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Effective Strategies for the Patient with Poorly Controlled Type 2 Diabetes

Narrator:

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Dr. Russell:

Welcome to Diabetes Discourse here on ReachMD. I am your host, Dr. John Russell, today joined by Dr. Serena Cardillo, from the University of Pennsylvania endocrinology. Dr. Cardillo, welcome to the show.

Dr. Cardillo:

Thank you.

Dr. Russell:

So today's challenge is what to do for the type 2 diabetic who we are just not having under control as well as we like. And if I can pick your brain, as a primary care doctor, what I should be thinking about in all these new medicines, and certainly there have been a couple new classes of medicines that have emerged over the last few years.

Dr. Cardillo:

Sure.

Dr. Russell:

So, are you still in 2015 starting with metformin?

Dr. Cardillo:

Absolutely.

Dr. Russell:

Do you have any kind of tips or anything to make it a little more tolerable? You know, when do you use the extended release, any thoughts on that?

Dr. Cardillo:

Metformin has been around for a long time. It is a tried and true medication. It is very, very effective. It is a weight losing medication which makes it a particularly attractive option for many of our patients with type 2 diabetes who are also struggling with obesity. You know the limiting factor that we always come up against with metformin is the GI side effects and the question of whether the patient is going to tolerate it or not. Some tricks that I use in clinical practice is number one, start slow and ramp up gradually. So, starting a patient at 500 mg once a day for a week and then each week thereafter adding an additional 500 until you get to that maximum effective dose of 1000 twice a day. So that titration schedule will happen over the course of a month. I find that patients more easily tolerate the medications and get acclimated to some of the GI side effects if you inch it up very gradually. I always start with the immediate release formulation of metformin because I feel that anecdotally and in practice I have seen it a little bit more potent and you get a little bit more of a glucose reduction with the immediate release than you do with the extended release. However, I think the situations in which I would consider using an extended release metformin are, one, if the patient is having GI intolerance to the immediate release. I always will try dose reducing to see if that fixes the problem, but if the patient has persistent GI complaints, diarrhea specifically, despite lowering the dose of metformin I will usually try switching over to extended release before giving up on it entirely just because the benefits are fantastic with this medication, so I don't easily abandon it. The second reason for using the extended release formulation is, if you are coming up against adherence issues with some of your patients. If the patients are telling you, "You know what, I always get in that first pill of metformin in the morning, but I frequently miss that evening dose." That's a patient in whom I might consider switching over to extended release, just so I can optimize and get the most out of the medication at a higher dose.

Dr. Russell:

Now, with metformin, I know there has been some stuff written in this past year. Are you looking more to creatinines or more to GFRs for deciding who to keep it on it?

Dr. Cardillo:

I am looking more at GFRs rather than absolute creatinine cutoffs. And I think there is a lot of controversy about when to discontinue metformin and much of the more recent literature is really suggesting that we can consider dose reducing at GFRs below 50. Traditionally, if we were relying on absolute creatinine cutoff, specifically, we would discontinue the metformin much sooner than that, but consider dose reducing if GFR is under 50 and then discontinuing with GFRs less than 30 has pretty much been my approach in clinical practice, but I think we often, again, it is such a good medication and I think we often give up on it too soon. I think as long as you are watching patients with renal insufficiency very closely and monitoring their creatinine, I think we can probably push the limit a little bit on the GFR.

Dr. Russell:

So, you have a patient who is a type 2 diabetic, you have maximized their metformin, how about sulfonylureas, do you still find much of a role for them or is that a very 1980s medicine?

Dr. Cardillo:

You know, I do. This is always this question as to whether or not introducing sulfonylureas is going to accelerate beta cell burnout and progressive insulin deficiency in some of these people because you are just taxing those beta cells that are sort of struggling to keep up to begin with, but I really believe that for patients that are having significant postprandial hyperglycemia who really need that insulin push, that insulin surge, to match the rise in their blood sugars that are happening during the day with eating, I think secretogogue therapy has a definite role in treating patients with type 2 diabetes. So, I think, you know recognizing patterns in blood glucose elevation and optimizing treatment based on those patterns is definitely foreign, but for those patients with post meal spikes, absolutely considering sulfonylurea or secretogogue therapy. The downside, of course, is weight gain, so that is always a conversation that you are going to have with patients because it is a medication that can be once or twice a day and relatively easy to take with the side effect of potentially hypoglycemia, but the weight gain is often quite concerning. So definitely, that issue has to be on the table when you are making the next decision about where to go with additional medication.

Dr. Russell:

So, the TZDs, do you still find a role for the TZDs or are you seeing kind of the whispers that we worry about safety? Is that keeping you away from using them?

Dr. Cardillo:

I will say that in practice I have been using them less than, perhaps, as compared to 5 years ago, 5, 6 years ago or so. There is certainly a role for TZDs in mediating insulin sensitivity, changes in some of these patients. I consider TZDs for my patients who are perhaps not, despite intensifying regimens, increasing insulin doses, they are just having a hard time processing it and there is a significant component of insulin resistance that is underlying it. I will consider TZDs for those patients, but I have to be honest with you, they are probably not my second- or third-line choice in medications. They are a little further bit down on the list and that is primarily because of the potential for significant weight gain that can be associated with some as well as the potential for volume retention and edema as well as worsening CHF in patients with underlying comorbidities. So, I think you always have to take all of those factors into consideration when you are thinking

about adding a TZD. Granted, they are a lot less popular now, but they do address one of the underlying pathophysiologic problems of type 2 diabetes, which is insulin resistance.

Dr. Russell:

You are listening to Diabetes Discourse on ReachMD. I am your host, Dr. John Russell, and I am joined by Dr. Serena Cardillo from the University of Pennsylvania endocrinologist. Now, talking about the three newer classes of medicines that we will use in patients with type 2 diabetes. The DPP-4s have been around for a while. Where do you think they fit in?

Dr. Cardillo:

So, the DPP-4s are an attractive option for patients that are having mild fasting hyperglycemia and mild postprandial hyperglycemia who perhaps may have an A1c in the high 7s, maybe low 8 range. They are going to address gluconeogenesis issues so they are going to lower fasting glucose by decreasing hepatic glucose output. They are also going to help mediate some additional insulin production, so that will help with some of the postprandial rise that we see in some of these patients, but these are not going to cause hypoglycemia and they are weight neutral, so that makes them an attractive option. I find them very helpful, again, in elderly patients as well; those in whom I am really concerned about precipitating hypoglycemia and the associated morbidities that can accompany that. So, I find them to be a nice, attractive option for elderly patients whom you are trying to conservatively manage. Another population in which you can consider the DPP-4s are those with renal insufficiency or more advance kidney disease since there may be contraindications to some of the other more traditional medications including metformin and sulfonylurea. You can renally dose the DPP-4s so that makes it a nice option for some of our patients with some of those other considerations.

Dr. Russell:

So there have been an addition of a lot of new GLP-1s over the last few years. How are they fitting into your practice?

Dr. Cardillo:

So the GLP-1s are popular for a number of different reasons. One, they have a pretty significant glucose lowering potential and can be a nice adjunct to either oral therapy or basal insulin therapy. They will impact both fasting blood glucose levels as well as postprandial glucose levels but to a greater degree than the DPP-4s do without causing hypoglycemia in and of themselves. So, the decreased risk of hypoglycemia, the potential for blood glucose lowering as well as the appetite suppression and weight loss potential make these an attractive option. Now, the downside of these meds is primarily the fact that they are injectable and that discourages some patients from using them. And then the GI side effect profile is another concern for some of our patients. The potential for persistent nausea, vomiting or diarrhea with some of these medications is certainly a concern. There are some, you know, there is still the traditional twice daily options in exenatide, there are once weekly versions of that medications that are currently available. There is the once daily Razitide* 10:36, and then other once weekly versions of various GLP-1 agents that have been available. I personally like to try a shorter-acting GLP-1 agent in practice first to see if the patient is going to tolerate it. I don't traditionally jump right to a once weekly GLP-1 therapy. I will often try either a twice a day or a once a day option first for about a month just to see how they do with it and if they are tolerating it fine and there aren't significant GI complaints I may then switch that patient over to a once weekly

option. But you really do get some nice glucose lowering and nice weight loss results with these medications.

Dr. Russell:

So recently for both the classes of the increment* therapies that we just talked about, there have been safety concerns about cancers and about pancreatitis. Do you think that's real?

Dr. Cardillo:

So, there has been associations that have been reported. I don't think we have enough data currently to say whether there is a causation that's here. I mean, in animal models there have been some demonstration of beta cell proliferation with some of the GLP-1 agents and, in some respect, that may be promising for preserving some beta cell function down the line but there have been some clinical reports, pathologic reports of beta cell reproduction and hypertrophy with these agents that are concerning as well as case reports of pancreatitis prompting the safety warning. In clinical practice, I do present that association. I have background information when I am discussing the potential for starting some of these medications. I will always outline what the potential benefits are and I will mention all of these potential safety concerns. And the way that I will pose it to my patients is I essentially tell them, "Look this is an association that hasn't yet been studied intensively enough or rigorously enough to really come to a solid conclusion as to whether there is a direct causative effect between these medications and the onset of some of these issues." If I have a patient with a history of pancreatitis or multiple risk factors for pancreatitis I do steer away from using these medications in practice.

Dr. Russell:

And our last category, the SGLT-2s, how are you using them?

Dr. Cardillo:

That has been a very interesting new addition to the classes of medications that we have available because it is a very novel mechanism. It is basically the way these drugs work is they stimulate glucose disposal through the urine. The situation in which I use those medications is I will typically add them on as a second- or potentially third-line treatment in patients with type 2 diabetes who are probably already on metformin and potentially sulfonylurea who need a little bit of extra postprandial lowering as well as some weight loss. So they are a nice oral weight losing option for patients, and again, one of the themes here that comes up with all of these meds, what is the effect on weight? And so, you know, many of the new algorithms that have come out with respect to treatment of type 2 diabetes will basically lay out metformin is your first-line and then second-line treatment can be any of the options that we have discussed. So, the SGLT-2 inhibitors are a nice oral option for patients that are more interested in taking oral medications as opposed to injection, but are also looking for the potential for some weight loss. So if you are faced with a decision of adding a sulfonylurea which potentially can precipitate some weight gain versus an SGLT-2 which can give you some weight loss, the patient may be more likely to try the SGLT-2. Now, there is always the concern about the most common side effect which is the urinary tract infections. Again, that is always _____ 14:21. I think it is important to educate them about the signs and symptoms of a UTI and the need to notify if those occur, but you get some pretty nice postprandial lowering as well as weight loss with some of these medications. In practice, I can tell you that while the studies will show a small A1c reduction with some of these meds, anywhere from 0.4 to 0.7, 0.8% with

the SGLT-2s, I have in practice seen some pretty dramatic glucose lowering with some of these agents, have been pleasantly surprised in using them.

Dr. Russell:

So Serena, if you had the final recommendation to the average primary care doctor across the country taking care of type 2 diabetes and you could give them kind of one pearl, what would you like to see us doing a little differently?

Dr. Cardillo:

I think involving patients in the decision making process and the selection of medication is important. There really is no cookie-cutter approach to managing type 2 diabetes. There is no universal algorithm that can be applied to everyone. Some of us feel more comfortable with some of the older medications because there is more data. Others are excited to try some of the newer agents because they are novel mechanisms, but I think one of the messages that I would like to get across and that I try to implement in my practice is, there is no one right solution, one right answer, one right drug regimen that you can apply to everyone. I think once you get past metformin you can present to the patient three or four different options, describing to them all of the potential benefits, all of the potential risks and coming to a consensus with the patient, that the patient feels comfortable with because they are ultimately the ones that are going to be committed to adhering to the regimen that you ultimately decide on.

Dr. Russell:

Well thank you so much for being on the show today.

Dr. Cardillo:

Thank you.

Narrator:

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To learn more about this diabetes diet and lifestyle support program from AstraZeneca, visit Fit2Me.com. That's fit, the number 2, me.com.