palate. So we always want women of childbearing potential to have a negative pregnancy test before we prescribe this drug. And we want a monthly pregnancy test at home while they're on it. Naltrexone/bupropion. Well, we know this one can increase blood pressure, so we want to be very careful in prescribing it to patients with hypertension. And bupropion can unmask seizures. Liraglutide and semaglutide. They have the same side effect profile as all drugs in this class. And we're pretty familiar with the class of GLP-1 receptor agonists from diabetes medications, but we do not prescribe them in patients who have a personal or family history of multiple endocrine neoplasia type 2 or medullary thyroid cancer.

Dr. Vega:
So that's a great run-through of a fairly complicated but important landscape that we know we haven't been taking advantage of anti-obesity medications as we should. I do think we're in a new age. One of the principal barriers was cost and coverage. And now there's just this much broader acceptance, not just in the healthcare community, but more broadly in society of obesity as a disease, a chronic disease. I think that we're going to see more coverage of these drugs, and therefore we'll be able to prescribe them more, particularly in primary care, which is outstanding. But at the same time, who are the right patients? Who should we be selecting to use anti-obesity drugs to treat obesity?

Dr. Ryan:
Great question, Chuck. We're really looking for patients who need to lose weight for health reasons. So all of these medications are indicated for a BMI of 30 or higher or a BMI of 27 with at least 1 complication of obesity, or comorbidity. These drugs should not be used for cosmetic weight loss.

Secondly, I think that prescribing these medications, since they mostly work through appetite, is a real opportunity to improve diet quality. And so we need to take advantage of that. These drugs change what patients want to eat, not just how much they eat. So it's a real good opportunity to move patients to a healthier diet. And it's also a good opportunity to increase physical activity. Because we want patients to lose not just weight, we want them to lose fat, and we want to preserve as much lean mass as possible.

I think we have to propose to patients that what we're undertaking with these medications is a more intensive weight-loss effort. And for patients, there's a timing that this really seems to work best, and that these are windows of opportunity to really embark on a more intensive effort at weight loss. And that might be the new diagnosis of pre-diabetes, a new diagnosis of diabetes, a diagnosis of metabolic syndrome, maybe new laboratory findings. And these are open windows. When we see these, it's an opportunity to propose to the patient that we undertake a more intensive effort to produce more health benefits.

But most important is that patients themselves have to be part of this decision-making process. They're the ones who are actually going to have to undertake the changes that are going to result in effective weight loss. And we also need to be cautious. Older patients and patients who are sicker, we really probably should not be proposing more intensive weight loss. And we need to be careful about older patients and losing weight, because we don't want patients to lose lean mass and become more frail. Pregnancy, a contraindication for weight loss. We may want to maintain weight, but we don't want our patients in negative energy balance during pregnancy.

And the last thing we want to do is propose a weight-loss effort and have it send patients away, have patients believe that we're judging their body size. So if patients say, "No, it's not a good time for me to try to lose weight," we have to accept that, Chuck. It's okay. We say, "That's fine. I support you in that." We reinforce the importance of the changes to improve health, though. "The single best thing you could do would be to make some changes, and we're going to talk about this at the next visit." That's what I say. I get them to agree to take up the topic later on.

Dr. Vega:
Right, that's such a great point. You have to go where the patient allows you to go, and that's going to create real change. Trying to

force it is not going to be successful ultimately and actually can drive them away, like you said, from other good things we can do like, you know, gosh, vaccinations, good blood pressure control, etc.

So fantastic points. Thank you again, so much. Do you have any final take-home messages for our audience?

Dr. Ryan:
I do, Chuck. You know, I think our primary care offices are full of patients who have a lot of chronic diseases, and many of them are complications of obesity. Good weight management is a pathway to better chronic disease management. And I think it's time. We finally have the tools to help our patients achieve weight loss and weight loss maintenance. It's time for us to take this on.

Dr. Vega:
Yeah, let's go upstream.

That's unfortunately all the time we have for today. So I want to thank very much first our audience for listening. We know you're very busy and we hope you found this discussion pragmatic and helpful to your practice. Thank you very much, Dr. Donna Ryan, for joining me and sharing your very keen insights. It was great speaking with you today.

Dr. Ryan:
Oh, thank you so much for having me. I enjoyed it.

Announcer:
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