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Discovering the Link Between GLP-1 Receptor Agonists and Weight Loss in Patients with HIV

Dr. Turck:
Welcome to *Clinician's Roundtable* on ReachMD. I'm your host, Dr. Charles Turck, and joining me today is Dr. Darcy Wooten to discuss her study, titled "GLP-1 Receptor Agonists Promote Weight Loss Among People with HIV," which she presented at IDWeek 2023. She's a Clinical Professor of Medicine and a Program Director for the University of California San Diego ID Fellowship Training Program in the Division of Infectious Diseases and Global Public Health.

Dr. Wooten, welcome to the program.

Dr. Wooten:
Thank you so much. It's wonderful to be here with you today.

Dr. Turck:
Now before we dive into your study, Dr. Wooten, why was this such an important topic to present at this year's IDWeek?

Dr. Wooten:
Yeah, thank you so much for that question. I think probably anybody in clinical practice taking care of people with HIV seeing that these patients are doing really, really well on antiretroviral therapy and are living longer but what that also correlates with is an increasing number of comorbidities, which we see in the general population, as well as increasing weight, being overweight, and obesity and trying to think of different strategies and approaches in terms of how to deal with weight issues, which tend to be the root cause of a lot of cardiometabolic complications and outcomes.

And I think over the past couple of years, this has been increasingly recognized, and there's been a lot of attention and talk about the potential role of antiretrovirals and the impact that they might be having on this additional weight gain and other cardiometabolic outcomes. Particularly, we all think about the second-generation integrase inhibitors, dolutegravir, bictegravir, and then TAF compared to TDF, for example, as being ones that we tend to associate with maybe having some impact on weight gain. But to date, the studies that have been done looking at switching antiretrovirals in an attempt to mitigate that weight gain really haven't panned out. They haven't been the silver bullet in terms of helping to address weight, and so I think a lot of us in trying to help our patients maintain health and wellness have been looking for alternative strategies to help with patients who are overweight and obese and have these cardiometabolic complications.

And there's been emerging data over many years in terms of the role of GLP-1 receptor agonists, not only in terms of their initial role in managing diabetes and blood sugar but also that secondary benefit of sometimes massive amounts of weight loss, sometimes even equivalent to the amount that we would see with the gastric bypass surgery. So these looked like a really good option in terms of helping our patients deal with weight-related issues, but to date hasn't been a tremendous number of studies looking at the use of these agents in patients with HIV, and so that was the impetus for trying to look at this question in our own clinical practice here at UCSD.

Dr. Turck:
So how did your study aim to fill in some of our knowledge gaps on GLP-1 receptor agonists and weight loss in patients with HIV? What are some of the other unmet needs?

Dr. Wooten:
Yeah. So what we looked at was, it was a retrospective objectional study, which, of course, you've got to keep in mind all of the caveats

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and confounders that might go along with that type of study, but we wanted to look and see how these medications were being used in which types of patients, and then looking at our primary outcome in terms of changes in weight, BMI, and then also looked at hemoglobin A1c.

What we saw from our study was that not surprisingly, and what's been described in again, the general population with these agents is that people did have a fair amount of weight loss who were prescribed these agents. Our study looked at just over a two-year period just for convenient sampling and some patients didn't have even that long of follow-up. So despite those limitations we still saw across the board that people tended to lose weight on average about five kilograms. And people that had been on the medications for a longer period of time, as well as those who had an initial higher BMI, demonstrated more significant weight loss compared to people who didn't meet those criteria.

So that was just a proof of principle, in terms of these medications, do contribute to improvement in weight outcomes, but I think there are also a number of additional questions that our study raised, as well as that are ongoing and unanswered that will hopefully be addressed by future studies.

Dr. Turck:
For those of you who are just tuning in, you're listening to *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Darcy Wooten about her research on GLP-1 receptor agonists and how they could promote weight loss among people with HIV.

So, Dr. Wooten, I was wondering if you would share any other key findings from the study. Any other highlights or any surprises?

Dr. Wooten:
I think one of the things that maybe wasn't necessarily a surprise, but the specific agent dulaglutide, which is one of the earlier GLP-1 receptor agonists and really has been developed and is on-label for the use of patients with diabetes—not so much for use in patients with weight issues—that was not associated with as much weight loss compared to some of the other agents, like semaglutide, which have been approved and are indicated for weight loss and have been shown to have more substantial weight loss in the general population. So that wasn't a surprise finding but definitely reaffirming what we see in the general population with these agents.

And I think with that, as well as some of the other considerations in terms of insurance approval and efficacy of these agents, our clinic has come up with a little bit of an algorithm in terms of which patients we should be thinking about which agents for. Sometimes it ultimately doesn't matter what the clinician wants to do in terms of which agent they want to prescribe. It often will come down to what insurance will cover or what's even available at the pharmacy during the study period. And ongoing, we've really been struggling with issues of medication shortages and pharmacies running out of these medications, and so sometimes we've had to get creative and have patients partner with patients in terms of searching at different pharmacies to see if we can find alternative agents. But I think that will be something that will be interesting to look at moving forward in terms of which specific agents and formulations make the best sense and we think will work the best for specific patient populations.

One of the things that was interesting that we looked at was that many patients who did not have a diagnosis of diabetes—so presumably prescribed the medication specifically for weight management—were able to get medications that don't have the label indication for weight loss but do so for diabetes, and how that all played out in getting the insurance approval for that is something that I don't know the details of but I think just an interesting observation. Sometimes we'll use things off-label but not sure if it's going to get covered by insurance or not, and these are just the very kind of practical issues and logistical barriers that sometimes come up in the real world when we're trying to use these medications.

Dr. Turck:
So global picture here. You had mentioned that your practice site developed a treatment algorithm on the basis of your study's results. How could the rest of us use these findings to better care for our patients with HIV?

Dr. Wooten:
Yeah. So I think if you're thinking about using these for your patients, typically, we're going to think about using these patients who have obesity, so BMI of greater than or equal to 30 or patients who have an elevated BMI greater than or equal to 27 with additional comorbidities, like dyslipidemia, high blood pressure, cardiovascular disease, etc. One of the other things that we want to think about, of course, is making sure that patients don't have an absolute contraindication to these medications, which to date are pretty rare conditions, like medullary thyroid cancer, MEN2, but important to screen for those.

And then the other consideration, which I wouldn't consider a contraindication but something to have shared decision-making around with your patient are the side effects. So the way that these medications work in large part is really impacting gastric motility and

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slowing that down, and so patients who have underlying gastroparesis or chronic nausea and vomiting. There's also been issues related with pancreatitis or people who have had gastric bypass surgery. These are people that you're going to want to have a very detailed conversation about and follow very closely if you do indeed decide to move forward and think about using these agents.

From there, the other consideration is most of the agents come as an injectable form that's given long-acting. Patients self-administer once a week. There is an injection that's once a day as well. There is an oral formulation for patients who don't want to do an injection. But I know for some of my patients, the idea of giving themselves an injection is off the table, so that's something also to think about in terms of which agent you might prescribe and decide with a patient on which one to use.

From there, I think it really comes down to then what can you get covered because these medications are at least right now fairly expensive, and so to be able to pay for them out of pocket is going to be probably cost prohibitive for most patients, and so it's looking and seeing which ones you can get approved for your patient.

I think, again, practical implications in terms of starting patients on this and counseling them about the follow-up, the side effects to look out for. And there's for each of them there's a dose titration, so usually, we'll start at the lowest dose and do that every week for four weeks, and if the patients are tolerating it okay, then go up to the next dose, do that for another four weeks, so on and so forth. And so depending on your patient's comfort, degree of health literacy, they might be able to do that on their own, but they might need more frequent visits, nurse visits, telephone visits to check in at each of those four-week time intervals to make sure that they're doing okay and to see if you want to continue to escalate the dose versus maybe maintaining at a medium dose until they're tolerating it okay. So that's the algorithm and the approach that our clinic has taken.

The unanswered questions—are there safety concerns about these medications or any downsides? There was another oral abstract presented at IDWeek, which was a randomized controlled trial, placebo versus semaglutide in patients with HIV, and similar to our study, found that patients lost a fair amount of weight, as well as fat. The other finding there was that the patients receiving semaglutide in comparison to placebo had a fair amount of muscle loss, and what that means and what those implications are, especially for older adults, adults with frailty, what are going to be the implications there, and is there anything to mitigate that? Can we also include an intense strength exercise training program along with these medications that would maybe help preserve some of that muscle mass?

The other topic that was brought up in relation to muscle loss was lipoatrophy, and could these medications exacerbate people who had experienced significant lipoatrophy on older formulations of antiretroviral therapy?

And I would say the other big unanswered question is how long do we continue treatment for? We know that when patients stop these medications they tend to regain the weight that they've lost, and so is this something that would be indefinite? Is there some maintenance dose that we should bring people down to if they continue to lose weight on the higher doses? How to manage these medications once people have achieved their target weight, and we want to maintain but not necessarily have that recurrent weight gain. And so I think that will be another important, again, very practical question that we'll need to get answers to.

Dr. Turck:
Well, those are some great thoughts for us to think on as we come to the end of today's program. And I would like to thank my guest, Dr. Darcy Wooten, for sharing her research and insights on GLP-1 receptor agonists and weight loss in patients with HIV.

Dr. Wooten, thanks so much for joining me today.

Dr. Wooten:
My pleasure. Thank you for having me.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. To access this episode and others in this series, visit *Clinician's Roundtable* on ReachMD.com where you can Be Part of the Knowledge. Thanks for listening.

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