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An Individualized Approach to Optimize Obesity Treatment

Narrator:

Welcome to CME on ReachMD. This segment: **An Individualized Approach to Optimize Obesity Treatment,** is sponsored by the Endocrine Society, developed by Vindico Medical Education, and supported by an educational grant from Novo Nordisk. This activity focuses on the pharmacologic management of obesity and how to tailor treatment to individual patients.

Your host and moderator is Dr. John Russell, who is the Director of the Family Medicine Residency Program at Abington Memorial Hospital in Abington, Pennsylvania. Dr. Russell will speak with Dr. Louis Aronne, Sanford I. Weill Professor of Metabolic Research at Weill Cornell Medical College and Chairman of the American Board of Obesity Medicine. Dr. Aronne is also the Director of the Comprehensive Weight Control Program at Weill Cornell Medical College.

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Dr. Russell:

Dr. Aronne, welcome to our program.

Dr. Aronne:

Thank you very much, Dr. Russell, a pleasure being here.

Dr. Russell:

So, doctor, over the past few years, there have been several new treatments approved by the FDA for weight management. Could you tell us a little bit more about these agents and how they work?

Dr. Aronne:

Thank you, Dr. Russell. We're in the middle of a revolution in the field of obesity. Where back in the old days we had a few medicines that were available only for short-term use, we now have 4 new medications that are approved for long-term use. The 4 medications include: lorcaserin, the combination of phentermine and topiramate, the combination of naltrexone and bupropion, which is extended-release, and liraglutide, 3 mg. Liraglutide has been available for diabetes. It's now available for the treatment of obesity. In the past we had orlistat, which was approved 19 years ago. It's now available as an over-the-counter agent. And phentermine, which is, by far, the most widely used, is a generic. It's been around for many, many years. It's approved for short-term use, but it is often used in the longer term.

Dr. Russell:

So, doctor, all these drugs you talked about have different mechanisms of action, so, for me, why would the mechanism be important to which patient I would put on which medicine?

Dr. Aronne:

Well, let's think about other fields of medicine, and what we're seeing is that obesity is a disease of hypothalamic signaling pathways. That's why it's so hard to treat people who are obese. Something changes in their brain that makes it difficult for them to lose weight. Let's think about treating other chronic diseases like hypertension or diabetes. For hypertension we have over 100 medications in 10 different therapeutic categories. We have beta blockers. We have alpha blockers, calcium channel blockers, ACE inhibitors, ARBs, diuretics. And the question is: Why do we need all these? Because some people don't respond to one; they respond to something else; they have an allergy with one; we often need 2 or 3 medicines to control blood pressure. And what we're finding is that obesity is remarkably similar, that using one medication, may try it, it doesn't work. That doesn't mean someone can't lose weight. The approach that we use here at our Weill Cornell Comprehensive Weight Control Program is that if a medicine doesn't work or it's not tolerated, we move on to the next option, and the next option, and the next option. So, right now, we're in the phase of step care. I don't know if you remember when we used step care for the treatment of hypertension. We're in exactly that era now where we'll start with something that we will make our best guess at what could work and what will have the fewest side effects, and if that doesn't work, we'll move on, we'll move on, we'll move on. We'll, obviously, avoid things that would be contraindicated in the patient.

So, the 4 medications have very distinctive mechanisms of action. Lorcaserin works as a serotonin 5-HT2C agonist, so it stimulates the serotonin receptor mechanisms that work on appetite, fullness and craving. Phentermine/topiramate, topiramate is a GABA receptor modulator, and phentermine is a norepinephrine releaser, but the doses of phentermine that are used are very small. The lowest dose is 1/8 of a tablet of phentermine. Naltrexone/bupropion, naltrexone is an opioid antagonist, and bupropion, the antidepressant and the smoking drug, is a reuptake inhibitor of dopamine and norepinephrine. And finally, liraglutide is a GLP-1 agonist. And when we look at these compounds, they work in a variety of areas, but they all work in the hypothalamus. They all have some effect on the hypothalamus, which we're finding is the key part of the brain that is affected in obesity. It's the part of the brain that is damaged in the process of weight gain and which makes it hard to lose weight because of the signaling deficits. So, it's totally appropriate to be attacking this from different angles just to see which one works in any given person.

Dr. Russell:

So, Dr. Aronne, could we talk about efficacy, and could you help me learn about the weight loss effects that will be seen in the clinical trials and maybe comparing one agent to another?

Dr. Aronne:

When it comes to the weight loss effect of these, they are, in some cases, they're similar. Some of the drugs look about the same, 3.6% placebo-subtracted weight loss, 3% placebo-subtracted weight loss. When we talk about placebo-subtracted weight loss, that's over and above what a diet and exercise program would give, so if you have someone on a diet and exercise program, it gave a 4% weight loss and the drug gives 3.6%, as you see with lorcaserin, then you can expect a mean weight loss of 7.5%, which is well within target range that we seek for patients to reduce risk.

Phentermine and topiramate is the most effective, overall, because it's a combination of 2 medications. Phentermine/topiramate, you can get about a 6.6% placebo-subtracted weight loss at the recommended dose, the moderate dose of 7.5/46. At the higher dose, 15/92, you can get a mean weight loss of 8.6%. With naltrexone/bupropion, that is a combination, but it's a different type of combination. It's a sequential combination rather than a parallel combination, and that produces about a 4.8%, so not quite as much as phentermine/topiramate. It's, again, a totally different side effect profile. And naltrexone/bupropion, like liraglutide, they're not controlled substances. The other two are. And finally, there's liraglutide, single agent GLP-1 agonist. It produced about a 5.8% weight loss in the clinical trials. So, as a single drug, it's the single most effective compound.

Dr. Russell:

So, in choosing between these different agents, what would be the advantages and disadvantages associated with each of these medicines for weight management?

Dr. Aronne:

Well, right now, this is the key question, because our prescribing is based on side effect profile, the disadvantages of the medication and the cost of the medication and whether it's covered. So in a lot of cases, those are the issues that make us list one drug as the first one. So, for example, phentermine, it's inexpensive and produces reasonable weight loss, but it can increase pulse and blood pressure, so we would avoid it in a patient with cardiovascular risk. And there's no long-term data on cardiovascular safety, so we would, again, avoid it in someone with cardiovascular risk.

The combination of topiramate and phentermine gives very good weight loss. There's 2-year data, which is considered to be long-term data, but topiramate has been shown to be associated with oral cleft palate in chronic use for patients who have seizure disorders, and so it should be avoided in women around the time of childbearing. We counsel those patients very carefully to be sure they understand that this could happen and they should not get pregnant. It can also be expensive if it's not covered by insurance.

Lorcaserin is a serotonin agonist. We avoid its use with serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors. A significant number of people are taking those. And again, it too could be expensive if it's not covered by insurance.

And the other new medications, we have naltrexone/bupropion, produces greater weight loss. It works in food addiction. It reduces craving for food. And there's 2-year data. The side effect profile of it, it is tolerable for the majority of people. It can increase sensitivity to pain in some people, for example, and its price is not as high. They have rebate programs. Price is not as high as some of the others.

And then, finally, there's liraglutide, which is well tolerated by most patients. There's long-term data on it, 2-year greater data. Its use in diabetes has been years and years. It's expensive. It's quite expensive if it's not covered. It's an injectable compound. There's a slight increase in the risk of pancreatitis if it's used over the whole period of time. And so, again, if someone has pancreatitis, we would avoid using liraglutide. We would choose something else.

So, it's like any other field. You have drugs that fit in one place or another. We need more of these, and we will have a lot better treatment.

Dr. Russell:

So, individualization of care like all the other diseases we take care of.

Dr. Aronne:

That's right, exactly the same.

Dr. Russell:

If you're just tuning in, you're listening to CME on ReachMD. I'm your host, Dr. John Russell, and today I'm speaking with Dr. Louis Aronne, who is a Sanford Weill Professor of Metabolic Research at the Weill Cornell Medical College and Chairman of the American Board of Obesity Medicine, and we're speaking about the treatment options for patients with obesity and how they can be used for individual patients.

So, doctor, could we discuss a couple of clinical scenarios? So, say I have a male patient in his early 40s. He's got a BMI of 28 and metabolic syndrome with hypertension, elevated lipids, prediabetes. He also has anxiety and depression. He's currently taking atorvastatin for his lipids, atenolol for hypertension, and he takes paroxetine for his depression. He's having some trouble losing weight through the lifestyle interventions I've talked with him about, but he really is determined to lose weight and wants to talk about some of the new medicines that are out there. So, what would your approach be to this patient I have, and would he be a good candidate for medication?

Dr. Aronne:

Well, when we see patients like this, this is a classic patient for us, except the typical BMI would be, instead of 28 it would be 38. The first thing we look at in evaluating more complicated patients is the medicine that they're taking. Before we prescribe a medicine, we want to be sure that a medicine they're taking is not making it difficult for them to lose weight. The fact is that many medicines that we give patients can contribute to weight gain, and in looking at this, the patient has 2 medicines that can contribute to significant weight gain, the beta blocker, atenolol, and paroxetine for depression, both associated with significant weight gain. And we find that the more of these medicines the patient takes, the more likely they are to gain weight and the greater the weight gain.

So, the first thing that I would do is to see if these could be changed one way or another, one or the other. I'd consider an ACE inhibitor for blood pressure if he's just on it for his blood pressure. As far as the antidepressant, there are some agents -- there are not a lot of good agents to replace SSRIs, but paroxetine stands out as the biggest weight gainer, so we'd consider another SSRI or perhaps something else for the anxiety. We would counsel him on diet, exercise, behavioral strategies. So, when it comes to diet for somebody with metabolic syndrome, while the evidence is clear that whatever diet the patient likes the best, whether it's calorie counting, low fat, low carb diet is best, we generally feel that somebody with impaired fasting glucose or metabolic syndrome does better, most of the time, with a lower glycemic or lower carbohydrate diet, so that would be our first choice.

And then, finally, as far as anti-obesity medication, let's say we did all that and he wasn't doing well, because he has complications like

hypertension, we would consider using medications. We would probably avoid lorcaserin because he's on a serotonergic drug. We'd consider topiramate/phentermine. That has been shown to be effective in patients taking serotonin reuptake inhibitors. We might consider liraglutide. We might consider naltrexone/bupropion. So, that's the kind of approach that we would use.

Dr. Russell:

Okay. How about a different case? So, this case would be a male patient in his 50s. He has obesity and type 2 diabetes. For his diabetes he's taking metformin 500 mg twice a day. He takes glargine 20 units in the evening. He takes glipizide 5 mg twice a day, and his A1c is about 8. He's trying to lose weight but is unable to exercise effectively. Where would you go with this particular patient?

Dr. Aronne:

This is another example of a patient where medication is complicating his efforts to lose weight. We find that using insulin and sulfonylureas in patients as second-line or third-line agents makes it hard for people to lose weight and contributes to weight gain. And, in fact, the new guidelines, latest 2 guidelines from the American Association of Clinical Endocrinologists, recommend GLP-1 agonists as second-line therapy and the SGLT-2 inhibitors as second- or third-line, depending upon which guidelines you're reading. But, in any case, so we would make an effort in addition to putting him on an appropriate diet -- and again, this is another case where we'd use a low glycemic diet -- and we would try to do a cross-titration giving a GLP-1 agonist and cutting down on his insulin and glipizide at the same time to maintain his glycemia. He's also on an inadequate or subtherapeutic, potentially, dose of metformin. We use 1,500 or 2,000 mg of metformin a day. We often see patients who are just taking 500 or 1,000, and then something else is added. You absolutely get more of an effect if you increase it.

One tip is that we find that the extended-release versions of metformin are better tolerated. So, if you have a patient, you say, well, he can only take 500 twice a day because it upsets his stomach, switch to the extended-release, often people will be able to tolerate 1,500 or 2,000 of that if they can. But there are absolutely, I'd say, 5% of people, who cannot tolerate the metformin no matter which version you use.

So we'd increase the metformin. We'd add the GLP-1. If we were using liraglutide, we'd go as high as 3 mg. We favor liraglutide because it's also approved for weight, and we find that it is quite effective at that. And so, that's the type of approach we would use, and I would be very enthusiastic that someone like this would do quite well.

Dr. Russell:

So, you talked about individualizing care, so what safety and tolerability issues should be discussed with patients when assessing the risk-benefit profile of the medicines for chronic weight management?

Dr. Aronne:

Well, again, it depends on their overall picture. So, for example, phentermine we wouldn't use or we'd think very carefully if someone has an elevation in their blood pressure. If they have a rapid pulse, if they have problems with insomnia, anxiety, if they have cardiovascular disease, we would avoid phentermine. We might also avoid the phentermine/topiramate combination if someone has coronary disease. When it comes to orlistat, we don't use orlistat very much. It's available as an over-the-counter. But someone who has bowel problems, diarrhea, chronic diarrhea or irritable bowel, we would avoid it and make sure we inform the patients. With naltrexone/bupropion, it can cause nausea, headaches, constipation. We see these not uncommonly. We find that they can be more tolerable if you very gradually increase the dose of the drug, so we go up more gradually than is recommended in the package insert. There is also a sensitivity to pain that occurs, so if someone has kidney stones or taking pain medicine for something, we would not use the naltrexone/bupropion because naltrexone can negate the effect of pain medications. Then finally, liraglutide, if the dose is increased too rapidly, nausea and vomiting can occur, and so we gradually increase the dose and we tell patients that fullness -- that's what we're looking for is fullness -- and if you start feeling nauseated, cut back the dose. We find it's a lot more tolerable than the clinical trials have made it out to be. As far as the pancreatic inflammation, we would discuss that with the patient. People who are obese and people with diabetes have an increased risk of pancreatitis, and so we are careful to make sure we discuss that possibility. We would avoid it in someone with a history of pancreatitis, with a family history of thyroid cancer, which has not really been described, but in animal studies there is the admonition to not give this to patients who have a family history of thyroid cancer.

Dr. Russell:

So, Dr. Aronne, what key takeaways would you have for clinicians in primary care, like myself, who are treating a lot of patients who are overweight and obese? What can we do to optimize pharmacotherapy in our offices?

Dr. Aronne:

Well, recognize that not every medication is perfect for everybody, and it takes a little bit of trial and error to find the right medication. You shouldn't give someone medicine and then tell them to come back in 6 months. You need to see people on a regular basis, maybe weekly, maybe every other week, but certainly, once a month at the beginning when you first start treating them. You need a diet and behavioral program to do this best, and there are now, we're working on a diet physical activity program that everybody will be able to deliver in the office setting for free, and we think that's going to be transformational because doctors know they need to treat this. They use the medicine. They don't have the behavioral program, and we want it to be available for everybody so that their patients can benefit from it.

And finally, you've got to reevaluate the patient at about the 3- to 4-month point. If someone responds, if they lose 4 to 5% of their body weight after 3 months, you got a winner. That medication is going to work. The patient is definitely going to lose 5 to 10% of their body weight. There's a high probability that they will ultimately lose at least 5 to 10%. Studies suggest it's going to be closer to a mean of 10%. If it doesn't work at that point in time, then you should discontinue the medicine and you should move on to the next rather than going on and on and on, and by doing that, we get a very high response rate. If you look at the individual response rates, each one of these medications, if you look at the people who take it for a year, somewhere between 65 and 85% of people lose at least 5% of their body weight. Who takes it for a year? People who respond to it. So, I think that if you follow these instructions, it's very straightforward, it's a way that you can treat a very significant percentage of the patients in your practice.

Dr. Russell:

Well, thank you so much for being on the show today. I'd like to thank our guest, Dr. Louis Aronne, for helping us to better understand the treatment options for obesity and how it can be used for our individual patients. I'm your host, Dr. John Russell, and thank you for listening.

Narrator:

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