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## Exploring the Deintensification of Hypoglycemia-Inducing Medications

### Dr. Buse:

Hypoglycemia is a serious condition that if left untreated can be fatal. That's why preventative measures are necessary. And the current guidelines recommend individualized deintensification of hypoglycemia-inducing medications in order to prevent hypoglycemic attacks. But how frequently is this guideline followed in clinical practice?

Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse. And joining me today to share her insights on deintensification of hypoglycemic agents among older adults with diabetes is Dr. Anastasia-Stefania Alexopoulos. She's an endocrinologist and researcher and Assistant Professor of Medicine in the Department of Medicine at Duke University School of Medicine. Dr. Alexopoulos, thanks for joining me today.

### Dr. Alexopoulos:

Thank you so much. Thanks for having me.

### Dr. Buse:

Let's start with some background. What do the guidelines tell us about the deintensification of hypoglycemic agents for older adults with diabetes?

### Dr. Alexopoulos:

That's a good question, John. Well, the guidelines don't really have very specific framework for guiding deintensification in older adults. There is a framework for how to think about risk of patients in terms of hypoglycemia, and that's based on the existence of other illnesses, functional status, cognition, but really not a great framework for guiding providers in deintensification.

### Dr. Buse:

With that in mind, let's talk about your recent study published in *JAMA Network Open* that you were the lead author on. The study evaluated the rate of deintensification among older adults with diabetes after an episode of severe hypoglycemia. What made you interested in that area? What was really the objective of doing the study?

### Dr. Alexopoulos:

What really sparked my interest in this area is seeing the gap between current and evidence-based practices as it relates to hypoglycemia risk, both in the clinical setting and in research. So there are several studies that have shown already that overtreatment of older adults is quite common, and it's also pretty infrequent to deintensify older adults in many scenarios where we really should be, so those things together really sparked my interest.

In terms of the objectives of the study, we specifically examined an older adult population, as you mentioned, who had been either admitted to the hospital or presented to the ER for hypoglycemic episodes, so this is by definition a population who has severe hypoglycemia, and our aim was to really understand what kind of management changes happened after that event, so who was deintensified, the incidence of deintensification of specifically sulfonylureas and insulins after that event, as well as specific patient factors associated with deintensification.

### Dr. Buse:

Yeah. I mean, it seems that if people are admitted to the hospital or go to the emergency room for hypoglycemia, something should be done. What did your results show? What were the key findings of your study?

### Dr. Alexopoulos:

We found that deintensification of sulfonylurea and/or insulin—so those are the main culprits typically for causing such episodes—occurred in fewer than 50 percent of older adults with diabetes after hospitalization or ED visit for hypoglycemia, which is pretty striking. The incidence of deintensification of sulfonylurea specifically was around the 40, 44 percent mark, whereas it was as low as 25 percent for insulin. Now, the only caveat being that we are likely to have underestimated insulin deintensification to some extent just because it's challenging to capture insulin doses, using administrative claims data, but overall, these data do suggest that deintensification of hypoglycemia-inducing agents is not as high as you would expect after presenting to the hospital with severe hypoglycemia.

**Dr. Buse:**

Very interesting. For those just tuning in, you're listening to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse. And today I'm speaking with Dr. Anastasia-Stefania Alexopoulos about the deintensification of hypoglycemic agents in adults with diabetes.

Stef, now that we've shared some of your key findings, let's talk about how to apply them to practice. What do these results tell us about the current approach to treatment, where are the gaps, how should we move forward based on what you found?

**Dr. Alexopoulos:**

So, how we move forward, I think there are a number of things that we can do to reduce, the risk of hypoglycemia in older adults and many of which I think we're not doing as good as we could, as we could be. So, one is that, first of all, we need to identify people at high risk. Right? We need to be able to respond to clinical situations that happen so if a patient tells you that they had hypoglycemia while driving or if they, you know, if they had a hypoglycemia admission, like we just talked about, I mean, these are pretty big events that should prompt us to think about, their diabetes regimen very carefully. And then I think that there are a number of things we can do in terms of, for example, considering non-insulin agents that potentially could replace, if possible, insulin or sulfonylureas in older adults. And I find there's often a pretty big hesitancy to try some of these newer agents, for example, like GLP-1 receptor agonists or SGLT2 inhibitors in older adults even though they're a population who could certainly benefit from a lot, a lot of the benefits of the medications and also from this reduced hypoglycemia risk.

**Dr. Buse:**

Yeah, I mean, it's a very good point. There's a study that, we reported in 2014, using a product called IDegLira, so the combination of liraglutide and insulin degludec, and it was a very artificial kind of study where we brought people in who were on insulin at baseline, and then had people in a double-blind fashion either titrate, insulin degludec further up or they were switched to the combination product of insulin degludec with liraglutide. And what we were aiming for is to have people exposed to exactly the same amount of insulin in both arms, one on the background of placebo and the other on the background of liraglutide, a GLP-1 receptor agonist. And what we showed is that the group that got the liraglutide and 42 or so units of insulin, got to a hemoglobin A1c under 7 percent, versus about 8 percent for the patients who were only on the insulin degludec, but they got to that lower level of A1c with about a third less hypoglycemia. And that was really striking that the same amount of insulin, in 2 groups of patients—one that's taking a GLP-1 receptor agonist, one group that's not, and the group that takes the GLP-1 receptor agonist has lower glucose and lower hypoglycemia. We don't really know why, but the notion is perhaps the GLP-1 receptor agonists improve alpha cell function, just like they're, posited to improve, beta cell function. But I agree with you. Thinking of non-insulin therapies, particularly GLP-1 receptor agonists, is potentially valuable.

And then I take it from the introductory remarks that you made, you know, the straightforward thing is just to reduce the insulin dose, perhaps do other, counseling to minimize the rise in glucose, to lower the risk of hypoglycemia as well.

**Dr. Alexopoulos:**

Yes, definitely. I think there's also 2 concepts. There's the concept of deintensification, and there's also the concept of simplification, which is important among older adults, and those are overlapping but not really the same thing, so thinking about in addition to deintensification being more reducing the potency of a regimen, and simplification being, you know, from the patient perspective what's simplest to take or what's simpler to take. And I think when you're dealing with an older adult population, trying to also simplify is really, really important. And then in cases where potentially due to cost or other reasons that someone has to be on a complex insulin regimen, CGMs have also been immensely helpful in that setting. So, I know the guidelines recommend considering CGM in people with type 1 diabetes, but of course, that's expanding more and more and a lot to type 2 diabetes, and that has certainly helped a lot of people in terms of preventing severe hypoglycemia episodes and also morbidity and mortality related to hypoglycemia.

**Dr. Buse:**

Yeah. I think everybody understands that insulin is associated with hypoglycemia. I think sometimes people underestimate, the sulfonylureas as a cause of hypoglycemia, particularly in the elderly. And there is evidence that perhaps glimepiride and particularly, and glipizide, would be associated with lower risk of hypoglycemia than glyburide, at least in trials. And then there are formulations of insulin that the guidelines suggest and the data suggests may be associated with a lower risk of hypoglycemia, specifically insulin degludec and Glargine U300. Anything else that you think are key takeaways for our audience?

**Dr. Alexopoulos:**

I think a big takeaway is just—one of the big challenges I think related to deintensification is the conversation with the patient, right? And that can be a time-consuming process to actually engage in, shared decision-making related to this, because many patients may also be the barrier here. Patients may not want to lower their insulin levels. They may perceive lowering or discontinuing medications as giving up on their health or something that they don't feel comfortable doing, and so I think just really emphasizing hypoglycemia is a complication that can be more immediately life-threatening to patients than some of the chronic complications that we're trying to manage—right? rather with lowering glucose levels long-term, and I think that's really key, just taking the time as much as possible. I know that can be challenging in clinic settings, but taking the time as much as possible to talk about the risk/benefits with patients and the reasons for discontinuation or for lowering doses. Otherwise, you know, it may be perceived in a different way from the patient's perspective and not adhered to.

**Dr. Buse:**

Yeah, that's really important. You know, I think another issue worth mentioning is, at least the way I try and fish out people who are having issues with hypoglycemia that they might not otherwise share is ask them, you know, what the lowest blood sugar that they've seen over the last couple of months is and how did they feel when they had that episode. And, you know, if the number is 70, it's not terribly worrisome, but if they say, "Yeah, my blood sugar was 70, but I didn't notice at all," that's certainly more worrisome and something that you need to dig deeper on.

**Dr. Alexopoulos:**

I agree. That is such a good tip. There are also a lot of people, I think, that just get desensitized having low blood sugars, and they don't perceive it as a risk to themselves, and so I think that that's a really good way to start the conversation.

**Dr. Buse:**

Well, thank you. I'd like to thank the audience and my guest, Dr. Anastasia-Stefania Alexopoulos, for sharing key findings from, this study and helping us better understand the deintensification of hypoglycemia agents in adults with diabetes. Dr. Alexopoulos, thank you for joining us.

**Dr. Alexopoulos:**

Thank you.

**Dr. Buse:**

For ReachMD, I'm Dr. John Buse. To access this episode and others from our series, visit [ReachMD.com/diabetesdiscourse](https://ReachMD.com/diabetesdiscourse), where you can Be Part of the Knowledge. Thanks for listening.