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## Is the 'Weight' Over? Next Generation of Anti-Obesity Therapeutics

### Announcer Intro:

Welcome to CME on ReachMD. This activity, entitled "Is the 'Weight' Over? Next Generation of Anti-Obesity Therapeutics", was developed through the joint providership of the University of Cincinnati and CORE Medical Education, LLC. and is supported by an educational grant from Novo Nordisk A/S.

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### Dr. Russell:

Dr. Kushner, welcome to the program.

### Dr. Kushner:

Thank you for having me.

### Dr. Russell:

So, why don't we start today by looking at the big picture, and I don't think anyone in medicine would have anything but saying obesity is huge issue in the United States. Can you put some numbers to that? How big a problem is it?

### Dr. Kushner:

Sure. Well, first of all, obesity is the most common non-communicable disease globally, so that says a lot right there. In the United States, it's an epidemic as well as the most significant noninfectious disease. You know, we're coming out of COVID which is the biggest threat to our health over the past 2 years. Obesity is ongoing. The latest statistics in the United States is over 42% of American adults suffer from obesity, and that's defined as a BMI of 30 or more. Alarming, 9% - suffer from severe obesity, which is a BMI of 40 or more, roughly 100 pounds overweight. The youth - we also see the numbers going up. The latest data is 18 and a half percent have obesity, so this is serious. So, obesity is not only associated with the most chronic, serious diseases, such as cancer, heart disease, fatty liver disease, and so forth, but the one I - I want to point out, Dr. Russell, is the coexistence with type 2 diabetes, and a lot of us now call it diabetes, and here's the numbers: since 2000 - so over the past 2 decades or so - the prevalence of diabetes has gone from 9.8% to over 14%, right? So, that's pretty significant. If you take those individuals with type 2 diabetes, approximately 80% of them have coexisting obesity, and if you add overweight to that, you're probably at 90 to 95%, so that's why we call it diabetes. They coexist, and obesity actually makes diabetes even worse.

### Dr. Russell:

So, one would think if this is involving more and more of us in the United States that we would probably be a little bit more accepting, but certainly over the last few years we've seen increased stigma and bias, especially during COVID with patients who have excessive weight, and it seems to be worsening. So, how does this stigma and bias affect our patients with obesity?

### Dr. Kushner:

You know, that is probably one of the most significant issues we need to face. It wasn't too long ago that we would stigmatize people who were addicted to opiates or alcohol or had mental illness. We no longer stigmatize those individuals, but obesity for a variety of

reasons is still stigmatized and suffers from we call weight bias, and just to remind you and the listeners, weight bias is negative attitudes towards individuals with obesity, and we tend to stereotype individuals with obesity, and we stigmatize them, we often reject them we have prejudice against them, we discriminate against them, and that is in the form of verbal discrimination and stigma, physical relational, and cyber, particularly cyber bullying, which we see so much among our youth which is so sad to see and interestingly, physicians are the second most common source of stigma. The number one source, is family, right? You think about sitting around at the Thanksgiving or Christmas dinner, right? There's no filter when you sit around a table. It all comes right at you. That's number 1. Number 2, though, sadly, is physicians, and many clinicians believe that patients with obesity, believe it or not, and this has been through survey data, are lazy, undisciplined, unlikely to be adherent to recommended changes. They often feel working with individuals with obesity are a waste of time, and what that leads to is our patients are not coming to see us, and they're not getting preventive care, which is so darn important, and probably one of the most important aspects of weight bias is called weight bias internalization, and we're all familiar with if you're told you're not worthy enough or you're not good enough over and over again, we start to believe that we're not good enough, right? So, weight bias internalization is along those same lines. When individuals who live with obesity are continually stigmatized against, they start to internalize those negative feelings, and when they do that, they often develop eating disorders and behaviors just the opposite of what you would think they should do, but they start eating more, they start bingeing, they have maladaptive weight control behaviors, disordered eating and so forth, they have reduced motivation. It also affects them physiologically, so stress hormones start to go up like cortisol, C-reactive protein goes up which is inflammatory marker, and hemoglobin A1C starts to go up, so they develop glucose intolerance, and as I've already said before, they start to resist going to healthcare providers because they don't want to be stigmatized or be shunned by those. So, they don't get their pap smears or colonoscopies, breast exams, and so forth, which is really a terrible effect on individuals. They have psychological issues like depression and anxiety and other physiologic health issues like – or glycemic control or increased blood pressure, so this has all been identified. So, we get this vicious circle that we stigmatize individuals with obesity, they start internalizing it, and they may even gain more weight. So, it's a very sad circle, and we really need to start breaking that not only internal or implicit but also explicit stigma or bias that we often express.

**Dr. Russell:**

So, as a thought leader in this area, what is the current thinking of this? the role of disease or the role of some level of personal responsibility?

**Dr. Kushner:**

Well, I think it's both, Dr. Russell. We certainly don't want to take out personal responsibility of any healthcare behaviors. However, I think the biggest paradigm shift regarding obesity probably over the past 2 decades or so, is that obesity is now thought of a chronic disease – not just a – a problem that one's afflicted with or a moral problem or sloth and gluttony or if they only tried harder, they would get their weight under control. We really have moved beyond that now. It's the same as – if you're depressed, just think happy thoughts, and you won't be depressed, you know? It's really quite of that simple.

So, obesity is thought as a chronic disease, and it's been declared from multiple societies from around the world – probably the most prominent the United States is the AMA – and in 2003, they recognized obesity and overweight as a chronic medical condition and urgent public health problem that needs to be dealt with, and the pathology of obesity falls into two different realms the way you kind of think about it. One is an energy balance dysregulation, and that is the balancing of how many calories we consume and how many calories we burn is dysregulated. There isn't that harmony that should be intact from a physiologic point of view, and the second is organ system impairment from a condition we call lipotoxicity, so let me just unpack both of those just quickly.

So, the energy balance dysregulation has been now understood as poor signaling that an individual who suffers from obesity is getting from their gut and from their fat tissue up to the brain. In other words, the brain is not getting the proper signaling to either reduce appetite or to burn more calories, and because of that improper signaling individuals may be consuming more calories than their body needs from a physiologic point of view, and that's manifested by increased hunger their never feeling full having increased cravings for food, increased enticement of food from the environment, and that all leads to a dysregulation and increase in body weight, and some of the targets I hope we talk about later from a pharmaceutical point of view start to leverage some of these signals and give it back to individuals like you would give insulin in someone with diabetes, and when it comes to the other pathologic problem, which is lipotoxicity, this primarily comes from products that are secreted from fat tissue. We call them adipokines, and many people know cytokines that come from inflammatory cells like macrophages or monocytes – adipokines come from fat tissue. These are things like TNF-alpha, interleukin 6 other products like angiotensinogen, free fatty acids, PAI-1. All of these are circulated throughout the body in an endocrine fashion and really cause havoc throughout the body, such as insulin resistance in the muscle tissue or adipose tissue, increasing fat in the liver or in the heart endothelial contraction to increase hypertension or even development of atherosclerosis. So, these two things – appetite dysregulation and lipotoxicity – is what gives the meaning of obesity as a disease by itself – not just a pass through for developing complications like hypertension or GERD or fatty liver disease.

**Dr. Russell:**

So, thanks so much for sharing that, Dr. Kushner. let's switch gears a little bit. So, if 30 to 40% of the patients who walk in my office are dealing with obesity, what are some of the challenges that myself, yourself, and our colleagues in medicine face when treating patients who have obesity?

**Dr. Kushner:**

Well, it's a great question, and as healthcare providers, we need to deal with our patients and become part of the solution, right? And not a problem as I've already talked about regarding bias. The first is we need to think about the myths about obesity, and I think the most prominent myth is that obesity is a choice, you know, as if your patient who weighs 270 pounds, that's his goal in life is to be your biggest patient in your practice, right? That's absurd. Individuals don't choose to be overweight and be ostracized and stigmatized in our society and all the health complications, so that's number one bias. What I've already said, that obesity is caused by a complex interplay of multiple determinants that lead to the disease, such as endocrine and metabolic dysregulation, certainly the environment will increase the likelihood of obesity including enticing foods and engineering out physical activity in daily life. Genetics plays a huge role in developing obesity, and all you have to do is think of your parents or your cousins or your grandparents who struggled with their weight but the monogenetic causes of obesity are not the most common cause. The most common is polygenetic, right? We inherit multiple genes that lead to this energy dysregulation, and, of course, there's behavioral and psychosocial elements that lead to it as well. So, although obesity is in part due to this calorie imbalance – increased calories in, reduced calories out – it is not that simple. We have to think of all of these conditions that play into it, and – and, Dr. Russell, we also have to reframe our mindset about how we're going to be seeing these patients. So, if you think of it as a chronic relapsing disease – and I'm going to use diabetes as a comparator – when you see someone with diabetes, you need to think about regular follow-up visits just like you would with diabetes. You want to standardize your approach to this patient, and I'll bet every listener who sees a patient with diabetes, they already have an algorithm and a flow in the structure in their mind and including the narrative that they're going to use to talk about someone about diabetes and how you're going to treat it. Not so much with obesity, but that's what we need to do in order to frame our mindset. We want to learn to track metrics like body weight and trajectories in body weight. We want to look at the BMI and the electronic medical record. We want to measure waist circumference in individuals at – that's going to be helpful, and that's usually a BMI under 35. It turns out that the individual with upper body fat distribution is the high-risk phenotype, and if we measure waist circumference on screening, we can identify the patient we want to spend more time with. We certainly want to build trust with our patients just like someone with diabetes. If we need to reach out to specialists because of complications of the obesity, such as sleep apnea comes to mind right away, we're going to reach out to a pulmonologist or send them for a sleep study, and we want to talk to the patient, as well as accept ourselves, that there are going to be ups and downs over time.

**Dr. Kushner:**

There's a lot of techniques to frame our encounters with patients. Probably the one that I think a lot of people are familiar is called the 5 A's and that was originally developed for smoking cessation and now used for alcohol misuse. Another variation of that is called the 6 A's, and we use that for behavior change in weight management. So, 5 A's is Assess, Advise, Agree, Assist, and Arrange – I'll go over those with you in a minute – but let me focus on what we added uniquely for weight management, and that's – we've changed the first A to Ask, and the reason that's important is because of this – the stigmatization and discrimination that we talked about earlier. When you abruptly talk about someone's weight, it can be very off-putting. So, by asking them permission – is this a good time to talk about your weight? – it really shows a lot of respect for an individual, and they often come into the office with a legacy of healthcare professionals talking to them and really being quite discriminating to them. So it goes something like this: I've noticed you've gained about 10 pounds over the past several years I know you've been struggling with your weight we've been working to try to get your diabetes under better control, and we now know that body weight or excess weight can contribute to a worsening diabetes. Is this a good time to talk about your weight? So, that's how that Ask would actually be used in practice. The other ones – Assess when in t – comes to weight management is to assess an individual's body mass index status, whether they're a high risk or a low risk phenotype, to assess other complications of obesity, as well as to assess in more detail their diet and physical activity, and it's only after you get that information do you turn to the next A, which is Advise. Give them information about how weight loss may actually benefit the medical problems that they have, give them advice about diet and physical activity, and perhaps using shared decision-making, give them and some advice about how medication can help. You then turn to Agree along with the patient about what action plan you're going to go towards as well as goal-setting. Make sure the next A is to Assist them – maybe thinking about joining a commercial weight manager program, assisting them in making a visit or a having a visit or arrange with a registered dietician or going to their gym or seeing an exercise physiologist or assist with a referral to an obesity medicine specialist if that makes sense, and the last A is to Arrange, and that gets to the whole idea that obesity is a chronic relapsing disease, and patients need to be seen back.

**Dr. Russell:**

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. John Russell, and I'm speaking with Dr. Robert Kushner about

newly available strategies in weight loss management. So, as we turn our focus to therapies, in certain ways, it's never been a more exciting time and never had more options open for our patients who are dealing with this problem, correct?

**Dr. Kushner:**

Yes, absolutely correct, and I've been in practice for 40 years, and it is indeed an exciting time, particularly regarding pharmacotherapy, but before we turn to that, which is I think a huge paradigm shift in the treatment of obesity, I want to mention that we have a continuum of care for individuals with obesity who are struggling to get their weight under control, and I often like to use a pyramid. If you kind of imagine in your mind a pyramid where the base of the pyramid is lifestyle modification – so that's physical activity, diet, and behavioral change – and I like that because if you think of a pyramid the biggest part of the pyramid is the bottom. So, everything rests on that, and it's also what we need to do with all of our patients. So, choose a healthy diet that's balanced in its pattern, reduced in calories, you're not skipping meals, you're not doing crazy diets that you can't follow long-term, you're getting daily physical activity – at least 150 minutes of – of moderately vigorous activity that you accumulate every week or even more – and you put it in the context of your daily life so that you're planning your meals, you're fitting in a physical activity according to your busy schedule, you're getting the social support of your family, you're using planning and different prompts to make it happen.

The second part of that continuum, and it sits right above lifestyle modification in this pyramid that I have you thinking in your mind, would be pharmacotherapy, and we call it anti-obesity medications, and the role of them is to help you follow a lower calorie diet with more resolve and more consistently. And then the top of the pyramid, which, of course, is the smallest part in our completing the continuum of obesity care, is that's where you would find bariatric surgery or different endoscopic procedures. So, which approach you use depends upon the patient sitting in front of you – their BMI their phenotype how many complications or comorbidities they have – and using shared decision-making deciding upon what the best approach is. So, a take-home message at this point, which is so important, is there are so many things we could do to help someone better manage their weight, but keep in mind lifestyle management, pharmacotherapy, and bariatric surgery as the continuum of options to choose from.

**Dr. Russell:**

So, why don't we transition into the anti-obesity medicines? So, what are the FDA-approved medicines that you and I could use on our practices?

**Dr. Kushner:**

So, we have about six or so medications that are approved by the FDA and these are not all available globally, but in the United States, we have that availability. All but one of the medications I'm going to mention to you work through appetite regulation, and that's important to keep in mind. One is, the disease of obesity points to a dysregulation of appetite, so these medications target this appetite dysregulation and try to bring it back to normal, if you will, so that individuals normally feel a reduction in hunger and increased fullness when they're eating. The only medication that does not work that way is orlistat, which is a pancreatic lipase inhibitor approved in 1999, so that one works in the intestine by malabsorbing about 30% of the fat. All of the other ones I'm going to mention to you work through appetite regulation, and I encourage all the listeners to do additional reading to really understand and familiarize themselves with the use and indications, side effects of these medications, but they include phentermine, which was approved in 1959. It's the oldest medication in our country. It also happens to be the most frequently prescribed medication in this country, and I think that's in part because it's been around so long, and it's generic so has the lowest cost. Other ones are phentermine/topiramate, which is a combination drug approved in 2012. Another one is naltrexone/bupropion, and you're all familiar with these as single agents, but they actually come as a combined agent, and that was approved in 2014. The first hormone available for obesity was approved in 2014 – that was liraglutide. The same medication at a lower dose is approved for diabetes care, but it was approved for obesity care in 2014, and that is a GLP-1, or glucagon-like peptide-1 receptor agonist. So, the hormone is GLP-1 produced from the gut, and if you mimic it and give it back in pharmacologic doses you can get an effect on not only diabetes but appetite control. Setmelanotide is kind of an orphan drug approved in 2020, and that is specifically for monogenetic obesities like leptin deficiency or MC4 deficiency. The last one approved just in 2021 is called semaglutide. That is also a GLP-1 receptor agonist, and this one was dubbed by the media as a game changer and it was dubbed the game changer in part because of the multitude of studies that were published one after the other in 2021. They're still being published in 2022. They're called the STEP program – stands for Semaglutide Treatment Effect in People with Obesity (STEP) – and it's the STEP 1 trial in particular that was published last year that showed for the first time a continuous weight loss all the way out to one year – we never saw that before. Number 2 – it caused an average weight loss of 15% - we've never seen that kind of weight loss before. The third was that it was given by self-administered shot once a week. So, for those reasons, it was dubbed a game changer. Now, if you line up all of the medications almost side by side, and you look at the effectiveness of these medications versus placebo, and all of these drugs, by the way, have been tested in randomized control trials going out at least one year, some of them two to three years, four of the earlier drugs – phentermine, phentermine/topiramate, naltrexone/bupropion, and even liraglutide – average weight losses were about 8 to 12% after one year. As I've already said, semaglutide at 2.4 mg dose once a week caused a weight loss of 15%

on average, and when I'm going to mention one more drug here, it's not approved yet for obesity care, but it has been approved for diabetes care, and that's called tirzepatide. That drug we thought semaglutide 2.4 was a game changer – tirzepatide is causing an average weight loss of over 20% after approximately one year, and those drugs that program for obesity called SURMOUNT is ongoing, and it's going to be reviewed by the FDA in April 2023 potentially for approval of obesity.

**Dr. Russell:**

So, Dr. Kushner, we talked about the past – late 1950s and phentermine. We talked about 2021 and endocrinologic approach. What's the future?

**Dr. Kushner:**

Future is exciting. I wish I'd practice for another 20 years so I could take advantage of this. The GLP-1 receptor agonist which is semaglutide as an example – you know, GLP-1 seems to be turning into the anchor drug for many new hormonal approaches for obesity, and what we're seeing now are multiple agents in phase 1, 2, and 3 that are trying to mimic gut hormones or pancreatic hormones and leverage their effect on appetite regulation. So, GLP-1s receptor agonists like semaglutide sits by itself. Tirzepatide is a GLP-1/GIP receptor agonist that is going to hopefully be approved soon for obesity, but on top of that, we have very exciting agents that's combining GLP-1 with glucagon, we have others that are combining GLP-1 with an amylin analogue called cagrilintide, and even triagonists where we're combining GLP-1, glucagon, and GIP. So, this really appears to be the future of obesity, and stay tuned. Put your seatbelt on over the next five years to see all of these agents coming up, which I think will be very, very exciting efficacy endpoints of 5, 15, or even 20% weight loss. Tirzepatide which came out in the SURMOUNT-1 trial in New England Journal, showed an average weight loss of 22% and ongoing weight loss out to a year, and – and probably equally important and even more exciting is that one-third of individuals in that SURMOUNT trial with tirzepatide lost 25% of their body weight. So, this future that I'm talking about is already being shown in a drug like tirzepatide, and we anticipate even more effective medications with these dual and triagonists.

**Dr. Russell:**

So, Dr. Kushner, we've covered a lot of ground today – a very timely, very important topic. So, this is your life's work, what are the takeaway points that you could pass on to the clinician listening about how to approach and help our patients with obesity?

**Dr. Kushner:**

Yeah, thank you. Let me summarize, I think, one of the key points. We talked about the prevalence of obesity that's continuing to increase among adults and children, and a lot of the survey and the futuristic studies are suggesting that is only going to be worse over the coming decades. We talked about obesity considered a chronic disease that requires lifelong treatment. It's not episodic, acute care – it's chronic relapsing care. You want to be aware of the harms of weight bias when you interact with your patients, and think about this vicious circle of this internal weight bias. Treatment approaches include lifestyle management, pharmacotherapy, and bariatric surgery when indicated, and you have to think about that using shared decision-making with your patients. Consider using the 6 A's as a framework for behavior change in weight management. That's how you frame when you're interacting with someone. We talked about the multiple medications that are available that primarily work through appetite suppression, and the most effective current drugs are semaglutide and tirzepatide – again, the latter one is not quite approved for obesity yet – and lastly, stay tuned for more effective drugs that are hormonally-based that are on the horizon.

**Dr. Russell:**

So, really exciting ways to perhaps help so many of our patients who you and I take care of every day. So, I want to thank you for summarizing a very complicated topic Dr. Kushner, and that brings us to the end of today's program. I want to thank you for helping us better understand the latest updates in the management of obesity. Dr. Kushner, it was great speaking with you today.

**Dr. Kushner:**

Thank you, Dr. Russell.

**Announcer Close:**

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