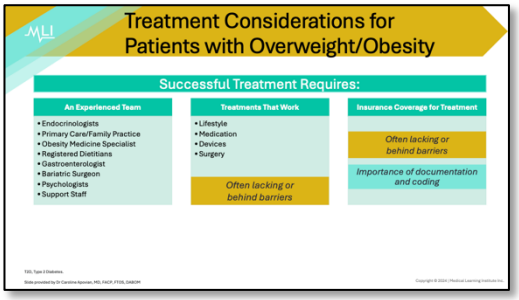
Chapter 2: No One-Size-Fits-All Approach: Individualizing Obesity Treatment

Jay H. Shubrook, DO, FAAFP, FACOFP: Welcome to Part Two, No One-Size-Fits-All Approach: Individualizing Obesity Treatment. I'm Jay Shubrook, a professor and diabetologist at Toro University, California, and I'm delighted to partner with Dr. Kushner. Dr. Kushner, could you introduce yourself?

Dr. Robert Kushner: Sure, Jay. I'm a professor of medicine and medical education at Northwestern University, Feinberg School of Medicine. I also have the opportunity to be director of the Center for Lifestyle Medicine at Northwestern Medicine in Chicago. I'm happy to be joining with you today.



Treatment Considerations for Patients with Overweight/Obesity

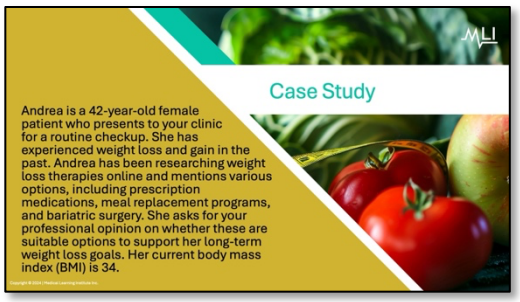
Jay, I'm going to start off with two points that I want to make before we get into this topic.

The first is when we're treating patients that present with both type two diabetes and obesity, we need to think of this as a team sport. That's the term I use. Team sport meaning we need a team of professionals working to help this patient. Primary care physicians, could be an obesity medicine specialist, perhaps an endocrinologist, but particularly important would be a registered dietician or a health psychologist if there's mental health issues.

The second is we need to think about an array of treatment options from lifestyle to medication, devices, and even surgery when it comes to obesity.

Lastly, unfortunately, we often have to think about insurance. The second point I want to make before we get any further is that there is still an existing bias and stigma that is associated with obesity, which we don't see with other conditions. In fact, that discrimination is as high in some studies as what we see in race and gender. We need to check in regarding our own biases and our own sense of discrimination these individuals, so we don't perpetuate this problem when we're seeing patients.

Dr. Shubrook: I think it's really important to highlight that as primary care clinicians, we don't have to go it alone. You need a team for such a complex condition. I think that you've brought up such important points, that the team can be quite broad depending upon the needs of the patient.



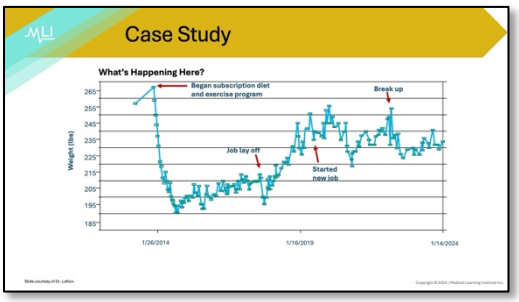
Case Study

We have a case, and I'd love to hear your thoughts.

Andrea is a 42-year-old female who presents to your clinic for routine checkup. She has experienced weight loss and weight gain in the past, cycled many times. She's been researching weight loss therapies online and mentioned some various options, including prescription medications, meal replacement programs, and even bariatric surgery. She asked for your professional opinion on whether these are suitable options to support her long-term weight loss goals. Her current BMI is 34. I assume you've seen someone like Andrea before and how would you evaluate her and initiate an evaluation for her?

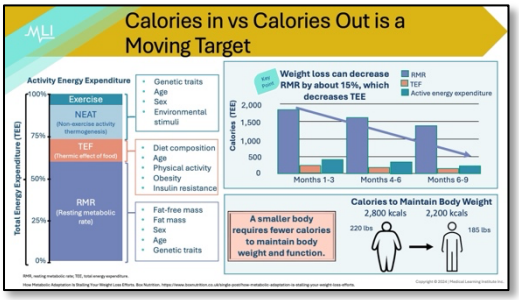
Dr. Kushner: It's interesting since we've had the availability of these highly effective medications, patients are coming to the clinic more often than ever, I've seen in my professional career. Coming in, not only wanting help but asking for specific help, such as, I've heard about these new medications, am I a candidate for it? How soon can I get it? It is absolutely incumbent upon all clinicians, particularly primary care clinicians, to be armed with information on how to respond to these patients, so the question is right on.

Dr. Shubrook: That sounds like a great place to start an important conversation.



Case Study

Dr. Kushner: The other thing that I do, Jay, which I've been doing for 20 years now, is take a life event weight graph history, and it's actually shown here in this slide. It is probably the most informative and useful information you can get from your patient in a graphic form. It's their own story to tell. What it gives you is an understanding of what their life graph is, what their weight losses or weight gains are associated with the life event as they see them. In this particular case, a patient began losing weight with a diet, the patient lost weight, started gaining a little bit, was laid off from their job, started a new job, a breakup, and so on.



Calories in vs Calories Out is a Moving Target

It gives you an insight to what we call the psychosocial and cognitive determinants, including social determinants of health, that may be impacting a patient's weight. It's so important to get that information to really walk in their shoes, if you will, about their weight. In addition to that, the main point I want to make now that we need to be aware of and translate this, communicate this to our patients, is the understanding of metabolic adaptations.

Patients often feel like they failed because they've regained weight. It is so important to understand the underlying biology of obesity, that regardless of what the intervention is, whether it's lifestyle, treatment, whether it's pharmacotherapy or even bariatric surgery, there is a change in the amount of calories one needs to maintain that lower body weight. In fact, there's an adaptation the body goes through, such that as you lose weight, you actually need less calories in order to maintain your weight, more than you even predict, and that's called adaptation. The patient is fighting against this adaptation regarding maintain your lower body weight, and in part, in addition to psychosocial variables, I mentioned, starts this unfortunate, unforgivable regain in body weight that no matter what they do, they find it very difficult to maintain their lower body weight. It's a lot of words I just used, but it's very important to convey the patient that it's not their fault. There's an underlying biology that occurs on top of the psychosocial issues that makes it difficult to maintain that weight loss.

On average, weight loss can decrease the resting metabolic rate, that's the amount of calories we need to burn just to maintain our weight, by about 15%, and that overall decreases the amount of energy that we expend.

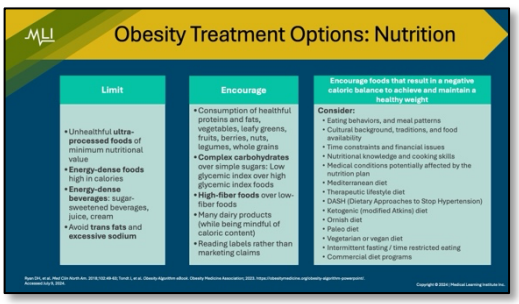
Obesity Management Goals

Dr. Shubrook: I want to highlight some of the things, Bob, you really talked about. I think we could be helping our patients by using patient-centered language. Again, being objective in our measurements when we're looking at excessive weight, and recognizing that we're there for multiple purposes, we're a resource of information, as well as tools that when we address excessive weight, we're helping not only improve the patient health, but we're improving the body weight and composition, which is going to affect downstream complications.

Obesity Treatment Guidelines

We have obesity treatment guidelines, and I think we want to highlight that BMI is an imperfect measurement but is a reproducible measurement that we use in practice.

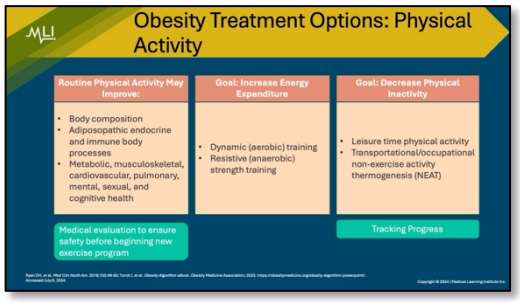
We have different BMI categories that we really should be documenting regularly so that we are paying attention to weight. As we start to address higher weights, we're going to need more help, and we need a multimodal approach that will include ourselves and other team members, including other specialists.



Obesity Treatment Options: Nutrition

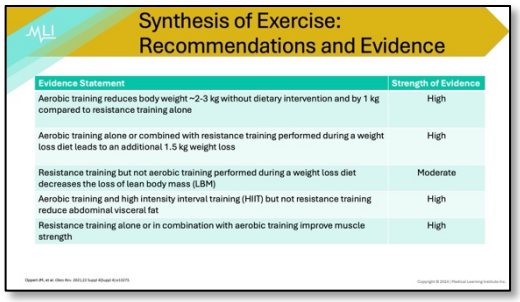
As we think about the different components of obesity treatment, as we think about nutrition, of course, so many clinicians have given empty advice as it relates to nutrition.

I think, again, if you're comfortable with this, this is something you want to take time with because it's a significant component of healthy weight management, but making sure we focus on the things that are high yield in terms of reducing ultra-processed foods, certainly being aware of what are the high energy dense foods that a particular person ingests, and so we can address those, certainly avoiding any sweetened beverages, and then being aware of trying to eat whole food diets that fit within the person's norm and cultural norms, because again, I think our dietary patterns are strongly linked to our family and social norms.



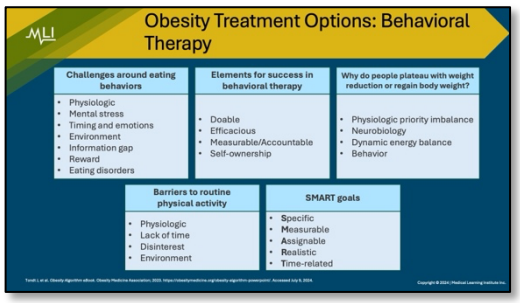
Obesity Treatment Options: Physical Activity

Dr. Kushner: Physical activity is not exceptionally powerful modality to have someone lose weight, but it is very important to maintain fitness, to improve other comorbidities from the benefits of being more physically active, to help maintain our body composition and our muscle mass and increase quality of life, so diet and nutrition both are foundational. We have evidence guidelines on how effective physical activity can be.



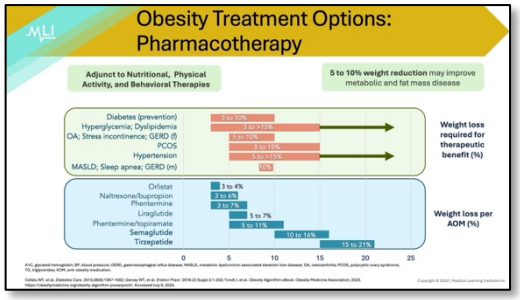
Synthesis of Exercise: Recommendations and Evidence

We know that it only leads to a small amount of body weight, and in fact, if you add both aerobic and resistance training, you really have a high level of evidence that could be beneficial. We also know that resistance training is the most effective way to maintain muscle mass, at least the best that we can, and aerobic training itself also may have an impact on abdominal visceral fat. Both nutrition and physical activity are extremely important as foundational treatments for caring for our patients with obesity.



Obesity Treatment Options: Behavioral Therapy

Dr. Shubrook: We already highlighted the importance of nutrition and physical activity as basis of all work that we do in terms of obesity management. I think it's also important to recognize the role of behavioral therapy because these are complex, multiple behavioral adaptations that have to occur for weight management. We should be looking at what are some of the challenges for someone on any given day in terms of maintaining those goals, and are they physiologic? Are they based on your schedule? Are they based on the environment or the people you're with? I think it's so important to recognize that most people, when they're setting personal goals for weight management, really struggle to set realistic goals. This is a great time to set the expectation of a SMART goal. A SMART goal, again, has these features of being specific, measurable, assignable, realistic, and time-dependent, and it's important that they are small, achievable, and we can set many small goals than one very big goal, and that can really reinforce a patient's success.



Obesity Treatment Options: Pharmacotherapy

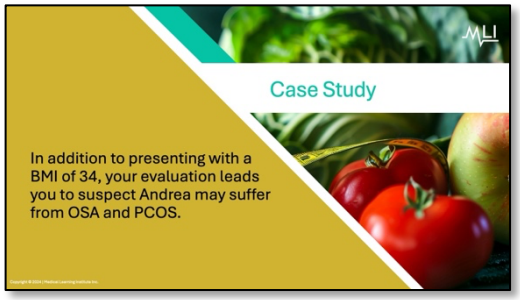
Dr. Kushner: Jay, just to build on what you said, and just to reinforce lifestyle, management is foundational, diet, physical activity, and behavior change. Another very important change that has occurred with obesity is our better understanding of how much weight loss is needed in order to achieve a particular health goal. It's not just weight loss as a goal, but really, more importantly, improving the health of the patient.

We always used to say that if you lose five to maybe 10% of your body weight, yes, that's fine. That's a goal for everyone. We now know through various studies that complications of comorbidities improve with varying amounts of body weight. It's important for us to know that because if we see a patient in front of us who needs a particular goal, we can then assign the amount of weight loss that's required and then lead us to what treatment we want to use.

For example, we know from data that improvement in blood sugar or improvement in blood pressure or improvement in triglycerides in the blood can be seen with as little as 3% to 5% weight loss.

However, if you have a patient who has diabetes and you're looking for remission of the diabetes, now you're talking about a 15% weight loss or a patient with fatty liver disease with steatohepatitis or someone with obstructive sleep apnea or cardiovascular disease, you need to achieve a much greater amount of weight loss now, 10% to 15% or so.

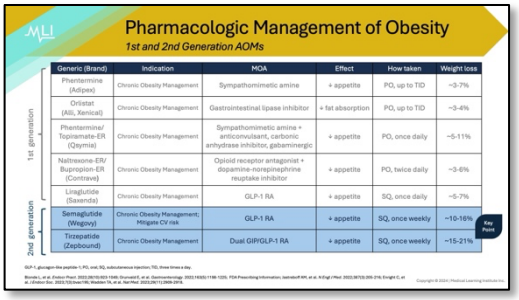
Dr. Shubrook: I love that as a point of focus because then you can really tailor the treatment plan to the goal that you are trying to achieve.



Case Study

As we go back to our case, Andrea presented with a BMI of 34, and of course you found that she does have sleep apnea and PCOS. Now we've identified that Andrea has some suspected comorbidities. How does this affect your assessment and your treatment plan?

Dr. Kushner: This really is an application activity to what I just said about targeting the treatment depending on the patient. The way this would look in the clinic is I would make sure that the patient knows the relationship between her body weight and the development of sleep apnea and having PCOS, I want her to have that understanding. I would convey to her that any amount of weight loss is likely to benefit both sleep apnea and her symptoms of PCOS. However, we know from studies that a greater amount of weight loss is likely to be necessary to see significant clinical benefits in these diseases. I would then convey to her those types of treatments that would more likely get her to that target. Those would be the more highly effective anti-obesity medications.

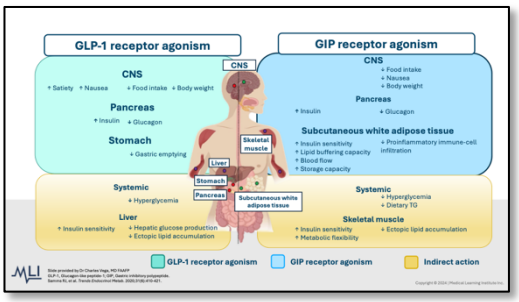


Pharmacologic Management of Obesity

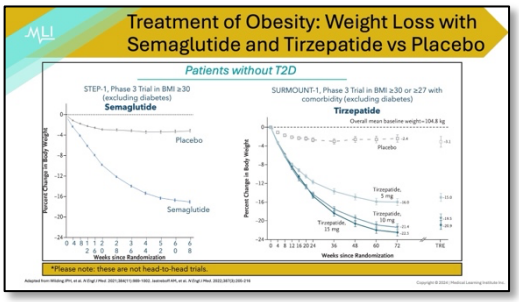
Dr. Kushner: Jay, what I'm looking at here are the currently available anti-obesity medications that are available in the United States. They are not all available globally. The earlier medications, we call first-generation or earlier medications, work primarily centrally directly in the brain, resulting in a weight loss of about 5% to 10% weight loss. The only first-generation medication that works peripherally, that is not on appetite suppression, is orilstat. It's also the only medication available over the counter for treatment of obesity. The others are dietary supplements.

Towards the bottom, we see the generation of these incretin-based medications. First, liraglude, which is available for daily injection, and more recently, the more highly effective weekly self-administered medications, that would be semaglutide and tirzepatide. Now, a few things I want to make note of. One is these medications, liraglutide, semaglutide, and tirzepatide, are available for diabetes at one dose and then obesity at other doses under different trade names. They are all incretin-based hormone analogs, which means they produce glucose-dependent insulin secretion, but the effect on weight loss is primarily through reduction in appetite by working in the brain, and we call this the brain-gut axis.

Instead of causing a mean weight loss of 5% to 10%, they are now resulting in a mean weight loss of 15% to 20%, and that's really what has gotten the public and influencers and social media all excited about this and what's driving basically patients into the clinic, asking, "I've heard about these medications, am I a candidate, and when can I get a prescription?" They really represent an inflection point in the treatment of obesity.



The two incretin hormones that are currently being explored and are approved are GLP-1 and GIP. They have a lot of overlapping characteristics or actions. I've already said the fact that they're incretin hormones, they because glucose-dependent insulin secretion, they delay gastric emptying, and they both work up in the brain on appetite control. GIP adds additional mechanisms, particularly on fat tissue, fat in the liver, and even on bone. Because of these small independent effects, it has been added to GLP-1 as a dual agonist in the form of tirzepatide. Of course, GLP-1 receptor analog by itself would be semaglutide as that example.



Treatment of Obesity: Weight Loss with Semaglutide and Tirzepatide vs Placebo

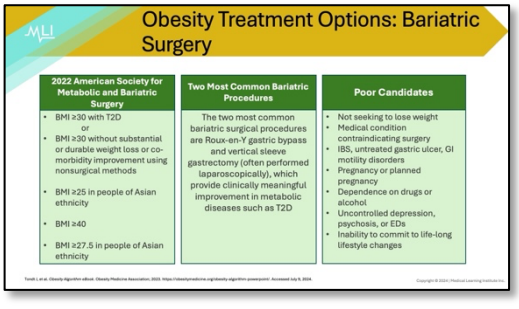
If we look at both STEP 1 and SURMOUNT-1 trials, it gives us very interesting information because we have two drugs that have a very similar research design that allows us to look at

the effects of these medications in two different populations, both treated for obesity. There's a few highlights here, Jay, I want to make. One is that during the early dose escalation period for both semaglutide and tirzepatide, what is weight loss occurs very early, even as the drug is being slowly increased, which means individuals respond early if they're going to respond at all. There's then a stabilization of the weight once you get out to either 68 weeks with semaglutide or 72 weeks with tirzepatide, both in a parallel weight loss pattern.

Although this is not a head-to-head trial, it appears that tirzepatide is more effective for mean weight loss than semaglutide, such that tirzepatide at the highest dose, individuals are losing about 21% body weight, semaglutide at about 15% body weight. I want to highlight one other thing, Jay, which is very important for clinicians to know. For semaglutide in these trials, about 15% of individuals did not lose at least 5% of the body weight. In other words, we call them non-responders. For tirzepatide, it's about 10%. We don't know whether it's pharmacokinetics, we don't know whether it's the biology of that individual, the phenotype of that individual, that is yet to be determined.

It's important for a clinician to look at what is an expected weight loss curve, and within two to three months, if a patient is falling off that curve, it is likely that they may not have the same response and to intervene early. What I mean by that is either change a medication, add another medication, or go in a different route.

Dr. Shubrook: I think this is consistent with the other weight loss medications, that you do monitor for responsiveness. Just one other point I want to add is, if you document a BMI regularly and you put the indication for the treatment, particularly for weight loss, when you're using a GLP-1, you're much more likely to get this covered. I think that too often, because medicines have multiple indications, insurances are requiring you to put the indication in the Sig so that they know what you're using it for and that it's being used for an indicated purpose.



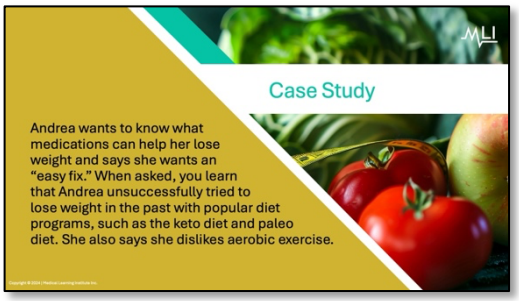
Obesity Treatment Options: Bariatric Surgery

Dr. Kushner: The other option we haven't talked about yet is bariatric surgery. Now because it's more invasive, it's a higher risk, requires hospitalization and a surgeon, you would naturally want to use this treatment for individuals who present with more health complications or comorbidities or higher BMI, that makes sense based on the risk-benefit ratio. The current indication had been a BMI of 35 or more with a comorbidity like type 2 diabetes or a BMI of 40 or more even without a comorbidity. The latest recommendations from the American Society of Metabolic and Bariatric Surgery, based on data by the way, is to lower that BMI threshold to 30 or more if you had type 2 diabetes.

That really comes from the outcome data that diabetes can go into remission and remain controlled even at a lower BMI, and the earlier you intervene in someone with type 2 diabetes because of the beta cell loss that goes on over time, the more likely you're going to be successful. Now having said

that, not all insurance companies are following suit and are approving bariatric surgery for an individual with a BMI of 30 or more with type 2 diabetes. A lot of them are still sticking to 35 or more. I want to end up this part of our conversation with weight maintenance. Regardless of whether it's a lifestyle intervention or pharmacotherapy or bariatric surgery, it is important that the patient maintains that weight loss long-term. To do that often requires staying on the treatment, such as pharmacotherapy, and you may vary the dose, or ongoing care by the clinician, registered dietitian, whoever the team member is. We've learned so much from previous behavioral interventions to get an idea of what is important to maintain that weight loss.

We have learned from these studies that continuing to follow a healthy diet with increased fruits and vegetables, diets that are low in energy density and high in nutrient density, increased physical activity on a daily basis, monitoring your weight and monitoring your eating in some way so that you're aware of what your behaviors are, of course having self-efficacy, and that is the ability that I can do it, and having good social support and reinforcement accountability by the healthcare professional. We know that these variables make a difference.



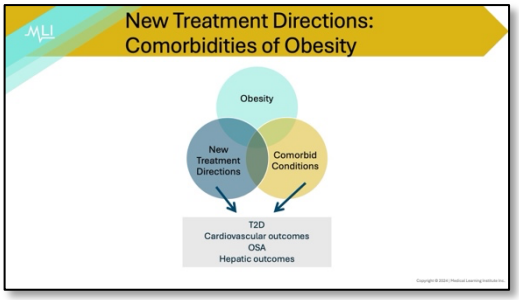
Case Study

Dr. Shubrook: Let's go back to our case. Andrea wants to know what medications she can use to help lose weight, and she wants an easy fix. There's a hint there. When asked, you learn that she has unsuccessfully tried to lose weight in the past with popular diet programs such as the keto diet and paleo diet. She also dislikes aerobic exercise. How do you address Andrea when she's asking for the easy fix and address maybe some of the things she's tried in the past?

Dr. Kushner: Again, this is a nice application activity for the points, Jay that you and I just made. I think it makes it even more explicit. There are no easy fixes for a chronic progressive relapsing disease, again, like diabetes, hypertension, heart disease, and so forth, asthma. There are no easy fixes. When someone says that to me, I call them out in a compassionate, understanding way, but I tell them there's nothing easy about this. I'm here to help you. I'll hold your hand. We have multiple treatments available, multiple resources and staff to help you, but there is no easy fix. This is something that may come back if you don't continue to focus on and make long-term changes.

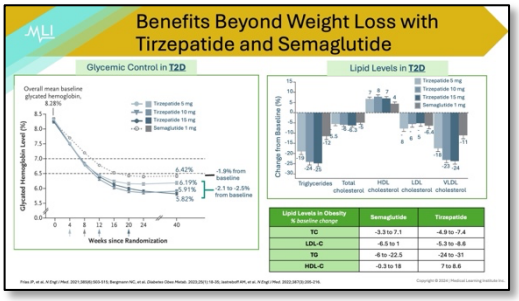
Professional Society Recommendations of Anti-Obesity Medications for Appropriate Patients

Jay, so you and I think, are giving a nice overview of obesity, but I do want to emphasize to our learners that there are multiple recommendations and guidelines available for them to look at when it comes to treating obesity, either alone or associated with heart disease or diabetes. Please access those guidelines as needed.



New Treatment Directions: Comorbidities of Obesity

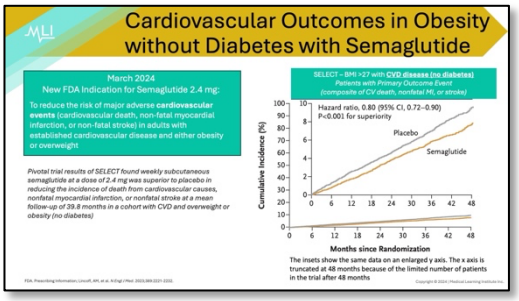
Dr. Shubrook: As we think about the treatment of comorbidities, I do think it's very important to recognize that obesity and comorbid conditions will overlap with each other. As we look at treatment options, we're going to want to be able to use treatments that are going to treat multiple conditions, and we do have that opportunity now.



Benefits Beyond Weight Loss with Tirzepatide and Semaglutide

As agents that treat both diabetes and obesity, tirzepatide and semaglutide really have what we would call a twofer. As you can see, patients are going to have significant reductions in their weight, but they're also going to have significant reductions in A1C, that make them a potent agent, as defined by the American Diabetes Association. This is important because you're going to see benefits for both, and they often will make room for removing other medications that are attributing to weight gain, such as insulin.

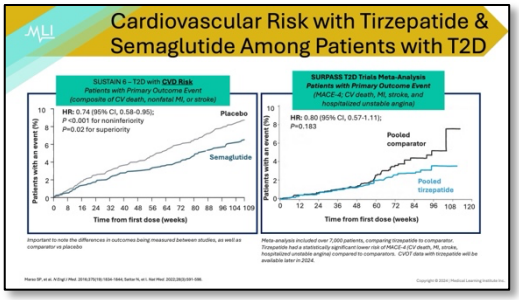
We also are starting to see metabolic benefits from these medicines, including benefits in lipid panels, benefits in triglyceride management, and even benefits at the liver.



Cardiovascular Outcomes in Obesity without Diabetes with Semaglutide

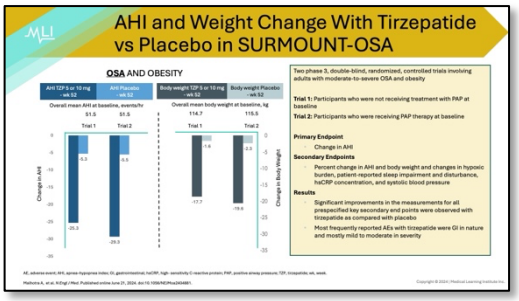
We're now seeing agents that manage diabetes that have not only benefits for weight and diabetes, but also cardiovascular outcomes. You can see here in the semaglutide study for obesity, this is the 2.4 milligram dose, it had independent benefits for cardiovascular outcomes above and beyond its effects on weight and obesity.

Dr. Kushner: The other thing I want to point out here is that because of the outcome, the results of the select trial, the FDA, for the very first time in history, removed a BMI criterion for use of this drug for patients with obesity and preexisting cardiovascular disease. Even though it still says overweight and/or obesity, it removed the BMI. You mentioned before about the limitations of using BMI. I think this is significant. We're going to see more of this from the FDA regarding their package insert and requirements.



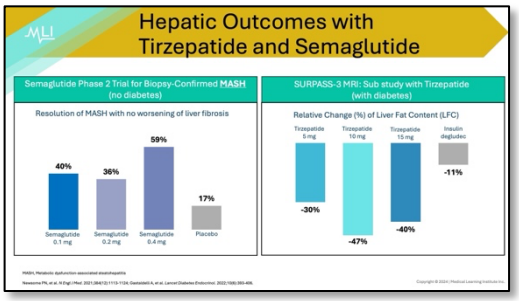
Cardiovascular Risk with Tirzepatide & Semaglutide Among Patients w/ T2D

Dr. Shubrook: Highlighting in this graph is really showing you the reduction in cardiovascular risk in those taking semaglutide and tirzepatide in patients with type 2 diabetes. You're getting agents now that are really treating a patient much more comprehensively by producing reduction in weight, reduction in glucose, and now reduction in cardiovascular risk.



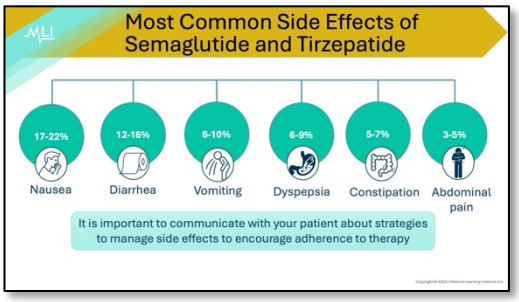
AHI and Weight Change with Tirzepatide vs Placebo in SURMOUNT-OSA

Dr. Kushner: An example of the benefit of these highly effective medications is now being seen in treating patients who have a comorbidity of sleep apnea. This is data from a recent publication from SURMOUNT-OSA, where they took individuals with obesity and existing sleep apnea, who either were not receiving CPAP at baseline or were receiving CPAP at baseline and randomized them to placebo or to tirzepatide. What you see really is a highly clinically significant reduction in AHI in both of these patient populations of 29 events per hour or so versus about five events per hour in placebo, which is achieved by a reduction of about 18% or 19% body weight.



Hepatic Outcomes with Tirzepatide and Semaglutide

Another comorbidity that we are looking at because of the pleiotropic effects of these medications, both in semaglutide and tirzepatide, is the effect on the liver. Now, we know that this metabolically associated steatohepatitis, new name for this now, is becoming very prevalent among the American population, those with overweight or obesity, and even including those with diabetes. These drugs are now starting to look at as independent treatments for this condition.



Most Common Side Effects of Semaglutide and Tirzepatide

I want to talk a little bit as we get to the end about management of patients on these medications. Both semaglutide and tirzepatide have common side effects in their gastrointestinal, in the form of nausea, diarrhea, vomiting, dyspepsia, constipation, or even abdominal pain. Now, they vary between the two drugs, but because of the individual variability, one patient may have no side effects, someone have severe side effects. I think it's most important to be

aware of what the symptoms are, and to proactively talk to your patient about the possibility of having these side effects so they know what to look for.

The other take-home message here is that we have learned to reduce or mitigate those side effects by taking very deliberate action on our part. The first is to slowly escalate the drug, starting at the lowest dose, and go in a stepwise manner over the subsequent dose increments. Usually, it's done every four weeks. You do not need to increase to the maximum dose. If someone responds to a lower dose, keep them in a lower dose, nor do you need to escalate them every four weeks. They could stay on the same dose until they tolerate it better.

The other thing we've learned from the Phase 3 trials to mitigate these side effects is the importance of dietary counseling. When a patient goes on these drugs, tell them to eat slowly, take smaller portions, don't skip meals, watch fatty and greasy foods, minimize those to the lowest possible intake, plan your meals in advance. Don't take it at a time that your diet is going to be unpredictable or not usual over the subsequent one to two days. For an example, if your patient spends the weekends eating out most of the time, do not take the injection on a Friday night or a Saturday morning. They're likely to have increased side effects.

The other, just to reemphasize what I said, is plan your meals every day. Since your appetite is reduced, you're not going to be as hungry, and before you know it, someone has not eaten all day long. That is something that they do not want to do. The other considerations we talked about a little bit earlier, is that you want to maintain muscle mass and you do that by actively engaging in resistance training and being physically active.

Dr. Shubrook: Bob, I want to call out what you said there to the audience, is that this is a time where you definitely want to do the education upfront, have the patient know what to expect, know that these side effects are time limited. If you do all that, they're much more likely to be successful with the titration and the long-term plan. This is a medicine we need for long-term management, so we definitely need them to have a good onboarding process.

Dr. Kushner: It is absolutely necessary that primary care clinicians become involved in obesity care, develop the familiarity and competency in treating patients and becoming part of the solution in helping patients become healthier.

Dr. Shubrook: This brings us to the end of part two of the series, No One-Size-Fits-All Approach: Individualizing Obesity Treatment. We've taken a look at barriers to treatment initiation and adherence, the evolving treatment landscape, and the integration of obesity medicines into clinical practice.

Please join us in part three of the series, *Best Practices and Shared Decision-Making to Enhance Patient Outcomes*.