

CARDIOMETABOLIC HEALTH CONGRESS

**Webinar #4: When Lifestyle Interventions are Not Enough
– The Spectrum of Comprehensive Methods for Long-
Term Weight Loss in T2DM Patients**

Chair/Moderator: Donna Ryan, MD

Faculty: Louis J. Aronne, MD; Christopher Still, DO

DR. RYAN: Hello, and welcome back to the fourth in our Cardiometabolic Health Congress series on optimizing long term weight loss. Today we're going to talk about when lifestyle interventions are not enough. We're going to run through the spectrum of comprehensive methods for long-term weight loss in patients with type two diabetes.

I am Donna Ryan, and I am Professor Emerita at the Pennington Biomedical Research Center in Baton Rouge, Louisiana. And I'm fortunate to have two experts with me here today, Lou Aronne, who is Sanford Weill Professor of Metabolic Research at Weill Cornell Medical College and the head of the Comprehensive Weight Control Center in the division of Endocrinology, Diabetes and Metabolism in New York. And also, Chris Still, who's a Professor of Medicine in the Department of Clinical Sciences and the Director of the Geisinger Obesity Institute in the Geisinger Health System. So, we have two prominent experts.

First Lou Aronne is going to be talking to us about pharmacotherapy for weight loss, and then Chris Still about bariatric surgery for weight loss. So, without further ado, let's begin. Lou Aronne.

DR. ARONNE: Thanks so much, Donna. I really appreciate those kind words. Very happy to be here talking to you all today about anti-obesity pharmacotherapy. Going to talk a little bit about the medicines that are currently available, comparing them and then giving some practical advice on how we prescribe them. And finally, let's talk about a case. Here are my disclosures.

Now the rationale for obesity pharmacotherapy has become really clear in the last year or so, as we've seen the evolution of medications which are highly effective. You know, there are more than 200 medical disorders that affect every organ system related to obesity. This accounts for about 4 million deaths worldwide and is really the driving force behind cardiometabolic disease.

There's a rapid increase in prevalence, and what we need to do, in my opinion, is to begin to treat obesity like the disease that it is, to recognize it early and to begin treatment instead of waiting for all the complications to develop.

Here are a few examples, not all of them, of the diseases that are associated with obesity. So, since obesity is a multi-system disease associated with all of these complications, doesn't it make sense to treat the obesity and treat them all at the same time instead of waiting for them to get severe? Instead of waiting for the complications to get severe, and then try to treat them one at a time?

Here's the current or what I would call the old treatment paradigm for cardiometabolic disease management. We would ignore obesity because we don't know what to do and it doesn't really work. And we know that treating complications can improve health and outcomes. So, we would treat the dyslipidemia, the hypertension, the diabetes or impaired glucose tolerance. We might not do much with diet and monitoring, but we would use medications to manage those because we're comfortable with that.

And when it comes to the weight problem, what we would do is ignore it. Most physicians would ignore that because if you have the glucose under control, if you have the lipids under control, well, that's okay, that's good enough. That's the best we can do.

But I think that we're in the midst of flipping this over, turning the pyramid over on its head, and we're getting to the point where treating obesity first makes a lot of sense since we now can treat obesity both safely and effectively.

An important point is that we now recognize that more weight loss provides more clinical benefit, and some of the frustration that doctors and nurse practitioners and other providers have had over the years with trying to get clinical benefit from treating obesity, has been because the magnitude of weight loss is not enough to achieve all of the clinical benefits. So, we see that there are different magnitudes of weight loss that produce different degrees of benefit for some of the metabolic diseases like diabetes, hyperglycemia, improvement in HDL, sleep apnea, etc.

Some of these only improve with greater weight losses, such as sleep apnea. And with the new highly effective agents that we're seeing --some of the combination medicines, semaglutide and most recently tirzepatide -- with the weight losses that we're seeing with those of 10% and greater, we will be able to get all of these problems, all of them, by just treating obesity and achieving that kind of magnitude of weight loss.

Something I've been saying for a number of years is this: is obesity the new hypertension? Looking at parallels in the evolution of obesity and hypertension as recognized disease states. And I would say that obesity is the new hypertension and is going to evolve into a field of chronic treatment.

So that treating obesity with medication in addition to behavioral intervention on a chronic basis, is going to provide the kind of benefit that we saw with hypertension back in the sixties, seventies, and eighties. And recognize that there are more than a hundred medicines to treat hypertension. We have six drugs and two are combinations of older drugs.

One of the important principles is that ongoing treatment is necessary. If medication is stopped, people will regain weight and go back to the effect of lifestyle intervention alone. So chronic treatment is going to be necessary. It may be that patients can take it less often. It may be they can take a lower dose. But in my opinion, we've got to get used to the idea that treatment of obesity is chronic and needs to continue in the long term.

Now we have guidelines for medical treatment of our obesity, or pharmacologic management of obesity. These are from the Endocrine Society Practice Guideline from 2015, and unfortunately only 2%, only 2% of patients who qualify for treatment based on these guidelines are being treated. And there are a number of guidelines, and what they say is that someone with a BMI of 27 to 30 with comorbidities, someone with a BMI of 30 and above would qualify for treatment with medication.

But again, only 2% of those who fit in those categories are currently being treated. And some of the reasons why that is not being followed, those guidelines are not being followed,

are a poor understanding of obesity and its causes, the limited efficacy of the medicines that previously were available.

Concerns about safety of the medicines and side effects that have prevented the wide adoption of these medications. And finally, there's the lack of insurance coverage. Many patients do not have coverage for these treatments. And if we did have treatments, if we had equality of coverage, I think we would have far more people getting this kind of treatment.

Now I'm going to compare the weight loss with the medicines that are currently available. It's a little bit complicated because there are different names used to describe these treatments. So, there's the observed-on treatment or efficacy estimand or completers. These are people who are actually taking the medication at the end of the study. There are a number of other names used, but these are the most common.

Then there are those who are in the study with the intent to treat them. So, they're in the study, but they may not be on the drug.

And then finally, there's the placebo subtracted weight loss, which is the weight loss achieved by people who are in the study minus the weight loss from the placebo weight management program.

So, this is confusing. And when you see numbers for weight loss, you may see sometimes higher numbers, sometimes lower numbers. The highest numbers are from those who complete, including the effect of the behavioral program. The lowest are the placebo subtracted weight losses.

So, the medicines that we use to treat patients are on this slide. And on the left we have those that are approved for weight loss. In the middle, we have ones that are used for the treatment of type two diabetes that promote weight loss or are at least weight neutral. And then on the right there are those that are used for other illnesses that can cause weight loss. And we use all of these medicines in a sophisticated obesity medicine practice, like our own. We use all of these in combination, in various combinations.

So, the ones I'm going to talk about are phentermine, semaglutide, liraglutide, phentermine/topiramate combination, the bupropion/naltrexone combination, orlistat and then Gelesis 100, which is not a medication, but a device. It's a fiber product that is approved as a device.

These are the weight losses, the placebo subtracted weight losses of the currently approved anti-obesity drugs. And you can see that the first one on the bottom, orlistat, produced about a 3% placebo subtracted weight loss, and the weight loss with Gelesis 100 is very similar to that.

Liraglutide 3.0mg, which is a daily injectable, produced about 4.5%. The combination naltrexone/bupropion, about 4.8 or 5%. Phentermine in a short-term study that we did a number of years ago, phentermine alone produced about a 5% weight loss. Then the combination of phentermine/topiramate extended release, the highest dose produced over

9% weight loss, about 9.5% weight loss. And then finally, the best results are with semaglutide, up to 2.4 milligrams, which produced a 12.5% weight loss.

And again, this is placebo subtracted, and the placebo in our trials is a good weight management program. So, you can add about 3%, add 2-3% additional weight loss for a comprehensive weight management program to get the total efficacy seen with these compounds.

Here's another way of comparing agents. And here what I've done is to take the results of all the phase three, the major phase three trials and compare them looking at the percent of subjects who achieved at least a 5% weight loss in the phase three trials. And you can see that there are some similarities and some differences so that it's not uncommon for subjects in these trials to get a 60 to 70% achievement of 5% weight loss or more.

On the right, on the far right, you see the newest compounds, in which 85-95% of subjects are achieving 5% or more weight loss. And a 5% is a major milestone because it's the point at which there's a 50% reduction in the risk of developing type two diabetes.

But this doesn't give you a full look at the magnitude of benefit from the newer agents because the total weight loss, as with the phentermine/topiramate extended release is so much greater and with the semaglutide so much greater than we see with the older agents.

So, some of the basic rules for prescribing these medicines, we try to avoid side effects because that has been one of the issues with medications in the past, older medicines. Those that which are no longer available. And note that they're different, they're different side effects for the different drugs. And so, we take those into account. I don't have time to go into the details.

We look at how much a drug costs and whether it's covered by insurance or not. Very, very important. Titration is critical to tolerability of these drugs. We start with a low dose and gradually titrate them up to tolerance by the patients. We don't do like is done in clinical trials where we're forced to titrate the drug up to a certain dose. Clinically what we do is to go gradually.

We note that the efficacy is greater for phentermine/topiramate and the injectable GLP1's like semaglutide. So, we use those, preferentially, in higher classes of obesity, class two and class three. And we discontinue drugs that don't produce the 5% weight loss at a full dose in three months.

So, if we titrate the patient up to the full dose of medicine at three months, and we haven't lost 5% of their body weight, we would discontinue that medication. So, here's a question. which of the following statements about semaglutide, phentermine/topiramate, and naltrexone/bupropion is correct? The maximum dosage should be started initially for all three agents. The side effect profiles are similar. They should be discontinued if 5% weight loss is not achieved at full dose after about three months, or the weight loss is about the same with all three agents.

The correct answer is number three. They should be discontinued if 5% weight loss is not achieved at full dose after about three months. So, here's the current treatment landscape.

We have here in the spectrum of care, the left Gelesis and orlistat, producing a little bit less than five percent, you know, four, three percent weight loss. Which can give some clinical benefits, particularly for people who are in the lower end of the weight management spectrum and Gelesis product is approved to a BMI below 27 (25 to 27), which gives you an agent to use in patients who are overweight.

Phentermine produced some more weight loss, five plus percent weight loss, naltrexone/bupropion you see there, and then phentermine/topiramate producing the best weight loss. And now we have semaglutide, which produced 17.7 kilos: a total of 16.9% in the completers of the trial. And you can see that's just about as much as was achieved with lap band surgery. Total was about 39 pounds or 17.7 kilos.

The newest drug, which we just reported on, tirzepatide, produced as much as 22.5% weight loss. I don't have it on here, but it produced just a little bit less than a sleeve gastrectomy.

And finally, gastric bypass, over 30% weight loss. And Dr. Still will be talking about those in a couple minutes.

So, let's talk about a case. Let's meet Robert, a 43-year-old man, BMI of 48, 291 pounds presented in 2016 to our center. He had coronary artery disease, a myocardial infarction in 2012. He had percutaneous stents put in twice. He has prediabetes, kidney disease, nephrolithiasis rather. A remote history of seizure disorder. And he gained a significant amount of weight after his MI when he stopped smoking. His current medications include aspirin, rosuvastatin, metoprolol, lisinopril, paroxetine. His HBA1C is 5.8%. His labs are otherwise normal.

So, one of the first things we consider in evaluating patients are the medications that they're taking to see if they have any medicines that could be contributing to weight gain. And in looking at Robert's case, we thought that it's possible that he's taking metoprolol that can make it more difficult to lose weight in people with diabetes and prediabetes. There's evidence from trials suggesting that.

And so, we recommended a switch to carvedilol and nebivolol, beta blockers, which are more specific and have been shown to have less of a cardiometabolic effect.

And then the antidepressant he was taking, paroxetine, is associated with the most weight gain. And so, we considered switching to either fluoxetine or sertraline, which are in the same category, but seem to cause less weight gain. Bupropion is another agent which could have been used, but he had a remote history of seizure disorder. And so, we did not prescribe it because bupropion has been associated with an increased risk for seizures.

And here is what we did. Here's his weight journey. We made the switch from the metoprolol to carvedilol, from paroxetine to fluoxetine, and we started him on metformin, which is often our first line agent. It's off label, but for people with prediabetes we are often prescribing metformin. And you can see that his weight went from 291 down to 262 in about six months.

And at that point he plateaued after losing 29 pounds and complained that he was getting hungrier, and we prescribed liraglutide. At that point he lost more weight. And stabilized at that point and felt very comfortable and able to maintain his weight.

So, remember that he had been gaining weight steadily at this point, and so now maintaining a 10% body weight loss for several years, we found that was very helpful for him and he felt very good. In January of 2020 we changed his medication to semaglutide after two and a half years on this plateau. And what we found was that he lost twice as much weight, more than twice as much weight by switching from liraglutide to semaglutide, a total of 67 pounds.

I'm happy to report that his weight is in the same range. Between 230 and 225 pounds now, even two years later. So, we were able to achieve about a 20% body weight loss by changing around his medical regimen and adding now semaglutide and metformin to his regimen.

So, the take home points, we choose weight losing and weight neutral medications when possible for any indication. We often find that we can take patients off some medications when we get them to lose weight. That was not the case in this particular case, but we often can do that. And liraglutide and semaglutide are associated with cardiovascular risk reduction and so, we often will choose them in a patient with cardiovascular disease.

So, the last question, which of the following antidepressants is least likely to cause weight gain? Paroxetine, Amitriptyline, doxepin, bupropion and sertraline.

The answer is bupropion. It's often associated with weight loss, and we find that it should be the first choice in many patients with obesity who develop depression. Thanks very much for your attention and I'm happy to answer any questions during the Q and A period.

DR. RYAN: Thank you. Thank you so much, Lou. You know, I'm really glad you talked about the medications that have an obesity indication. I think oftentimes for our patients with type two diabetes, we forget about those medications because we think we're bound by just using medications that have a diabetes indication. So, I'm going to come back to you in the discussion period and we're going to talk a little bit about medications for diabetes. So, I'm giving you a heads-up Lou, I'm coming back to you on that point.

Now it's my very great pleasure to introduce you to Chris Still, who's going to talk to us about bariatric surgery. Chris?

DR. STILL: Thank you, Donna. Great job, Lou. You're always a hard act to follow. So, I'm honored to be here with Lou and Donna today to talk about something that I love to talk about, and that's bariatric surgery. And I'll come back to that in just a minute. Here are my disclosures.

So, as Lou alluded to, you know, components of an effective weight management program -- diet, exercise, and behavior modification -- are often overlooked or given lip service. But I think they're the most important cornerstone to the best medications that Dr. Aronne talked about, and even the best surgery that I'm going to talk about.

So, we can't lose sight of that, but my talk is to talk about bariatric surgery in conjunction with diet, exercise, and behavior modification.

So, as Lou nicely pointed out the landscapes, we talked about diet and exercise, which is about 5% efficacy, and then the medications and they're gaining on bariatric surgery efficacy. But you can see the lap band is, as Dr. Aronne said is about 16%. The sleeve gastrectomy is about 27%, and the gastric bypass is about 30, 30 to 35%. And then finally the duodenal switch, which I'll talk about, can be greater than that.

But the fact remains is that, as Dr. Aronne said, I think that we need to intensify treatment options based on the disease burden of the patient or the comorbidities of the patient. And really not wait too long with diet and exercise. We really want to get to the next stage because as Dr. Aronne nicely said, we want to try to achieve at least that 10% weight loss. And if you look at this spectrum, we really have to consider pharmacotherapy and or bariatric surgery to reach that.

And then we have endoscopic intervention. So, these are the balloons, the aspire system, some pacemakers. They're helpful in some individuals. My biggest problem with a lot of the endoscopic procedures, they're only short term, so they have to be removed after six months. And as Lou said, obesity is not a short-term disease. It's a long-term chronic disease that needs long term treatment.

So, let's talk now about bariatric surgery. Like indications for pharmacotherapy, bariatric surgery also has indications. So currently the indication for bariatric surgery is a BMI of 35 with a comorbid medical problem: like diabetes, sleep apnea, fatty liver disease, or 40 alone. And as Lou alluded to with pharmacotherapy, only 2% of patients that meet the criteria for pharmacotherapy are actually prescribed pharmacotherapy.

Unfortunately, less than 1% of patients that meet the criteria for bariatric surgery are actually currently undergoing bariatric surgery. So, both for pharmacotherapy and bariatric surgery, we have an opportunity, if you will, to really talk to our patients early on about safe and effective treatment for their chronic disease.

So, this is why I love to talk about obesity or bariatric surgery as an internist and obesity medicine specialist. Because we can resolve and ameliorate a lot of medical problems that were talked about earlier. We can see on average obstructive sleep apnea, which is the one of the most misdiagnosed or underdiagnosed comorbid medical problems, you know, up to 80 to 90% can be resolved. Steatohepatitis, the leading cause of liver transplantation in the world today, we can have a significant benefit on long term treatment with cirrhosis from NASH. And really weight loss and bariatric surgery to date is our only real effective treatment option since there's really no pharmacologic agents on the market today.

Osteoarthritis: also, significant impact in improving offloading joints with just every pound we lose, takes off 5.4 pounds per square inch on our knees and joints. So we can know we have a significant impact with offloading you know, greater than 20% weight loss.

I think the biggest bang for our buck that's been around for a long time is the remission, or at least the significant control of type two diabetes. And I'm going to share a study about that in just a minute.

Hypertension, also gout, phlebitis. All of these comorbid medical problems have this significant impact, not only with modest weight loss, but to a greater degree of weight loss with bariatric surgery, as Dr. Aronne pointed out so nicely.

So, Lou had six tools in his toolbox for bariatric surgery. We have four. So, the four most common procedures endorsed by the ASMBS (American Society of Metabolic and Bariatric Surgery), are the laparoscopic sleeve gastrectomy, the laparoscopic bypass, the adjustable gastric band, and then finally the duodenal switch.

So, if we look at the laparoscopic sleeve gastrectomy, which is the number one performed surgery in the world today, by about 70% in the United States, but also I think that holds up worldwide. So here is an example of the sleeve gastrectomy. It's just a partial gastrectomy. They take out 90% of the stomach and they leave a sleeve, so that's where they get the sleeve gastrectomy.

This is just a restrictive procedure, but I'll show you the efficacy in just a minute. It does produce a significant weight loss as we alluded to. One of the reasons why they think that it leads to a significant decrease in appetite, at least short term, is when they take out 90% of the stomach, they're taking out 90% of the ghrelin-secreting cells. As you recall, ghrelin is a hunger hormone, but unfortunately with the chronicity of the disease of obesity, those 10% remaining ghrelin cells tend to over produce and over time ghrelin levels tend to increase. But for now, this is a very safe and effective restrictive procedure.

One thing about the sleeve gastrectomy to use caution for your patients, if they struggle with severe reflux disease or GERD, you want to be cautious with this because like the Laplace's Law, the highest pressure is at the top of a tube. This can make actually reflux much worse. And so, that's not what you want to do for your patients. But very effective, 70% of all procedures are currently done in the United States by the sleeve gastrectomy.

Second most common is the gastric bypass, which was the number one, but took second fiddle to the sleeve gastrectomy. But this is a both restrictive and malabsorptive procedure. So, food comes down the esophagus. They make a 30 ml pouch about the size of the egg. They bypass the majority of the stomach in the first 150 centimeters of the small intestine, and then they bring the jejunum up. So, food comes down the esophagus into this 30 ml pouch and then down into the jejunum, where then it mixes with enzymes from the Roux limb and normal digestion occurs.

Finally, the adjustable gastric band, which was very popular back, say 10 years ago, has really fallen out of favor because of the long-term efficacy. And actually, more bands are being ex-planted than implanted today. But it's a simple procedure. It's a band that's put around the top part of the stomach and there's a port that comes out underneath the skin, and then you just instill saline into this band, and it produces a restrictive procedure.

And then finally the duodenal switch. This is the most malabsorptive or effective procedure, but it's really reserved for the higher BMI with a lot of disease burden and really compliant patients. Because this procedure, although the most effective, we really can have problems with micronutrient deficiency, protein calorie malnutrition in the long haul. But very, very

effective. It's basically a sleeve gastrectomy, but they bypass the majority of the small intestine, and there's just a small common channel for absorption of calories.

So, this is one study I'd like to talk about. It's called the STAMPEDE trial. So, this was bariatric surgery versus intensive medical therapy with patients with obesity and type two diabetes. And it's over five-year outcomes. It's a very simple, very nice study, very clean. They randomize 150 patients to either intensive medical therapy alone. And what I'd like to point out, it's not what Dr. Aronne talked about, intensive obesity treatment. It was just intensive diabetes treatment, and there's a difference there, especially back when this study was performed. Fifty got medical therapy plus a gastric bypass. And then 50 got medical therapy plus the sleeve gastrectomy.

So, they looked at initial three years and then five-year data. So, what I want to show you now is weight change after five years. So, the top dotted line is individuals with medical therapy. There was about a 5.3-kilogram weight loss after five years. And then you see the sleeve gastrectomy, which 18.6 kilograms versus the gastric bypass of 23.2-kilogram weight loss.

I was surprised that the efficacy of the sleeve and the bypass were so close. But I want to point out a couple things with this cohort. The average BMI with the gastric bypass was 37. So that's not a very high BMI. At least in our cohort at Geisinger here, our average BMI is 54 with a lot of disease burden. And with our cohort we see about two thirds the amount of weight loss with the sleeve than we do within the gastric bypass. But very, very effective, especially compared to medical therapy for diabetes care.

Now this is a busy slide, but I just wanted point just one panel really, which also I was surprised about. This is, hemoglobin A1C after five years. So you can see this is medical therapy. It went from about 8.8 hemoglobin A1C to 8.5. But you can see both with the sleeve gastrectomy, as well as the gastric bypass, significant improvement in hemoglobin A1C, which was not much different between the sleeve and the gastric bypass. Again, in larger, heavier, more disease burden cohorts, we don't see that, we see a little greater, by and large, a little greater improvement in hemoglobin A1C compared to the sleeve.

But this was a nice study that did for once look at medical intensive therapy for diabetes, the sleeve gastrectomy. versus the gastric bypass.

And then finally, this right-hand panel just looks at the reduction in diabetes medication. And you can assume that the gastric bypass had more than the sleeve reduction, more than the intensive medical therapy. So, one reason for considering bariatric surgery, like weight loss as Dr. Aronne alluded to, it can really significantly reduce medications, which is always important.

Like pharmacotherapy guidelines, this is a team sport and so there's guidelines for patients undergoing bariatric surgery. These are the 2019 guidelines for the perioperative nutrition, metabolic, and non-surgical support for patients undergoing bariatric surgery. You can just Google this. They're free. I suggest anybody that you refer for a bariatric surgery, they're going to be coming back to you at some point, so this is a nice reference for you to.

So nutritional metabolic deficiencies after bariatric surgery; we should not ever talk about surgeries without talking about potential deficiencies. Both gastric and bypass are at risk for iron deficiency and thiamine deficiency. With the gastric bypass, we see more calcium and vitamin D deficiency. We see more iron deficiency, B12 deficiency. And then not depicted here, but what I alluded to with patients with the duodenal switch, we really want to look at fat soluble vitamins, malabsorption, protein calorie malabsorption as well.

And then finally, thiamin deficiency. Thiamine deficiency is really the only medical emergency, if you will, other than say a surgical emergency of a leak or something. Thiamin deficiency, we all should be aware of that in patients undergoing bariatric surgery. So, patients usually present with nystagmus, ataxia, they can have decreased refluxes, irritability. And patients were often misdiagnosed because think of B12 deficiency. It's really thiamine and deficiency. And this is really important because at least to Wernicke's and it can lead to encephalopathy and an irreversible pontine stroke.

So, one thing about the physiology or pathophysiology about thiamine deficiency, the stores are relatively small, three to six weeks is all they last. B12 can last months. They often occur in bariatric surgery patients or any patients that has decreased gastric production, altered GI anatomy, decreased food intake, persistent nausea and vomiting. And then the key is when they go into the emergency room, they give DEX drugs, that just plummets thiamine even further. So, anybody that has nausea and vomiting after bariatric surgery, you don't need to measure thiamine levels, just give it.

So, these are the routine vitamin and mineral supplementation for sleeve and gastric bypass patients, and multiple vitamin one or two a day, calcium and vitamin D. Calcium should be considered in the salt of calcium citrate versus calcium carbonate, because in the alkaline environment such as a sleeve and especially in the gastric bypass where there's very few parental cells, calcium citrate is absorbed about 40% greater than calcium carbonate.

Elemental iron, especially in menstruating women, and then B12 administration as well. So not a lot of vitamins, but there are definitely essential vitamins for you to prescribe and to monitor.

We've come a long way with mortality with bariatric surgery, and I think a lot of this has to do with minimally invasive. Ninety-six percent or 98% of all bariatric procedures are done minimally invasive or laparoscopically. And if you look at comparing mortality to say a CABG, a hip replacement and a lap-chole, bariatric surgery has even less mortality than a lap-chole at 0.52 and a bariatric surgery at 0.13 mortality. But the big kicker or the most important point is when performed in a center of excellence. That is key. We will not find these improvement in these mortality rates in low volume institutions. So much better mortality, but when performed in a bariatric surgery center of excellence.

So now let's go on to my case presentation, Mrs. Jones. So, Mrs. Jones is 38 years old. She has a history of depression, migraine headaches, PCOS, seasonal allergies, who was referred by her PCP for weight loss.

She was frustrated in that she actually gained 10 pounds over the last six months despite following diligently a low-fat meal plan. She admits to not much physical activity due to her

work schedule. Her medications are propranolol, paroxetine, diphenhydramine at 25 milligrams at night for sleep. She has frequent early morning headaches and daytime somnolence. Her weight is 371 pounds, 69 inches, with a corresponding BMI of 54. You can see her A1C was a 6.2 and her AST/ALT was two times normal and she has elevated fasting insulin.

So, this was our experience or what we did with Mrs. Jones. So, she came in and we sort of changed a lot of her diet, exercise, behavior modification, a lot of things that Dr. Aronne does. So instead of a low-fat diet, we started a Mediterranean type of diet. She had a lot of visceral adipose tissue by definition of waist circumference greater than 35 in women versus 40 in men. So, we put her on more of a Mediterranean type. We increased her physical activity. She had severe sleep apnea when she was tested, so we started her on CPAP.

As Dr. Aronne alluded to, the paroxetine, and diphenhydramine, great medications, but they can cause significant weight gain. So, we actually switched her from paroxetine to bupropion/naltrexone, for that dual benefit of the depression and weight loss. And we also started metformin for insulin sensitivity, to improve her insulin sensitivity.

So, you can see she lost weight very nicely. She actually switched insurance and was interested in bariatric surgery. So, she went through our process. She had her sleeve gastrectomy, she lost weight very nicely. With regards to patients after bariatric surgery, I always say nine months after surgery, everyone's a medical management patient. Because you want to really follow them with close accountability because they can and will gain weight.

But you want to really intervene early. You don't want to wait till they gain all their weight. So, we intervened again with metformin and naltrexone/bupropion. Which we had a great response before, and she had an even better response when we started her after her sleeve. And then she started to gain a little bit of weight, and then she went back for her second stage for her duodenal switch.

So, I tried to point out, to put everything together with diet, exercise, the pharmacologic changes. But the point is that just because they have pharmacotherapy, just because they have bariatric surgery, doesn't mean the two should not be mixed. I think obesity is such a chronic disease that often time pharmacotherapy and bariatric surgery should be used hand in hand.

So bariatric surgery is highly effective treatment for morbid obesity, and most importantly, it's comorbid medical comorbidities and should be offered to patients whom conservative management fails. Compared to medical management, surgery results in more profound and long-term comorbidity. But as Lou alluded to, but stay tuned, pharmacotherapies are on the heels of the efficacy of bariatric surgery. To ensure optimal outcomes bariatric surgery should be performed in a multidisciplinary program. And then bariatric surgery finally should be a part of treatment for patients to treat their morbid obesity and their comorbid medical problems.

Thank you very much, and I looked forward also to questions, easy questions from Donna.

DR. RYAN: Thank you, Chris. That was wonderful. You know I have a good question for you about bariatric surgery and type two diabetes. You presented that wonderful study of the two different bariatric surgery approaches, and the really incredible impact on type two diabetes in those patients who had either the sleeve or the bypass.

What do you think the best criteria are for selecting patients with type two diabetes for bariatric surgery? What should we be looking for?

DR. STILL: You know, that's a great question, and I'll just preface this by, I'm biased towards the gastric bypass in patients with diabetes. But having you seen that objective study, you know, I can stand to be corrected.

I like to look at how long the patient has been diabetic, how well they've been controlled, and I'll just tell you in our data that we've published, the gastric bypass for those individuals tends to produce greater weight loss, better and longer improvement in hemoglobin A1C. But you know, there's a lot of surgeons that do a lot of bands, that will dispute that. But I can just say that with regards to diabetes and glycemic control, I think the age of the patient, how long they've been diabetic and how, you know, you may even want to look at their functioning pancreas with a C peptide or something like that.

Because clearly, I think the studies that have been done show greater benefit with the gastric bypass on longer term diabetes resolution.

DR. RYAN: So just to be clear, you want younger patients who've had diabetes for a shorter period of time, is that correct?

DR. STILL: So, you could look at it that way because that's the best chance of early intervention. But my opinion would be either way, if they have diabetes, in the long term, you know, gastric bypass may be better. Having said that, I think this is all a big asterisk because of the new pharmacologic agents. I mean, you know, there's a very prominent surgeon that does sleeve, a great surgeon that does sleeves on everybody, and if that fails, then they'll do pharmacotherapy and or convert to a bypass.

So maybe that's where we are because it is a much easier procedure to do. It's more widely done. I'm just more (biased towards the bypass) just because of my patient population with a heavier BMI and more disease burden. But yeah, the key to what you said is the early intervention, I think is the best.

DR. RYAN: Good. Okay. Now over to you, Lou. So, You know, I think we're lucky in our patients with type two diabetes because we have some good diabetes medication choices as well as some bad ones. So, can you give us a brief tutorial on medications that are approved for diabetes and their effects on weight?

DR. ARONNE: Sure. You know, I think that the old way of managing people, what I would call the glucose-centric management paradigm, is clearly incorrect. Has been proven to not be in the best interest of the patient, because by focusing on glucose you may wind up increasing the patient's weight. And that's if you're using older medicines like insulin and sulfonylureas, you can cause substantial weight gain trying to keep glucose under control.

And I think that there are studies showing that this can produce a higher mortality rate. As opposed to the newer agents, well, some older agents like metformin, which I think people still agree is first line therapy. But now agents like the SGLT2 inhibitors, which are at least weight neutral and can be associated with weight loss by causing glycosuria. Those are associated with reduced mortality and cardiovascular morbidity. And followed by the GLP1 agonist, whether it's oral or one of the injectable agents, there are a number of injectable agents.

You know, I think that that is really the standard right now. Metformin, followed by an SGLT2, followed by a GLP1. And in managing patients like that, I mean, you can't imagine the weight loss that we see. I mean, it's totally different than what used to see on in patients with type two diabetes.

We're seeing this. I just saw a patient, that's why I have my white coat on. I was just seeing patients. I saw someone's 350 pounds. He's a doctor himself and was on insulin trying to keep his glucose under control. We changed him to a GLP1, SGLT2, and Metformin, and he's down below 300 pounds for the first time that he can remember. So that's what's possible.

DR. RYAN: You know Lou, I think everybody is excited about tirzepatide. The latest GLP1 GIP dual agonist, because of the amount of weight loss that it is producing. It seems to be the antidiabetic agent that produces the most weight loss on average. But you know, the FDA recently approved semaglutide up to two milligrams for type two diabetes and dulaglutide for up to four milligrams for diabetes.

So relative to that weight loss that we're seeing with tirzepatide, which is in people with type 2, about 12% or 13%, how much weight loss are we seeing with those higher doses dulaglutide or semaglutide?

DR. ARONNE: Semaglutide, you can get greater weight loss by increasing to the two-milligram dose. You can get another 2-3% weight loss, so it is approaching the efficacy of tirzepatide. But, in my opinion, I think that tirzepatide still edges it out. Dulaglutide, on the other hand, I don't see much greater efficacy by increasing the dose to anywhere near what we're getting with either semaglutide or tirzepatide.

So, I think those are turning out to be clearly superior. The way we manage patients is we look at what's covered. We'll start those, and if we don't get the kind of result that we need, we would then take the time to argue with the insurance company for the more effective agents.

DR. RYAN: You know, one thing that diabetes has taught us is the use of multiple medications together, not stopping and adding a new one. And so, I think that's something we've carried over into obesity management. But are there any medications we shouldn't be using together? And I'm thinking of like the DPP4 inhibitors and the GLP1 receptor agonist. Should we not use those together?

DR. ARONNE: Well, there's overlap in the efficacy between them, right? The DPP4's increase levels of GLP1. So using it along with a GLP1 is not recommended. You know, as far as others, if someone is on insulin or a sulfonylurea, we find that those kind of lock weight in place. So, our strategy is to try to wean people off those as soon as we can, then

get them to lose weight, and then if necessary, if we see that their A1C is rising again, we may go with an insulinotropic agent or insulin if necessary. But we want to get the weight loss because they'll need less insulin and be able to maintain a lower body weight.

DR. RYAN: Right. That's wonderful. So, what about reimbursement? Give us an update on what's going on in reimbursement for bariatric surgery, Chris. And reimbursement for these medications, for diabetes and for obesity Lou.

DR. STILL: I'll chime in first. So, you know, it's good and bad. We have pretty good coverage for bariatric surgery, unlike pharmacotherapy. It's getting better and Lou can talk about it. But even though you know Medicare and Medicaid in most states, a lot of the insurances will indeed cover the criteria of 35 with a comorbidity and, and 40 alone. But even that, as I said, less than 1% of patients are getting or are undergoing bariatric surgery. So, reimbursement is good, the uptake is not so good.

DR. RYAN: Lou, what about for medications?

DR. ARONNE: Well, for medications, Donna, you know, the strategy that we've adopted is we prescribe on-label medications if they're covered in every circumstance. But if they're not, we don't stop. We're patient advocates, and so if we have to prescribe generic medicines in combination, we will do that. And we have strategies for getting every medication at a lower price.

We're using a very low dose of it. So sometimes we'll use GLP1's in very low dose in addition to generic medications, and we're able to get very good results. I mean, good enough results that we have you know, four or five month wait list for patients to get into our center, as I know, most centers are.

So, you know, we prefer doing things that are on-label here as everybody does.

You know, in New York City we see a lot of patients who have commercial insurance and I'm surprised that we're seeing, in my opinion, more coverage for semaglutide. The problem we have is that it's so popular we cannot get it. We cannot get the low doses of semaglutide to start patients on it even though they have coverage. So, it brings up a whole new conundrum in management.

DR. RYAN: When is that is that likely to change? When will we be able to get those supply issues solved?

DR. ARONNE: Well, I heard recently that it's going to be late fall until the end of the year, of this year, December, you know, possibly as late as December before the supply chain issues are solved.

DR. STILL: I would just like to chime in Donna if I could. I think that this is going to, my hope, and this is just my hope. With the efficacy that Lou alluded to and the cardiovascular superiority, and you know, I think that it's going to be malpractice not to, and it's going to like a statin was way back in the day. You know, it's going to be common practice for cardiometabolic disease. Now the supply is a totally different issue. But I hope that that insurances, especially for self-insured patients, are going to want your patients. Just like

diabetics, they're incentivized to be on metformin and a GLP1 and SGLT2. Hopefully insurers are going to see that as well.

DR. RYAN: You know, it really is wonderful to at last have some tools to help our patients lose weight. Because weight loss really is the pathway to better chronic disease management. And look, six out of 10 US adults have a chronic disease. We need to do something about this. But look guys, I've been going easy on you. I'm going to ask you a hard question now and both of you have to answer it. So, you know, our patients with diabetes always seem to lose less weight than those who don't have type two diabetes.

Why is this? Why do patients with diabetes lose less weight? Lou?

DR. ARONNE: Well, there, there are a couple of possible reasons. You know, frankly, our patients with diabetes don't lose less weight. I think they lose, in some cases, more weight. And I think there are a couple of reasons.

One is the diet that we use. If you look at this standard diet that's used in a clinical trial, it's a low calorie, balanced deficit diet. It has a lot of carbohydrates in it. So, it's possible that the higher insulin levels associated with carbohydrate intake blunt the weight loss that's seen with other meds, with medication in a clinical trial. There's the use of other medicines like sulfonylureas and insulin. That's going to blunt the amount of weight that's lost.

But again, we see people who have, and I don't want to call it miraculous, but just dramatic weight loss. When we put them on a low lower carbohydrate, low glycemic diet and wean them off insulin. I mean, it's like a dam is broken and it's quite remarkable. So, I believe that it's an artifact of the time, primarily an artifact of the type of care that's delivered as part of the trials.

DR. RYAN: And Chris.

DR. STILL: That was such an easy question. I agree a hundred percent with Lou. I mean, I think he hit it right on the head. I mean, if you look physiologically by definition, there are more insulin resistance and often time at more visceral fat. And so, by physiologically changing, you know, their meal plan, like the Mediterranean type of diet or a low-glycemic index, trying to increase their physical activity, we can overcome that. But you're right, in all the studies that you alluded to, there seems to be a lower weight loss traditionally in patients with type two diabetes.

DR. ARONNE: Some of these trials, Donna, there is no dietary intervention.

DR. RYAN: Exactly

DR. ARONNE: It's just the medicine versus the placebo.

DR. RYAN: And then the other thing is frequently they don't have a protocol for lowering the sulfonylurea or the insulin. And so that tends to blunt the weight loss. You know, Lou, if you put patients on a negative energy diet, you need to reduce their insulin and sulfonylurea. Because otherwise they're going to eat to defend against hypoglycemia.

DR. ARONNE: Yeah.

DR. RYAN: So now we'll finish up and I'll ask each of you to give a takeaway message to the attendees today. Chris, why don't you start, and Lou, you can have the last word.

DR. STILL: Thanks Donna. So, with regards to bariatric surgery, as I tried to point out, is very safe and very effective, but it's not a standalone easy way out. Obesity is a chronic relapsing disease, and what's needed is frequent accountability, frequent monitoring of micronutrients, macronutrients, but also don't be afraid to use adjunctive pharmacotherapy in patients that have had bariatric surgery.

The further you follow your patients out, the higher risk they have of regaining weight, and it's nothing that they're doing. It's the hormonal and metabolic adaptation. That happens. So, I think it's very safe, very effective, but it's not a standalone, and we really need to encourage accountability and frequent follow up even after bariatric surgery.

DR. RYAN: Great.

DR. ARONNE: And I would say, Donna, that I believe that we've finally reached the inflection point in treating obesity as a disease; treating obesity using medication, surgery, and the other more advanced tools because the evidence is building to a level that we have never seen. Showing that losing weight is the healthiest alternative.

And I think that you know, when we look at some of the trials in type two diabetes with semaglutide, you know, we can see the writing on the wall that there's a reduced risk of cardiovascular events. I think we're going to see that in obesity in the coming months. And then, you know, as Chris pointed out with statin drugs, I vividly remember when statins initially came out it was like, oh wow, great. We're treating cholesterol, who cares?

But then when the outcome trials showed that you could prevent a second heart attack in people by treating their lipids with a statin. It was like, oh my God, I'm going to kill this guy if I don't prescribe it. I think that that moment is coming very soon.

DR. RYAN: I want to thank both of you for your generous time and efforts today. I think it's a great program. You really brought out that weight loss is a pathway to more than just diabetes improvement. It's really many cardiometabolic improvements as well as improved quality of life, improved physical functioning. Many, many benefits. And now to finally have some tools to help us, help our patients lose weight is incredible. So, thank you all for attending.