EPISODE 12: MEDICATONS FOR TYPE 2 DIABETES

Rita Kalyani, MD: Welcome to ***Diabetes Deconstructed***, a podcast for people interested in learning more about diabetes. I'm your host, Dr. Rita Kalyani at Johns Hopkins. We developed this podcast as a companion to our ***Patient Guide to Diabetes*** website. If you want a trusted and easy to understand resource for diabetes or to listen to previous podcasts, please visit HopkinsdiabetesInfo.org.

Today we are thrilled to welcome Dr. Michael Quartuccio to our podcast. Dr. Quartuccio is a medical graduate of Thomas Jefferson University, [he] did his residency at the University of Maryland Medical Center where he was chief resident, and completed a clinical research fellowship at Johns Hopkins. Dr. Quartuccio also served as managing editor of the *Johns Hopkins Patient Guide to Diabetes* website from 2015 to 2017, and is currently an adjunct faculty member at Johns Hopkins. He is also a clinical endocrinologist in the Rochester Regional Health System and he'll be speaking to us today about medications for diabetes. Welcome, Dr. Quartuccio.

Michael Quartuccio, MD: Thank you very much for having me.

RK: I was wondering if you could start off by telling us when a patient with diabetes might need medications. Does everyone with diabetes need medications?

MQ: Before we get into the conversation, I think it's important to distinguish between the two basic types of diabetes: type 1 diabetes and type 2 diabetes. Most cases of adult onset diabetes are going to be type 2 diabetes – approximately 90% of them. And [for] those folks, the issue is mainly around insulin resistance. In general, at least early in the course of the disease, the body is still making insulin. It just doesn't respond to it as well. This is very different than people with type 1 diabetes, in which case the main issue is the body is no longer making any appreciable amounts of insulin. So, in those with type 1 diabetes, insulin therapy is always needed.

And in type 2 diabetes, a lot of times medications aren't needed at first. And actually, the mainstays of treating type 2 diabetes are really the lifestyle changes. It's going to be trying to optimize the diet and trying to get as much exercise as possible. Especially early in the stage of type 2 diabetes or in people with prediabetes, we try to encourage limiting the amount of carbohydrates in the diet, especially simple carbohydrates like candy and cake and sweetened beverages like sodas and juices. Trying to choose more complex carbohydrates – higher fiber carbohydrates – will often make it a lot easier to control the diabetes. We always encourage exercise. Generally aiming for at least 30 minutes of moderate intensity exercise most days of the week. And people who are able to make those changes very often don't require medications… at least not at first. Unfortunately, type 2 diabetes does tend to progress and many and most people do need some types of medications at points in their disease. Those could include insulins, but also could include a variety of non-insulin medications depending on the response, depending on the risk factors, and depending on the severity of the diabetes.

RK: So in your practice, when you see a patient for the first time newly diagnosed, let's say with type 2 diabetes, how do you decide which medication might be most appropriate for them? Initially, is there one that's more commonly prescribed? First, I think Metformin is often described as the first one. Can you talk a little bit about the first medications you think about and how you decide what other medications might be needed along the way?

MQ: We usually look at the severity of the diabetes – how high the blood sugars are to help guide us. A lot of times we'll look at the hemoglobin A1C which is essentially a three-month marker of glucose control. Generally for those with a diagnosis of diabetes, for most people we're aiming for an A1C goal less than about 7%, or so. We know people with an A1C greater than 10%, it shows maybe some worse control and it might influence our decision about maybe starting insulin as the first-line medication when we get into more extreme high sugars. That being said, a lot of times the folks we're seeing have A1Cs maybe in the high 6%/7%/8%. In cases like that, generally, the first-line medication is going to be Metformin. So, Metformin is an older medication. It's pretty well tolerated. It's inexpensive. It's oral. It's a twice a day medication. It's in the class of diabetes medication called biguanides. It's the only one currently approved in that class in the United States. It works predominantly by preventing the liver from making extra sugar when it shouldn't be. Because people with diabetes when they're in the fasting state, and they're normally there, their liver's not supposed to be making extra sugar. In people with diabetes, it does and Metformin limits that from happening. It also might sensitize some of the tissues in the body to the effects of insulin, as well. Those are both mechanisms by how it works and it's fairly effective; and for those depending on how high the A1C is when they start on Metformin, might lower the A1C by one and a half – perhaps even as aggressive as 2%. So, it's a pretty effective medication. Again, it's by mouth; it's twice a day. But as a side effect profile, most people do well with it; but, loose stool and diarrhea are common side effects. A lot of the times, we start at a low dose and then gradually increase it, we can mitigate that. There also is an extended-release version of that medication that often is better tolerated. But, that's the most common side effect would be loose stool or diarrhea. There potentially are more severe side effects. There's one that's called lactic acidosis. That's rarely been recorded with Metformin therapy. In general, that happens with people with fairly severe kidney dysfunction and potentially those with heart failure. So, for people with known chronic kidney disease or people with advanced heart failure, we might consider not using Metformin depending on how advanced those are. The Metformin itself is not directly detrimental to the kidneys. It does not harm the kidneys; but, in people with kidney dysfunction, we may choose a lower dose or not to use to use it, and that's the large consideration. We actually like Metformin and those who have a higher body weight when starting it because Metformin could help with a small degree of weight loss. So, that can be a beneficial side effect of it.

RK: It's so great to hear about all the beneficial aspects of Metformin and it's definitely one of the more common medications that we use in clinic, as well. It's definitely been on the market a long time. We know it's safe and it's effective. But, there are times where it may not be tolerated, or we have to think about other medications, particularly if someone's not at their A1C target or isn't having the desirable glucose-lowering effects that we hope. If someone comes to your clinic and they're on Metformin already, and they're not at their glycemic goal, what might you consider in choosing the next agent for them?

MQ: While Metformin is considered first-line for most patients with diabetes, the next agent has undergone a lot of change as far as what we're recommending. If it were 10 years ago, things were different, but now we're really trying to personalize the second medication to other comorbidities, other medical conditions that the patient has. We look into: 'is their body weight elevated? Do they have known coronary disease or heart disease? Do they have known heart failure?' So we really try to personalize it to what other disease processes are going on and it really gets to how these other medications work. Like for example, another group of medications that we're using commonly would be medications that are called SGLT-2 inhibitors. Generic names are canagliflozin, empagliflozin, dapagliflozin. This would be for brand names Invokana®, Jardiance®, and Farxiga®. They are oral medications. They are once daily medications that act through the urine and help the body urinate out extra glucose.

As far as effects on glucose control, they on average will lower A1C around 0.75%, perhaps 1%. So a little bit more modestly than Metformin. But over the years, they have shown other beneficial side effects besides their diabetes control. And [for] people with chronic kidney disease, there is very good evidence coming forward that these can actually slow progression of kidney disease. Whether or not it'd be diabetic kidney disease, actually, dapagliflozin is now approved for people without diabetes that have chronic kidney disease. So across the board, most do look quite good at slowing down kidney disease. Additionally, in those with heart failure this group of medications has been shown to lower the risk of admissions because of heart failure and volume overload, which is very promising. A few of the medications in this class additionally have an indication to lower the risk of future heart attack and stroke and those who have known coronary disease or cardiovascular disease. Now that is agent-specific; so, that's one that you would have to talk to your healthcare provider. But because of those benefits, we often will think about these medications more and those with chronic kidney disease and heart failure and with cardiovascular disease in general – they're an attractive option. In addition, they do help with a modest degree of weight loss on average somewhere between two and five pounds for most people. So that's a beneficial side effect, as well. So [for] those who have a slightly elevated body weight, they might be attractive in that sense.

Now, of course, we always think about potential side effects with this group of medications, as well, because they do act on the urine and this is that they put extra glucose or sugar into the urine. Things like genital yeast infections, or even urinary tract infections can happen more commonly. So in those who have frequent yeast infections or have had severe yeast infections, those who have indwelling catheters or very frequent urinary tract infections, we might choose not to use these agents in those situations. Very rarely there are cases where these medications can cause a form of ketoacidosis which is a form of acid buildup in the blood that we see somewhat uncommonly with type 2 diabetes. It can cause anything from abdominal pain to nausea to happen. Again, it's rare for it to happen, but in people on these medications, if they did develop any kind of severe nausea and belly pain, they would want to let their providers know right away. But in general, these are well-tolerated medications otherwise.

RK: In these medications, as you said, have been found to have so many benefits and patients with other comorbidities and are definitely the preferred agents when you're thinking about other medications to add on to Metformin. How about the class of agents known as GLP-1 receptor agonists? When might you consider the use of those and how are those given?

MQ: So, the GLP-1 receptor agonists are medications that boost the level of a different hormone that the body makes. So most people are familiar with insulin which helps to store away glucose. GLP is a hormone made by the intestines that is released when we eat. GLP enhances the release of insulin by the pancreas, but only when there's a certain degree of glucose present. GLP also helps prevent the release of glucagon which is an agent that also would cause the liver to release glucose. GLP slows down emptying of the stomach and GLP also might travel to the brainstem and promote a feeling of being full or a feeling of satiety. So the body normally produces this GLP. These medications, GLP receptor agonist, are basically boosting the level of the hormone that the body normally produces. Classically, these have been injectable agents in the past – though there is one oral agent that's approved. Those names that people might've heard of: the generic names are exenatide, which is Byetta ® or Bydureon®; there is liraglutide, which is Victoza®; there is dulaglutide which is Trulicity®; and then there is semaglutide, which injectable is called Ozempic® and orally is called Rybelsus®. Those are going to be the main ones that we see. Again, there's one of those there's oral semaglutide or brand Rybelsus® is the only oral option; the rest of these are injectable agents. Depending on which one is chosen, some of them are once a day and some of them are once a week. They in general either are in auto-injector devices; but, some of them also do come in pens that look similar to an insulin pen where a small needle is attached and it's given, in general, either on the abdomen or on the outer thigh.

Now because of how they work, we can kind of anticipate some of their potential side effects – since they do slow down the emptying of the stomach, nausea tends to be one of the more common side effects. It's usually mild but some people do have vomiting. Occasionally, there is some abdominal pain. Some people do have loose stool or diarrhea, but the gastrointestinal side effects are the most common. There was some animal data showing an increase of a hormone called calcitonin which could be linked to a very rare type of thyroid cancer called medullary thyroid cancer. To date, this really has not been seen in humans but in those who have a strong family history of medullary thyroid cancer or a history of multiple endocrine neoplasia, these medications are generally avoided. In addition, in those who have a history of pancreatitis, these medications are generally avoided because it could bring on another episode of pancreatitis.

Now, those are the potential side effects. But as far as the benefits besides the glucose lowering, since these medications do promote that feeling of fullness, and since they do slow down digestion, they oftentimes are associated with weight loss. And depending on the agent, that's anywhere between generally 5 and 12 pounds depending on the response. So they are effective with weight loss. Certain medications in this class also have been shown to reduce the risk of a heart attack and stroke in people with cardiovascular disease, as well. Again, that is agent-specific, but certainly have been shown to do that.

RK: And what kind of effect on blood glucose levels might you expect on A1C?

MQ: As far as A1C lowering, it's really agent-specific. But it's usually anywhere between 1 and 1.5%. Some of the very strong agents may even approach 2% but generally between one and 1.5% in A1C lowering is what we would expect to see.

RK: It sounds like for every medication, it's really a balance between the benefits and the goals that you're trying to accomplish in terms of lowering the A1C and reducing these comorbidities and then some of the side effects or potential risks that you mentioned – contraindications. You know, for a patient who's hearing about all these potential side effects, it might sound a little scary to think about them. How commonly do you see these side effects in your practice?

MQ: So in general, for medications like the GLP-1 receptor agonist that we just spoke about, nausea and vomiting from that; [for] mild nausea, we would expect somewhere around maybe 15% of the time depending on the agent, but nausea that's so severe to actually cause people to stop the medication is much lower, perhaps around 5%. So you can see the vast majority of people do not have those ill side effects. People who have the side effects tend to be a little bit more vocal. So you know if you go on the internet or if you talk to friends, a lot of times people will make comments that they have some of these side effects, but in the general population, they are fairly uncommon but certainly present. So it's all going to depend on the agent used, but in general, these are all very safe, effective medications and that's why we feel so comfortable using them.

RK: What about cost considerations? You know, the SGLT-2 inhibitors and the GLP-1 receptor agonist are relatively newer medications introduced within the past decade or so. How has cost impacted the ability to use these medications in practice?

MQ: So it certainly is a concern. These medications without any insurance coverage, the GLP-1 receptor agonist can cost thousands of dollars a month. The SGLT-2 inhibitors could cost hundreds of dollars a month, so they certainly can be expensive. Now because of all the benefits seen outside of diabetes control, insurance companies have actually gotten very good at covering these medications more aggressively, including for Medicare plans, as well. Unfortunately, this is plan-specific but a lot of them are quite affordable. People on commercial insurance plans since these are branded medications can often get coupons. So if they ask the pharmacist or their diabetes provider about that, there's often savings coupons that are available, but the issue often comes in people with high-deductible plans or people with Medicare plans with high deductibles or a doughnut hole. Sometimes these do become overly expensive and oftentimes we cannot use them. And in those cases sometimes, we can directly have patients apply to patient assistance programs and depending on their income, they can be quite effective in these medications. But other times in people that don't qualify, it does impact our ability to use these medications.

RK: It sounds like in general with insurance, the coverage has increasingly made it easier to use these medications and it's great to hear about the patient assistance plans that could be resources for people who might need additional support. Now turning to the other classes of medications that are available, SGLT-2 inhibitors and GLP-1 receptor agonists [are] really great for those with the comorbidities in particular. But in those who may not have cardiovascular disease or chronic kidney disease or heart failure, what might be the other options that you think about when considering another agent after Metformin in your practice?

MQ: One of the ones that we've used many times in the past had been a class of medications called sulfonylureas. These are pretty much all generic at this point and some of the common

names would be glyburide or glipizide or glimepiride. These are medications by mouth. Depending on which one is chosen, they'd be either once a day or twice a day medications and they help the pancreas release extra insulin. The benefits of these are the obviously the glucose-lowering ability. They have pretty good effects. Somewhat similar to Metformin we would expect A1C lowering usually around one and a half percent, so they are quite effective. They are oral and they're inexpensive, which are their other main benefits.

As far as potential side effects and cautions we would use, since they do enhance the pancreas releasing insulin – and unfortunately, that insulin release is not dependent on the glucose level – hypoglycemia or having low blood sugars is the main ill effect that we see from these medications. So when people using sulfonylureas eating on a very regular diet is important because skipping meals might enhance the low blood sugar risk. Exercising vigorously potentially could enhance the low blood sugar risks. Sometimes these medications are associated with a small degree of weight gain, not very much, usually a couple of pounds, but that's also a consideration. There was some evidence that perhaps these medications after a heart attack, we're not the best medications to help recovery of the heart muscle after an acute heart attack. That's somewhat controversial. It's not very clear; but that might be one situation where these medications are avoided, but otherwise, they're fairly well tolerated medication. Side effects are fairly minimal other than the risk of a low blood sugar. And again, they are inexpensive and they're oral options.

RK: Sulfonylureas have been on the market for a long time. We've had a long track record of experience and they tend to be inexpensive for the most part. [They're] really effective at lowering blood sugars. And like you said, the risk really is of hypoglycemia in those in particular who might be older and may not have the same ability to feel those side effects. And for our listeners, any of those medications ending in '-ide' as Dr. Quartuccio mentioned are really the class of medications that we're talking about here for sulfonylureas. So, in addition to sulfonylureas, what other classes of medications are available?

MQ: There are the DPP-4 inhibitors. The medications we have right now are sitagliptin, which is Januvia®; we have linagliptin, which is Tradjenta®; we have saxagliptin, which is on Onglyza®; and we have alogliptin, which is Nesina®. Those are gonna be the most common ones that are available. These group of medications also act on levels of GLP-1 in the bodies. GLP-1, the hormone I mentioned before that helps to slow digestion and enhance insulin release, is normally broken down by the body by an enzyme called DPP-4. Though these medications slow the degradation of GLP-1, which enhances the levels of that hormone in the body. They are a little bit less effective as far as glycemic control. In general, A1C lowering is somewhere between 0.5% and 0.75% so some modest results, but these are oral agents – they're pills – which is attractive. They are generally considered weight-neutral. Most of the studies show that they don't benefit or harm the heart. The one exception might be for saxagliptin which potentially may cause an increase in the risk of heart failure, though that's somewhat unclear. But otherwise, they are very safe medications. They do not cause low blood sugars when they're not being used with other medications. So they're safe medications, in general. The one side effect that was reported occasionally is a little bit of sinus irritation, but otherwise they're very well tolerated medications. And [for] those with chronic kidney disease, sometimes the dose does need to be adjusted depending on the level of chronic kidney

disease. And other types of medications in this class, they do not need to be adjusted. So, sometimes they are safe options for the chronic kidney disease patient. They're nice as far as not having many side effects, but unfortunately, their lack of glycemic benefit . . . they're not the strongest agent and they're relatively high cost because they are all still brand medications [which] limit our ability to use these more widely.

RK: It's true that the DPP-4 inhibitors are in general, very well tolerated, but they really have just a very modest A1C-lowering effect, really less than 1%. But for those who might just need additional… just a little bit more A1C benefit, they could be really great options as second agents. And we haven't really talked about the combination pills, but do you use those at all? You know, I know that the DPP-4 inhibitors, many of them are offered in combination as a single pill with Metformin.

MQ: Many of the DPP-4 inhibitors and actually, many of the SGLT-2 inhibitors, as well, are offered in combination pills along with Metformin, which does make dosing a lot more convenient. Obviously, where cost-wise we're limited by the cost of the more expensive medication, but in general, these combination pills are not more costly than the individual medications because the Metformin is very inexpensive. So, for those who really don't like to take pills, or might forget to take pills, the combination pills are a very attractive option for both the DPP-4 inhibitors and the SGLT-2 inhibitors.

RK: That's great to hear, especially to reduce the number of pills per day is a great bonus. What about the class of agents known as thiazolidinediones? Can you talk a little bit about those and do you use those in your practice?

MQ: There's thiazolidinediones or TZDs, as we commonly refer to them as, are group of agents that help sensitize the body to the effects of insulin through a mechanism called PPAR-gamma. These medications came out in the early 2000s and they are fairly effective medications. In general, A1C lowering is between 1 and 1.5%. Medication names include pioglitazone or rosiglitazone. We are using these slightly less than we did in the past and part of the reason was around 2006/2007, rosiglitazone, which is one of the medications in this class, potentially showed an increase in the risk of heart attack and stroke and it prompted an investigation by the FDA who initially had pulled the medication from the market and then did additional research. Ultimately, when they did additional studies, it looks like rosiglitazone probably was not linked to that increased risk of heart attack and stroke. But it did raise fears amongst healthcare providers that this group of medication could potentially do some harm.

We know because of the way they work they do potentially cause fluid retention – and especially in those with chronic congestive heart failure – they were thus an unattractive option. In general, I will occasionally use pioglitazone as medication in that class in those that do not have heart failure and you know, who don't have fluid retention issues. But I admit that because of potential weight gain, which is a side effect from this medication, I do have a little bit of trepidation in using it with many of our patients. And I think there is still a lingering fear for many providers about the potential risk of cardiovascular events with these groups. So I think a lot of times, they're used a little bit less because of that reason. Though I would say that pioglitazone really

has never been linked to that increased risk of heart attack or stroke. It really just was rosiglitazone, and that one's not used very much by providers these days.

RK: From what I recall, I think pioglitazone, in fact, may have had some benefits in cardiovascular disease and some of the trials, but nothing as definitive as SGLT-2 inhibitors and GLP-1 receptor agonist. But I agree with you. I think pioglitazone, or Actos®, can still be a medication that is used. And I know that I often use it, particularly in my older patients who may not have comorbidities that would make it a contraindication for them to use.

MQ: And the fact that it is a generic and it is inexpensive is also an attractive option. So the fact that it's oral, inexpensive and effective is are all benefits to it.

RK: What other classes of agents do you use in your practice or have we covered most of them?

MQ: There is a class of medication called alpha-glucosidase inhibitors and the main medication in this class is called acarbose. It's an oral medication that prevents the breakdown of carbohydrates in the intestines; and thus, will help lower A1C. The A1C lowering is more modest – it's definitely below 1%. And honestly, the GI side effects usually limit our ability to use these medications. Having excess gas – flatulence, as well as belching – can happen with these, as well as just general GI upset happens fairly commonly, which limits our ability to use these. And again, since they do have fairly modest glucose effects, and you know, potential GI side effects, we use them less, though they still definitely could be considered.

There are dopamine agonists like bromocriptine that technically do have an indication to treat diabetes. These were commonly used in other medical conditions but potentially could lower glucose control. Again, the A1C lowering is fairly modest. So we see these not frequently used in practice, And they also have, you know, a potential a fair amount of you know, neurological side effects that could occur. So I don't generally use those in practice, but they do have an indication to treat diabetes and they could be safely used. It's just we don't see them used very commonly for diabetes specifically.

RK: The medication known as colesevelam I believe also has diabetes indication brand name Welchol®. Do you ever use that in your practice?

MQ: Yeah, Welchol® basically prevents the limits the cycling of some of the bilirubin-derived components of the body and will help lower glucose, as well. I find that their glucose-lowering effects is again, somewhat modest. And because of that, because I try to limit bilirubin with patients, I don't generally use them in practice, though they potentially could be used.

RK: So I guess to round out all the classes, the last class of agents that are a little bit older, repaglinide and nateglinide belonging to the glinides, if you will, or sulfonylurea like secretagogues, have been on the market a while. I wonder if you could talk just briefly about how those are used and whether you still use them very much in your practice.

MQ: Yeah, so these meglitinide medications, for simplicity, I usually think of them as short-acting sulfonylureas. Whereas medication sulfonylureas like glipizide and glimepiride last a

long time in the body, these meglitinides are very short-acting, and they're designed to be taken just before a meal to help enhance insulin secretion with that meal. And generally take them about a half an hour before the meal. They're not the most effective medications; they are far less effective as far as A1C lowering than the sulfonylureas. But I can find them useful in patients that have an erratic diet or perhaps just need a little bit of extra help with high sugars after meals, especially in our older adult populations that might be at higher risk for hypoglycemia and an erratic diet. I oftentimes will reach for these medications to be taken with meals to lower the risk of potential hypoglycemia. So again, their lack of good A1C-lowering really limits our ability to use them on a very regular basis.

RK: And what are the brand names of these agents that our listeners might be familiar with?

MQ: So there is repaglinide, which is Prandin® and nateglinide, which is Starlix®. Those are the two currently available medications on the market. And again, both of them are designed to be taken just before a meal is consumed. And only if that meal is consumed.

RK: Well, thanks so much, Dr. Quartuccio, for summarizing all these different classes of agents. It's so exciting to hear that we have almost a dozen classes of agents that can be used in clinical practice. The question that always comes up is . . . when do you consider insulin? When does an individual need to have insulin added to the regimen? You know, after Metformin, we talked about the considerations and choosing a second, maybe even third agent, but we haven't really talked about when insulin is needed. Could you talk briefly about that?

MQ: So, the choice of when to initiate insulin is really going to depend on the level of glucose control the patient is currently having, the tolerability of other medications, and whether or not they just do not want to add extra pills or other medications to the regimen. So if in those that we've tried other medications, and unfortunately we are failing to achieve optimal control, we oftentimes will reach for insulin. In those who have very extremely high glucose and [at] the onset of the disease, oftentimes, we will use insulin as a more reliable and effective way to lower glucoses more quickly. And of course with those with type 1 diabetes, we must use insulin in those individuals. So it really depends on level of control, choice of whether we have any other agents available are going to be the main consideration.

There are two broad classes of insulin medications. We have the long-acting and short-acting. I can briefly talk about the intermediate-acting agents later, but in broad strokes, you have your long-acting and short-acting. So [for] long-acting insulins, the generic name would be glargine and detemir. Glargine has several different brands from Lantus® to Toujeo® to Basaglar® to Semglee®. Detemir has a brand name of Levemir®. And then there also is insulin degludec, brand name is Tresiba®. All of these medications have very long-acting effects. Depending on the agent, when you give the injection, their duration of action is anywhere between 18 to 30 hours-plus depending on which agent is used. So they are designed to deliver a slow and steady amount of insulin throughout the day. They do not have levels of insulin that peak after meals. It’s just a stable amount of insulin that occur all throughout the day. Now often in those with type 2 diabetes, we will start with one of these long-acting or basal insulin. And it's enough to give them the level of control and bring down the glucoses and oftentimes only a basal insulin is needed. However, in those who have difficulties with glucoses rising rapidly after meals, or

again, in those with type 1 diabetes, we oftentimes need to use mealtime or bolus insulin. The bolus insulins we currently have available are insulin lispro, which brand name is Humalog® or Admelog®; we have insulin aspart, which brand name is NovaLog®; and we have insulin glulisine which brand name is Apidra®. These are all short-acting insulins. I also should mention there are a newer class of ultra-fast-acting insulin that would be aspart or lispro plus another additive to make the onset quicker. The brand names for these ultra-fast-acting insulins would be either Fiasp® or Lyumjev®. In the normal insulin such as lispro and aspart, the onset of action after you give the injection is generally somewhere [between] 10 to 15 minutes. The ultra-fast-acting ones can have onset as soon as 5 minutes after injection. These medications are always designed to be taken just for a meal. Again, depending on which specific insulin is used, it might be anywhere between 5 and 15 minutes before a meal and oftentimes we will vary the dose given based on how large the meal is. But the main effect of these medications is to prevent the rise in glucose seen after meals.

So depending on how severely elevated the glucoses are or depending on what the pattern of glucoses are throughout the day, we may consider simply a basal insulin, or long-acting insulin. We may consider a combination of basal and bolus which is long-acting plus short-acting insulin. And that really is individualized based on the pattern and also based on a patient's desire. Sometimes giving up to four shots a day is far too cumbersome so that would impact our choice. Part of the discussion should involve intermediate-acting insulins and also mixed insulins. [For] intermediate acting insulins, the classic one would be NPH insulin. A lot of times Novolin® N and or Humulin® N are names that are commonly heard of. Intermediate-acting insulins have a duration of action that are somewhere between 8 and 12 hours. Instead of being a really flat profile like the true basal insulins, they do have a mild peaking effect that happens usually somewhere between four and six hours after administration. These intermediate-acting insulins can also be combined with shorter-acting insulins in a combination insulin, sometimes [they] will be referred to as 70/30 or 75/25. And if you use them as a mix, they're generally dosed before a meal and they provide some longer-acting coverage and some shorter-acting coverage. So they'd be given usually with breakfast and dinner to help in people who don't want to take more than two shots a day. It helps with control around breakfast and dinner meals more effectively. The choice of which insulin to use really depends on the level of glycemic control, how many injections are tolerable, and the comfort of the patient. The nice thing in the advances of insulin over the years is they have become easier to administer. In the past, it used to be these all required vial and syringe. Some of them needed to be rolled beforehand and it was a bit of a cumbersome process. Nowadays, many times these insulins are available in insulin pens. So they're devices when the insulin is pre-loaded, you would basically put a pen tip or a needle that is screwed on the top of the insulin pen and then you can simply dial up the dose and it makes administration significantly easier. And these insulin pens are becoming much better covered by insurance plans, including Medicare plans. Over the last couple of years, most Medicare plans have the option for lower cost insulins that cap the cost of insulin at $35 a month and that includes the use of insulin pens. So it has made things easier over time.

RK: It's so great to hear about the developments with insulin as well, just like with the oral agents and then non-insulin injectables, the GLP-1 receptor agonist that have happened over time and appreciate you making that distinction between type 1 and type 2 diabetes; that really in type 1 diabetes, the insulin the basal or long-acting with the mealtime insulin is really the standard of

care. Whereas for type 2 diabetes, that might be more progressive in those who aren't meeting their glycemic targets to add on insulin either as a second, third, or sometimes even fourth agent. One of the questions that patients will often ask and I'm sure you've heard this too, in your practice is, "can I ever get off my medications?" And the answer to this will depend on what medications they're on, whether they're on insulin or not, but what do you usually say to your patients?

MQ: I usually say it depends. I mean really it depends on where we're starting from. In those that perhaps have heavier weight on onset and those that perhaps have a lot of changes that could be made to their diet and exercise regimen, then there is a higher likelihood that with those aggressive lifestyle changes and perhaps using some non-insulin medications, perhaps we could stop their insulin. And those who are on non-insulin medications and have room to make improvements in their lifestyle, then yes, if they're able to make those drastic improvements, oftentimes we can stop medications. In other cases, unfortunately, if they have a longer duration of diabetes, or if the control is more difficult, oftentimes we cannot stop medications. It really depends on how everyone is responding to those lifestyle changes. Importantly, even in those who don't completely respond to lifestyle changes, those lifestyle changes – the diet and exercise – always will make a difference. Oftentimes, people get disheartened that they do need to start insulin that they just…there's no point in trying to keep the portion sizes lower. There's no point in exercising and that's definitely not the case. The lifestyle changes will always help and even if it's not stopping medications, oftentimes, we can lower the doses of the medications, lower doses of insulin, perhaps get rid of some of the medications, but it really depends on how the response is to lifestyle.

RK: Well, Dr. Quartuccio, thanks so much for being with us here today and sharing your great expert insights into the use of medications for diabetes and all the great developments that have happened over the past few years. So thank you so much for being here.

MQ: Thank you very much for having me. It's an honor.

RK: I'm Dr. Rita Kalyani, and you've been listening to ***Diabetes Deconstructed***, a companion podcast to the ***Johns Hopkins Patient Guide to Diabetes*** website which has all kinds of useful information about diabetes, including videos and animations, a lifestyle and nutrition blog, and a comprehensive diabetes glossary among other topics. For more information, visit *Hopkinsdiabetesinfo.org*.

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