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Type 2 Diabetes: Mastering Injectable Combination Therapies to Individualize & Optimize Outcomes

Narrator:
Welcome to CME on ReachMD. This segment, Type 2 Diabetes: Mastering Injectable Combination Therapies to Individualize and Optimize Outcomes, is jointly sponsored by the University of Cincinnati and Core Medical Education and supported by an educational grant from Novo Nordisk and Sanofi Genzyme.

The target audience for this educational activity includes physicians and other healthcare professionals who manage patients with type 2 diabetes. Your host is Dr. John Russell, and our guest today is Dr. Jack Leahy. Dr. Leahy is a Professor of Medicine and Chief of the Division of Endocrinology, Diabetes and Metabolism at the University of Vermont College of Medicine in Burlington. He is Director of the Vermont Regional Diabetes Center and an attending physician at the Medicine Health Care Service at Fletcher Allen Health Care at the University of Vermont.

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Dr. Russell:
For clinicians, the treatment of diabetes can be challenging. Because type 2 diabetes is a progressive disease, frequently a key to successful patient management is the need for additional therapeutic agents over time. With the availability of injectable combination therapies, there are more opportunities than ever to harness the extra glycemic benefits of these additional agents, accommodate patient preferences, and open the door for even more successful management. An online toolkit supplement is available to clinicians to download as a specialized resource on ReachMD.com/CME.

Dr. Leahy, welcome to the program.

Dr. Leahy:
John, it's a pleasure.

Dr. Russell:
So, Jack, would you summarize some of the important recent events in terms of type 2 diabetes?

Dr. Leahy:
Well, John, diabetes continues to be a huge health problem in this country, certainly for any primary care healthcare provider. A lot of their patients have type 2 diabetes. The numbers are a bit shocking. Nearly 30 million Americans are affected. The cost is stunning. Essentially, 1 in 9 healthcare dollars in the United States goes towards diabetes, and for me, maybe the scariest statistic is we're close to 90 million people in this country have prediabetes. Having said all of that, it's really, perhaps, one of the most exciting times through my whole career in terms of things that are happening in the diabetes world, because we really have reached a stage where I think we have much better diagnosis. Hemoglobin A1c is very common these days. We know what to do. We have standards of care that get adjusted every year for lipids and blood pressure and blood glucose control and aspirin use and on and on, and they're all based on effective outcomes. There's been amazing information that we've seen related to weight loss surgery in terms of benefits for diabetes and blood glucose management. Maybe the most exciting thing, a stunning thing, is within the last year or two, we finally have proven

cardiovascular benefits from some of our drugs, from empagliflozin, one of the SGLT-2 drugs. A trial called the EMPA-REG trial showed amazing benefits in terms of cardiovascular and congestive heart failure protection. We've seen similar cardiovascular protection and reductions in cardiac death with liraglutide, one of the GLP-1 drugs, a reduction in people who have had strokes having another stroke or heart attack using pioglitazone in the IRIS trial, improvement in terms of long-term benefits in the EMPA-REG trial for people who had known renal dysfunction in terms of slowing that or causing that to stabilize. Really, kind of amazing things are happening in the diabetes world.

The other thing that's been so important to us is that we just have so many new drugs, and I think it's hard for primary care providers to kind of keep it all straight, but the reality is we just have this incredible grouping of drugs now with different kinds of benefits.

Dr. Russell:
So, Jack, as a primary care provider, I suddenly have all these choices I didn't have 5 years ago. So, can you help me figure out how I would choose which drugs to use?

Dr. Leahy:
Well, this actually becomes difficult. I would say it's almost the art of medicine in many ways versus the science of medicine. I think a fairly typical thing to do for primary care providers is to go to national guidelines, and we have national guidelines from the American Diabetes Association, the latest ones just this past year. They have been done in concert with the European equivalent called the European Association for the Study of Diabetes. And if you go to that paper, what you'll see is, for instance, following metformin there are lots of choices of drugs, and interestingly enough, they don't take any preference in terms of one over the other. They say that essentially you look at those drugs and you look at their efficacy along with their other characteristics, what they might do to weight, what they might do for risk of hypoglycemia, cost, on and on. So, what that really does for providers is tell them is they need to be knowledgeable about all of these drugs and the different characteristics so that they can present them fairly to a patient. And when you start to think about those characteristics, a hugely important one is how effective they are so that if you look at the pills we have out there, for the most part they'll improve hemoglobin A1c less than 1%. So, for people who are really poorly controlled, we need to move into the injectable world, either insulin or a GLP-1 receptor agonist.

Another huge discussion point relates to how they impact weight, because we have conversations in patients on a daily basis about concern and frustration over weight gain, and some of our newest drugs, in fact, do have the ability to lower weight in many patients, the prototype drugs or the GLP 1 receptor agonists, the injected incretin drugs and the new oral SGLT-2 inhibitors. Some of our drugs cause weight gain, so there's really a lot of thought process that the average provider goes through and a lot of discussion with the patient trying to choose the best drug based on effectiveness but also based on their clinical characteristics.

Dr. Russell:
So, for the patients I take care of and most of the other folks in primary care, I think we're all going to start with metformin. I think we can all wrap our head around that. But then we have that patient we max out their metformin and their A1cs are still quite high, and looking at some of these algorithms, it's going to look like it's going to imply us starting some type of injectable agent. So, Jack, what do you think about me moving on to one of the injectable agents you just mentioned?

Dr. Leahy:
So, I totally agree. I think it's actually not in the patient's interest to add a medicine that's unlikely to get their blood glucose control to goal, so when you hit an A1c of 8 and start going up from there, it's unlikely another tablet is going to do it. So now we start to talk about injectables, and we talk about injectables -- kind of a weird word, frankly -- because it used to be insulin, but now it's more than insulin. We have the GLP-1 drugs. Still a favorite and time-proven approach is to add basal insulin, because when you add a long-acting insulin and target the fasting glucose, what happens is the whole blood glucose profile comes down and can have amazing effects on hemoglobin A1c. You can look at trials with A1c's in the high 8's, in the 9's, and look at the effects of basal insulin therapy, and the reality is that in many of those trials, A1c comes down to the very low 7's and sometimes even below 7 with simply adding that single injection of insulin.

Now, if you want the truth, in some respects that frustrates me because the message is not to providers, “Wait until you have no choice to add insulin; wait until the A1c is high 8's or 9's,” because the reality is when you look at large databases and look at the effectiveness of attaining an A1c of less than 7% against the starting level of hemoglobin A1c, the data is very clear. When you start with an A1c below 8, in the low 8's, the chance of getting to goal is much higher. You don't have a higher risk of hypoglycemia when you do that starting earlier. So, there is a mantra from the diabetes specialty world: When you think about insulin, think about using it earlier, which means don't allow control to get crazy out of control before you start it, and basal insulin is very effective.

But the other part of the injection conversation is the injected incretin drugs, the GLP-1 receptor agonists. We have a lot of those in the marketplace now. We have short-acting drugs. We have long-acting drugs. We have twice a day, once a day, and now several agents

that are given once a week, and as a class they are really effective, but they also have a quite different clinical profile than basal insulin. Because when you look at these agents, what you'll see they will do is a very good lowering of hemoglobin A1c but now with the potential for weight reduction in many patients, in part because of the biology of how they work, a low rate of hypoglycemia as well, lower than you would expect with insulin, and probably the biggest downside is some patients have GI problems, although they are often transient.

Dr. Russell:
So, you make compelling arguments for both basal insulin and the GLP-1's. How do I decide which medicine for which patient? If we're going to individualize care, how do I decide who I'm going to give basal insulin to and who to give a GLP-1?

Dr. Leahy:
I made a comment a few minutes ago when I was talking that this is sort of the art of medicine as opposed to science of medicine. So, I think we can start with an understanding, is that we have 2 injectable approaches that are actually pretty different from a description point of view in terms of what they might do for the patient but have reasonably similar improvements in levels of hemoglobin A1c, and so the real issue becomes that the conversation with the patient about the different characteristics and trying to decide which route to go. I will say part of the conversation is also the comfort level of the provider, and it turns out that, for the most part, primary care medicine has a longer history and experience with adding basal insulin than they do with one of these GLP-1 drugs, and so, frankly, there is still, I think, more usage adding basal insulin as opposed to a GLP-1 drug. But having said that, I think what is really useful is to look at clinical trials and ask a simple question: What can we expect adding basal insulin or a GLP-1 drug in a patient who's failing metformin, for instance? And there are a lot of those clinical trials, simply head-to-head comparisons of adding a basal insulin like glargine U-100 or detemir, as opposed to adding one of the GLP-1 drugs.

One of those first trials was a trial by Russell Jones that was done in 2009, and frankly one of my favorite trials. This is a 26-week trial, people who were on metformin who had an A1c of 8.2%, a pretty common patient, I think, in many people's practices. And so what the design was, was to add once-a-day glargine insulin, basal insulin, or once-a-day liraglutide, a GLP-1 drug. So, what was amazing and frankly a little surprising at the time is the drugs both markedly improve levels of hemoglobin A1c, but in fact, the GLP-1 drug, the liraglutide, was superior at lowering A1c. It brought it down to 6.9 on average as opposed to the insulin, which brought it down to 7.1. So, both did a good job, but certainly there was no obvious advantage of the insulin. And then when you look at the characteristics, you saw with the GLP-1 drug weight loss, almost 2 kg over those 26 weeks, as opposed to weight gain, about a kilogram and a half in the insulin group, and a very low rate of hypoglycemia essentially in both groups, some GI problems in the GLP-1 drug. So, that was really one of the first trials that told us you can expect similar or maybe even better improvements in A1c with the GLP-1 drug.

There are now numerous trials, head-to-head, basal insulin as opposed to GLP-1, and essentially in all of those trials, the GLP-1 drug was as effective at improving A1c as the insulin, and in many of those trials even better. And if you look at the defining characteristic of weight, which is such an important one, in virtually all of those trials, the GLP-1 drugs led to clear weight reduction as opposed to some increase with insulin.

So, again, the discussion in clinic is to go through these different things. Where is your comfort level? Where is my comfort level? Should we do basal insulin? We can adjust the dose. It seems more effective in that regard. But the GLP-1 drugs are pretty good. You could take it once a day. You can take it once a week. And that's kind of how the conversation goes to get us to our final decision.

Dr. Russell:
So, certainly as a primary care doctor, I've had a long and storied history with basal insulins, but the GLP-1's sound very exciting, and they both sound like they have their pluses and their minuses. And we talked about using it as an “or.” How about using it as an “and”? How about using the 2 classes of medications together?

Dr. Leahy:
Well, this is such an important question because in many ways this is how the specialty diabetes world is clearly thinking. So, I mean, let's sort of put this in perspective. We have 2 powerful classes of medicines, both injectable, but very different characteristics. So when you look at basal insulin, primarily what they do is improve fasting glucose and continue some of that during the day, but they come with some downsides, a risk of hypoglycemia, a risk of weight gain. GLP-1 drugs that are probably some better at trying to control blood sugars during the day, they do have an impact on fasting sugars, but the biology is to try and help to control daytime blood glucose values especially related to meals with the potential for weight loss, a low incidence of hypoglycemia. So, if you put those 2 things together, you might say, “Wow, 1 plus 1 might actually be better than 1 or 1.”

So, when you start with that background, again we go to clinical trials because that's where we learn. The first trial that really did this is a very famous trial that was done by John Buse. It’s published in 2011, a really interesting trial. This is taking people who are essentially on glargine insulin along with metformin who had an average hemoglobin A1c between 8.3 and 8.5. So, what the design was, was to

intensify the glargine treatment, and that was the control group, and that was simply based on the understanding that if someone's on basal insulin, we ought to be able to do better than an A1c of 8.3 or 8.5, so let's further intensify the basal and see where we get, as opposed to the intervention group which was intensifying glargine along with adding exenatide, a short-acting GLP-1 drug that you take twice a day. What was stunning in that trial is you begin with an A1c in the low 8's, and when you intensified the glargine, you got it down to the mid 7's, showing us we can do better if you're a bit more aggressive with basal insulin. But when you added the GLP-1 drug, the twice-a-day exenatide, to intensification of glargine, you ended up bringing hemoglobin A1c down to 6.7; you had weight reduction; you had a very, very modest incidence of hypoglycemia even though you brought A1c down to 6.7; and, yes, there were some GI side effects and some study dropouts because of that because they were fairly... but they were fairly modest, which is kind of what you see in the marketplace, so really stunning results.

There are now many trials that have done that, and in fact, that initial trial, I just mentioned, was a little criticized because what people said is, “Well, you didn't really use the proper control group because all you did was to intensify the glargine group.” What we would really normally do is take basal insulin and add mealtime insulin and turn it into a full basal bolus program, which is real but is also pretty complicated. I tell you that because there are now several trials of comparing taking people on basal insulin and adding a GLP-1 drug as opposed to adding prandial insulin. One of those trials added just 1 injection of prandial insulin, something called basal-plus, and at least 2 of them added a full 3 shots of prandial for a full basal bolus program. And what you see is actually amazing. Adding the GLP-1 to 1 shot had a better lowering of A1c. Adding 3 shots, full basal bolus, there was equivalent lowering of A1c with the GLP-1 drug and with the GLP-1 drugs with weight reduction, not what you saw with the insulin, and a very low rate of hypoglycemia. This is so important that one of the things that's happening in the specialty world now is we're realizing people who we thought had to move on to basal bolus insulin, actually maybe we can leave them on basal and add a GLP-1 drug and start to avoid using so much prandial insulin, so it's really a stunning development in the diabetes world.

Dr. Russell:
If you're just tuning in, you're listening to CME on ReachMD. I am your host, Dr. John Russell, and today I'm speaking with Dr. Jack Leahy.

So, Jack, back to that, so we talked about the “and”, we talked about the “or”. How about starting both medicines, basal insulin and a GLP-1, right from the beginning instead of kind of putting someone on basal insulin, not getting where I want to be, and then adding in the GLP-1 or vice versa?

Dr. Leahy:
So, John, this is perhaps one of the, for my thinking, one of the most important developments that's occurred in the diabetes world in the last few years. You can already tell from how I'm presenting this that I am a big convert and a true believer that basal insulin plus GLP-1 is really a very nice combination, so now let's go to the ultimate of that. What Pharma has done over the last 5 or 8 years is develop products of which in 1 pen, in a single delivery device, 1 injection, is you get both basal insulin and you get a GLP-1 drug. Two of those have been developed by different companies. One of them is a combination of insulin degludec, which is one of the new ultra long-acting basal insulins that we've had in this country for the last year, along with liraglutide, a GLP-1 once-a-day agent we've had in this country for several years. Second, from a different company, is a combination of insulin glargine U100, the standard glargine we've had for many years in this country, and the GLP-1 agent they're using as a short-acting once-a-day agent called lixisenatide. Both of these combination products were approved by the FDA on the 21st of November of this year so that both of those are now coming into the marketplace. They're a little complicated as we start to think about them because you have a ratio of insulin and GLP-1 drug in there, and the way that they will be used is you will be up titrating the dose of the insulin the way you ordinarily would in a clinic setting, and what will come with that is increasing amounts of the GLP-1 drug as the dose increases.

The reason that I think we're just so excited about this product is when you start to look at the development program with the clinical trials that were done, I'm going to focus on one of the first products, which is the insulin degludec and liraglutide. There are multiple trials that have been done, and in fact, the series of these trials are called the Dual Series, which is kind of a cute name. The first one which is done I think really shows you the power of this combination. So, this is simply taking people who were on mostly metformin -- a few of them were also on pioglitazone, so 1 or 2 oral agents -- and they had a hemoglobin A1c of 8.3. They had never been on an injectable, and so, the design of the trial was to look and see adding an injectable what happens. The first arm was to add the GLP-1 drug, which was liraglutide. It brought the A1c from 8.3 down to 7%. People over this 26 weeks had a 3 kg weight reduction, and they did have some nausea, pretty good result. The people who got basal insulin, the second arm, got just degludec. Their hemoglobin A1c came from 8.3 to 6.9. They gained 1.5 kg in those 26 weeks, and they had virtually no nausea.

Now, when you look at the combination product -- remember, from the beginning they're getting some insulin and GLP-1 together -- their A1c came from 8.3 to 6.4%. They had 0.5 kg weight reduction, and they had some modest nausea. Now, the reason I'm focusing on this

is the A1c is 6.4. We never in clinical trials see an A1c of 6.4, 6.5. And in virtually all of the series of development trials in the Dual program, that's where they got, 6.4 or 6.5, showing you that this combination is amazing for blood glucose control.

So, now that I've said that, let's go to the other product from the other company, which is the combination of lixisenatide plus glargine U100. And again, I'll start with one of their trials, which is very similar to the one I just quoted. This is now taking people for 26 weeks who were being treated with metformin and sometimes a second oral agent. Their hemoglobin A1c was 8.1%. Adding lixisenatide, GLP-1 alone, brought it from 8.1 to 7.3, a very low rate of hypoglycemia and 2.3 kg weight reduction over the 26 weeks, pretty good. Adding the insulin alone, glargine, brought 8.1 down to 6.8, which is what you expect with basal insulin. They had some weight gain, about 1.1 kg over the 26 weeks, and still a pretty low rate of hypoglycemia. I mean, we don't expect much in the terms of hypoglycemia with basal insulin. The combination product, 8.1, again brought it down to 6.5 with basically stable weight. They lost 0.3 kilograms over the 26 weeks and also a low rate of hypoglycemia. So, the combination from the get-go of basal insulin with a GLP-1 drug repeatedly gets A1c's in the mid 6's or even lower with very few problems and very little or no weight gain. I mean, really, it's an amazing approach.

Dr. Russell:
So, Jack, I think we've talked at length about the GLP-1's plus basal insulin. We've talked about basal insulin plus metformin. But I have a lot of other choices in my practice. How about some of these other agents and using them with basal insulin?

Dr. Leahy:
Well, you absolutely can, and I have focused mostly our presentation today on people who are pretty poorly controlled from the get-go talking about adding an injectable. I mean, you can add it even if they're not that poorly controlled, but I think that's a lot of the conversation we've had. So, the real question here is: What do you do if you've got someone who's on metformin, maybe they're on glargine insulin, and their A1c is 7.4, 7.5, 7.6? Do we have to go to a GLP-1 drug, or could we add some of the pills that are out there? And the answer is, sure, there is clear clinical information on adding DPP-4 inhibitors to the patients who are on basal insulin with type 2 diabetes, and what you see is what you expect. On average, a DPP4 inhibitor will lower hemoglobin A1c. It doesn't really matter what stage of the diabetes you add it. It lowers 0.5, 0.6, 0.7, somewhere in that range, and that's what the clinical trials show.

Now, the trials are interesting because they're often hemoglobin A1c's in the mid 8's or even a bit higher, and when you lower A1c 0.5, 0.6, 0.7, you haven't really got them to goal. So, my interpretation of that is if you're on basal insulin, maybe you're on metformin, you have an A1c of 7.5, maybe 7.6, if I had to 7.7, a DPP-4 could be tried. If it's much above that, I think you need to try something else.

That whole conversation can be had for the SGLT-2 inhibitor drugs, the drugs which promote glycosuria and also allow some weight reduction, but also usually lower A1c's in that same 0.6, 0.7, 0.8. There are clinical trials also of taking people who are on basal insulin who are not controlled and given an SGLT-2 with what you expect, A1c reduction 0.7 or 0.8 with some weight reduction. So, my same conclusion, if someone has an A1c 7.5, 7.6, maybe 7.7, I could be talked into an SGLT-2 inhibitor. Much above that I think you need the route of thinking about the injectable, the GLP-1 receptor agonist.

Dr. Russell:
So, Jack, yourself as an endocrinologist, myself as a primary care doctor, we're not going to be able to do all this wonderful care by ourselves, and how do you envision you and I's (sic) roles in an expanded role of team-based care in really getting our diabetic patients really where they need to be?

Dr. Leahy:
I don't think anybody has the expertise or time to do everything in terms of trying to manage our patients with diabetes. And maybe stated another way, there's just a whole large group of people out there in the healthcare world who have skills that we don't have. They are trained to have other skills that can be very useful to our patients. So, we have known for many years that the true optimal approach to treating people with diabetes is a team approach that puts together a variety of healthcare experts to meet their different needs. That can include physicians and physicians' assistants and clearly certified diabetes educators, nurses, social workers, exercise physiologists, whatever it happens to be. There needs to be a clear understanding within that group what the goals are, and the goals are to help the patient have an appropriate discussion with these different healthcare providers to understand diabetes and understand the available treatment choices -- that's a hugely important issue in these conversations -- but also establish with the patient some of the key goals; what are the short-term goals; what are the long-term goals; importance of proper healthcare management; doing blood glucose testing, establishing goals and reaching goals for blood pressure and lipids and not smoking and on and on; helping coordinate their care so that if comorbidities or other problems occur, make sure they get to the right healthcare providers, either a nephrology specialist, if needed, ophthalmologists, other kinds of healthcare providers that may be needed at different stages of their illness; and really, most importantly, to continue keeping your patient up-to-date on their treatment choices and the optimal therapies that are out there to help them get to the goals they need to get to.

Dr. Russell:

So, Jack, before we conclude, we talked about lots of things. What would be some of the key discussion points from our talk today?

Dr. Leahy:
Well, I've tried to be reasonably clear in sort of take-home messages, and I think probably the most important take-home message is the power of the injectable medicines in terms of type 2 diabetes. When I start to think about my patients, it is our job to help them to establish kind of goals and also to get to those goals, and given the choice of medicines we have now, to help them get to an A1c goal but to minimize unwanted effects. It could be hypoglycemia. It could be weight gain. It could be GI problems. It could be a variety of issues related with those agents, to really identify how to get them controlled in the most patient positive centric way.

We've talked about injectables because they're so powerful and they're useful, and in combination they're amazing. So, I use a lot of basal insulin, primary care uses a lot of basal insulin, and it is an amazing approach when used aggressively and used properly. There are some downsides. The biggest downsides are the potential for weight gain and hypoglycemia.

The GLP-1 receptor agonists are modestly underutilized in the marketplace. They are expensive. I agree with that. But having said that, they have amazing clinical benefits. There are some GI side effects. Frankly, they are relatively modest, but they come in many patients with some weight reduction and a clear protection against hypoglycemia, which is really important.

And then what I've presented today is those drugs when used in combination, either sequentially or even together as the first injectable, is an amazing combination. And I think, frankly, as you talk to diabetes specialists, they will tell you as they look to the future, they truly believe that the approach of GLP-1 along with basal insulin is just an amazing approach that has incredible potential for therapy now and to the future.

Dr. Russell:
So, I'd like to thank our guest, Dr. Jack Leahy, for discussing injectable combination therapies in type 2 diabetes. Thank you, Jack.

Dr. Leahy:
Thank you very much, John.

Narrator:
Additional resources are available to complement this program. An online toolkit supplement for clinicians is available at ReachMD.com/CME. These resources are fully downloadable and include: from the 2016 American Association of Clinical Endocrinologists and American College of Endocrinology, a management algorithm executive summary, the American Diabetes Association 2016 Standards of Medical Care, key publications for participants wishing to go into greater depth of some of the clinical trials discussed in our program, and lastly, a listing of key websites and resources for patients and their caregivers.

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