Advancements in Diabetes
Update on Diabetes Medications 2016

CAPT Chris Lamer, PharmD, MHS, BCPS, CDE
Pharmacist/Clinical Informaticist
IHS - Division of Diabetes Treatment and Prevention
IHS Office of Information Technology and Health Education Programs

Chris Lamer:

Okay, thank you, Jan. I started with IHS back in '98. I worked a number of years at Cherokee Indian Hospital. I then started working with the Office of Information Technology and was part of the Meaningful Use project. Recently, I have started working with the Division of Diabetes Treatment and Prevention for 60% of my time and with the Office of Information Technology for about 40, where I still do the Personal Health Record and Clinical Reporting System and a few other things.

My interest has always been in diabetes and in fact, that's what had drew me to the Indian Health Service was a job description talking about working at the Cherokee Hospital with people with diabetes and providing alternate types of patient care. I've always had that interest and it's been sticking with me and I've been fortunate enough to be able to provide presentations on diabetes medications on behalf of the Division of Diabetes Treatment and Prevention for a couple of years now.

That said, I'm certainly not an expert on medications, I only read about them. I think that the people who are actually prescribing medications, seeing patients who are taking their medication, and people who are taking the medications themselves are the real experts. And so, as I go through my slides, if there's anything that I say that doesn't seem right or you have further comments or further insight into it, please put your comments in the box and share them because I think firsthand experience and knowledge is the best experience and information to share. So with that, I'll go ahead and start going through my slides.

I do have a lot of information. I started off with over a hundred slides and I cut them down so I could fit the presentation within the time period and also, so I don't put everybody to sleep. But just to start off with the progression of diabetes, it's a progressive disease where the ability to secrete insulin diminishes over time. The first thing that goes is the ability to secrete enough insulin to cover postprandial blood sugars. Over time then, a reduction in basal insulin release and eventually, the pancreas stops secreting insulin completely.

We can slow this progression with various treatment recommendations. The primary treatment is going to be improving nutrition and physical activity. These interventions should begin -- really, they should begin before prediabetes in all patients. That definitely is the first line of therapy with somebody who is diagnosed with prediabetes or diabetes. And they're not one-time interventions. They're something that are -- they're going to be a lifelong change and they should be incorporated into the patient's treatment plan throughout their lifespan.

When nutrition and physical activity are no longer able to compensate for the failing pancreas, non-insulin medications can be initiated to help the patient manage their blood glucose. Eventually, when the pancreas can no longer secrete insulin, exogenous insulin or insulin shots are required. That doesn't mean that insulin is only used as the last line of therapy at the end of the disease. Insulin is

effective at any point after diagnosis of diabetes and can be considered as part of the patient's treatment plan at any point.

Today, I'm going to focus on the non-insulin medications. I'm going to provide a very brief overview of each drug class available now. I think a full presentation on each drug class could be given and I would definitely go into a lot of detail and a lot of time. But you can find a lot of information on these medications by looking at a tertiary reference or talking with your pharmacist.

This slide is a simple representation of what we know about glucose metabolism. Glucose enters the bloodstream by a few methods. It is absorbed from the intestines after eating. It gets secreted by the liver and other tissues through gluconeogenesis or it can be released as part of a breakdown of glycogen. Glucose enters insulin independent cells such as the brain, intestines and the pancreas. In the pancreas, glucose gets broken down and this causes a release of insulin. The first thing that insulin does is it stops gluconeogenesis.

The second phase of insulin secretion helps to transport glucose into insulin dependent cells such as fat and adipose tissue where it gets utilized as a source of energy. Excess glucose, if it isn't absorbed, makes its way to the kidney. Most, if not all, of the glucose that goes to the kidney gets reabsorbed and added back into the circulation. When the glucose levels get very high, they can spill over into the urine.

I wanted to highlight this process because it gives us a reference to where various medications for diabetes work, and how different medications may complement each other. The first group of medications I'm going to be talking about are those that affect the gastrointestinal absorption of glucose or are influenced by activities of the intestines. Next are the sulfonylurea and meglitinides, which stimulate the pancreas to secrete insulin. There are thiazolidinediones that improve insulin sensitivity at target cells, such as muscle and adipose tissue. Metformin works in a similar way but also has effects on the liver by reducing gluconeogenesis. And we now have a new class of drugs called the "sodium-glucose transport protein inhibitors". These medications block the reabsorption of glucose by the kidneys.

There are three groups of medications that affect glucose absorption. These include the alpha-glucosidase inhibitors, amylin analogs and the bile acid sequestrants. I'll start off with the alpha-glucosidase inhibitors, of which there are two in the market. Those two medications are acarbose and miglitol. These drugs block glucosidase which are enzymes that breakdown carbohydrates. So let's say we have a delicious pasta meal and it obviously wasn't chewed up very well. Those complex carbohydrates, the noodles, get passed over into the gut. Our body releases enzymes that digest the carbohydrates and convert them over to simple sugars which get absorbed into the bloodstream. This results in a peak of glucose which rises fairly rapidly.

When an alpha-glucosidase inhibitor blocks these enzymes, bacteria in our gut digest those complex carbohydrates. This is a slower process and the glucose peak is lower and longer. The theory is that a lower peak is more easily managed by the pancreas. One of the problems with this medication is the byproduct of carbohydrate metabolism. When enzymes breakdown carbohydrates, water gets released. However, when bacteria breaks it down, they release methane. This results in the major side effects that we observe with these medications. Gas, cramping, constipation and more gas are side effects that commonly result in people discontinuing these medications. By slowly titrating dose over a long period of time, we can help to minimize these effects. And by a long period of time, it could be weeks or it could be even months to titrate people up slowly enough so that they're not feeling miserable.

These products reduce the hemoglobin A1C by about a half percent, they are safe to use in pregnancy, the effects are unknown of what happens if you use them in lactation, and they're fine with mild renal

insufficiency. However, people who have severe renal impairment, which is defined as a serum creatinine greater than two should not take these alpha-glucosidase inhibitors.

The next medication, pramlintide, is an amylin analog. Amylin is a hormone that's released with insulin from the beta cells of the pancreas. It slows gastric emptying and increases satiety or the feeling of fullness. Pramlintide can reduce A1C by about a half of percent as well, and may also result in some weight loss, estimation around two to four pounds. Because it slows gastric emptying, there are some GI side effects such as nausea. You need to be careful whenever the patient is taking other oral medications as well because they may not be absorbed as appropriately as if they were not being taken with this medication. Oral medication should be administered about one hour before or two hours after dosing pramlintide, to assure that they get absorbed appropriately.

Other medications that may further slow gastric emptying, such as atropine or the alpha-glucosidase inhibitors should not be used in combination with the pramlintide because the additive effect, that's going to be a pretty intolerable to any patient. Pramlintide is rated as pregnancy category C, so it should not be used unless the benefit outweighs the risk in pregnancy. Use in end stage renal disease or end stage liver disease has not been studied and there are no studies performed among lactating women. Pramlintide is a subcutaneous injection that is marketed as a pen. It's important to note that needles are not included with the pen. It must be prescribed and purchased separately.

Amylin should not be mixed with insulin, and this major concern came out awhile back. Originally, amylin came out, released as a vial and expecting -- told not to mix the two, people are doing then, so the company that makes the amylin, stopped making it in a vial and only makes it in a pen formulation right now. Even still, they recommend you administer pramlintide two inches away from the spot where you're giving insulin if both are being used at the same time. The pen should be stored in the refrigerator until they are going to be used. As long as they are in the refrigerator and not open, they're good until the expiration date. Once you open them and start using them, you can store them back in the fridge again or you can keep them at room temperature, but they're only good for 30 days. After 30 days, the pens should be discarded even if they still have medication in them.

Pramlintide should only be used after eating a major meal, and they define the major meal by greater of equal to 250 kilocalories or 30 grams of carbohydrates. So patients need to have a decent understanding of carbohydrate counting and estimating carbohydrate and calorie load in order to take this medication effectively. The starting dose is 60 milligrams subcutaneously. If there's no nausea for at least three days in a row, the dose can be increased to 120 milligrams. If the patient is experiencing nausea at all, they should continue taking the 60 milligrams until they get used to taking that dose and are fine for at least three days again, then move up.

By itself, it does not cause hypoglycemia, but when used with other medications, especially insulin, hypoglycemia may occur. The package insert recommends that the patient that is taking insulin, the pre-meal insulin dose should be reduced by half while you're starting the amylin analog until you see how it affects the blood sugar. After you have taken the pramlintide for a couple of days and you see where the blood sugar is going, then you can begin to titrate the insulin back up, getting as close to the previous dose as where they were.

The next group of drugs are the bile acid sequestrants, and there's only one bile acid sequestrant, colesevelam, which has been studied for effects on reducing A1C. We know that the medication binds the cholesterol that reduces LDL cholesterol. But the mechanism by which it reduces hemoglobin A1C is not known. But at least I can't find that information anywhere. This agent can reduce A1C by about a half percent but must be used with caution with people who have elevated triglycerides like many people with diabetes because the concentration of triglycerides may increase by as much as 10% when taking this medication.

Colesevelam is available in tablets and powder. The dosing is to take six tablets at once or three tablets twice a day. I have a picture up here just to emphasize that these are pretty large tablets and some patients may have trouble swallowing them, especially if you're taking three or six at one time. The powder can be mixed with 4 - 8 ounces of a drink and there are a lot of different drinks that they can mix it in. It's important that the powder does get mixed and is not taken as a dry powder. So make sure people don't try to just rip open the powder packet and chug it down. They have to mix it with some kind of a liquid.

Bile acid sequestrants can cause constipation and other GI effects. If somebody has a bowel obstruction or chronic constipation or some other bowel problem, you don't want to use these medications. Again, they can increase triglyceride levels and it may decrease the absorption of fat soluble vitamins A, D, E and K. If you have a patient who's taking supplements of these vitamins, they should be taken at least four hours before the colesevelam is taken. The drug is rated pregnancy category C and may interfere with vitamin absorption in infants who are breastfeeding.

Moving on to the incretin mimetics, they are a group of drugs that act like or increase the levels of glucagon-like peptide, specifically, GLP-1. GLP-1 is predominantly released from the intestines and causes the alpha cells of the pancreas to stop producing glucagon. It may also stimulate the beta cells to increase insulin production. GLP-1 is rapidly inactivated by dipeptidyl peptidase 4 or DPP-4. This discovery has led to the development of two classes of drugs. GLP-1 agonists, which act like long acting GLP-1, and DPP-4 inhibitors, which prolong the duration of naturally released GLP-1.

There are four GLP-1 agonists on the market, exenatide which is available in a twice weekly or twice daily or weekly dosage, liraglutide, albiglutide and dulaglutide. There's a GLP-1 agonist with the brand name of Saxenda. Saxenda is liraglutide but not indicated for the treatment of diabetes. Instead, this medication is marketed for weight loss in people who have of BMI greater than or equal to 30, or a BMI greater or equal to 27, at least one weight-related condition, such as diabetes, hypertension or dyslipidemia. The only difference I can see between the Saxenda and Victoza is that Saxenda can be dosed higher, up to 3 milligrams per day than Victoza, which has a maximum dose of 1.8 milligrams per day. So when using it to treat for diabetes, the max dose for the liraglutide is 1.8 milligrams a day, but somebody with diabetes could be taking liraglutide in the Saxenda formulation, because of weight loss, the dose is up to three milligrams per day.

The GLP-1 agonists suppress glucagon secretion to lower blood glucose and they also slow gastric emptying. This combined effect can reduce the hemoglobin A1C by 0.5% to 1% and result in a weight loss of up to about 4 kilograms, which is almost 4 pounds. All of these agents are administered subcutaneously and are available as a pen. The dosing for each agent is on the table. Available starting dose which is increased after about a week of therapy. This is done to reduce the incidence of side effects. The primary differences between them are in how each of the agents are administered. exenatide in the Byetta formulation and liraglutide are administered daily while exenatide in the Bydureon formulation and all the other agents are administered weekly.

Which brings us to a question, HS is a middle aged man with type 2 diabetes diagnosed just over six years ago. He's been taking albiglutide, 50 milligrams every Monday for about 9 months now. He calls you on Thursday saying, "I forgot to take my medicine on Monday," and wants to know if it's okay to take it now or should he wait until next Monday. If you told HS to wait, don't worry you didn't kill him, but the best answer is really to tell him to go ahead and take it today and then continue taking it on Monday in his normal schedule. Weekly dosing presents a new problem when people miss a dose. Taking an extra dose could result in higher concentrations of the medication for an entire week, while missing a dose can considerably lower the steady state concentration.

For GLP-1 medications that are dosed weekly, the recommendation is that you should take the dose if you remember it and if it is within three days of the next dose. Since HS isn't due for his next dose until Monday, three days prior would be Friday. So he should take his dose today and the next one on his

regular schedule time, on Monday. What about switching a day you want to take it? Let's say Monday is not working out and you want to switch to another day. You can change the day as long as it is at least four days after the last dose. So you don't want to take it too close together.

In this example, if you're taking it on Monday, you can switch your next dose to Friday, Saturday or Sunday. If you wanted to take it on Tuesday instead of Monday, what you would have to do is -- what you would want to do is take it maybe on Friday or Saturday and then the following week, switch it over to Tuesday. Although skipping one day and going on to Tuesday on the next week probably isn't going to do any harm either.

One other thing now I want to mention about missing doses is that with liraglutide, if the patient misses doses for three or more days in a row, they recommend that the patient restart it back to 0.6 milligrams or the starting dose for a week before increasing back up to their normal dose. And that's because even after just three days of not taking the therapy, patients can experience side effects if they just start back taking the regular dose.

When switching from twice daily, Byetta to the once weekly formulation of Bydureon, they recommend that patient stop Byetta and on the next day, start the extended release formulation. So if the patient wants to switch over to the once weekly dose and they want to do it on Friday, they would take their twice daily dosage of exenatide up until Thursday and on Friday, they would stop and start taking the Bydureon, the once weekly formulation. Once they do that, it's expected that for about two weeks, their blood glucose levels may rise, and that just is going happen until the weekly formulation reaches the steady state concentration and then the blood glucose levels should come back down to where they were.

With albiglutide, the albiglutide pens are a little bit different than the others. The albiglutide pens have two chambers. One has a lyophilized powder in it and the other chamber has water. What the patient has to do is twist the pen and that combines the water and the powder and then they shake it back and forth as shown on the picture there, and then they have to wait until it mixes. For a 30-milligram pen, they have to wait about 15 minutes, and for the 50-milligram pen, they have to wait about 30 minutes. Once the medication is mixed, they have eight hours to use it, so patients who are taking albiglutide have to have a little bit of additional preparation to get their medication ready prior to taking it.

Just like any other medication that's affecting the gut, GI side effects are the most common. They subside overtime and injecting the medication after a meal can help. These medications may also affect the absorption of oral medications, so it's recommended that people take their oral medications at least an hour before the injection. And this could be a little complicated if somebody is taking oral medications, they're eating their meal, they need to take their injection and then they need to take other medications with food. They may want to try to find a different meal to either give the injection during or to take the medications.

There's a black box warning that GLP-1 agonists may increase the risk of medullary thyroid carcinoma, and in rest, the risk of cancer increase based upon the amount of medication they were taking and the duration of their therapy. And because of this, patients who have a personal or family history of thyroid cancer should not take these agents. And we are still learning more about these medications, especially through post-marketing reports and a number of different conditions have been coming out since these medications have hit the market. There are cases of pancreatitis from all the GLP-1 agonists and recently, it's been discovered that these agents may also have caused pancreatic exhaustion. This has been evaluated in mice, who received the medication forbearance in more than 50 days. Basically, after getting this medication, it's hypothesized that the pancreas is burning out. The effects on humans is not known at this time. This was just one study done in mice that are supposed to be very similar to human pancreatic cells, but the true effects remain to be seen.

There have been some cases of renal impairment that are associated with exenatide, dulaglutide and all the GLP-1 agonists are considered to be pregnancy category C. In fact, albiglutide, it's recommended that it be discontinued within one month of a planned pregnancy. So in using these agents in a female in her child bearing years it's important. None of these agents have been evaluated during breastfeeding and should be avoided if possible.

Next are the DPP-4 inhibitors. There are four agents on the market, including sitagliptin, saxagliptin, alogliptin and linagliptin. They block DPP-4 and help to prolong the duration of GLP-1 so that the endogenous GLP-1 remains available. Their functionality is also dependent on the ability of the intestines to continue to release GLP-1. If no GLP-1 is being released, these medications will not have much of an effect. The result in A1C decrease of about a half to one percent and they have no effect on weight. So there's no weight loss seen but there's also no weight gain. Unlike the GLP-1 agonists, DPP-4 inhibitors rely on the body's ability to make GLP-1. However, the ability to take them by mouth makes a more enticing option to some patients who may not want to administer an injection.

What about combining the two agents together? Current recommendations are to not administer GLP-1 inhibitors with DPP-4 inhibitors. In theory, the combination will further increase GLP-1 activity, first, by administering an agonist and second, by preventing the breakdown of the naturally occurring GLP-1. However, in current studies, the combination has not shown improved outcome, and in fact, may increase side effects.

Although these agents do not cause hypoglycemia on their own, caution should be used when combining with a medication that increases insulin levels, such as a sulfonylurea. Consider using a lower dose until the effects are known and then titrate back up as appropriate. Headache, nasopharyngitis and upper respiratory tract infections are the most common side effects and appear to be more tolerated. Here again, more information is coming up after post-marketing of these medications and reports have indicated that there may be associated cases of pancreatitis. Arthralgia, or really bad joint pain has occurred in a number of patients, and it seems that this side effect can happen at any time, whether when somebody is starting the medication or even after years of taking it. There have been cases where patients with suspected arthralgia discontinue the DPP-4 inhibitor felt better, restarted the DPP-4 inhibitor and got the same arthralgias back again. They don't know why that's being caused but it is being associated with some of the DPP-4 inhibitors, and hepatic failure has occurred with alogliptin.

Results from some ongoing trials such as the SAVOR and EXAMINE trial shows that alogliptin and saxagliptin may increase the risk of heart failure. However, these things were not designed to evaluate heart failure in patients taking this medication. It was just something that they observed, so the actual effect is really not known. But this is a risk and has caused the FDA to ask that the drug companies comment in the package insert about this. There is also another recent study with sitagliptin and basically showed no increase with the sitagliptin medication.

These medications appear to be safe during pregnancy. They are secreted in breast milk and the effects of that secretion in breast milk are not known. There's also some side effects with the saxagliptin and linagliptin. They are metabolized and affected by an enzyme system called the cytochrome P450, 384 and P-glycoprotein transport system. I was going to put some slides on here and detail it a little bit but I decided to spare you that. The key point is that with these medications, there are a number of different drug interactions that can occur. And so, you should always when prescribing these, take a look at drug interaction checkers or talk to your pharmacist when you're prescribing them to make sure that they're being administered safely.

So the next group of drugs are the sulfonylureas and meglitinide, and these stimulate the pancreas to make insulin. The sulfonylureas bind to and fall off of a receptor very rapidly. So there's a constant stimulation in the release of insulin from the cells. When glucose is present, the response is greater.

Sulfonylureas will generate almost a basal release of insulin when the patient's fasting, and further stimulate insulin release after taking a meal.

It's hypothesized that stimulating the pancreas can wear it down faster and there are concerns that sulfonylureas may cause the pancreas to lose the ability to release insulin more quickly. Data from the UKPDS trial however showed that there was no difference in the rate of glucose control among people having taking sulfonylureas. Somewhat contradictory to that, a study came out saying that there was a correlation between sulfonylureas and decreased levels of C-peptide over time, compared with people not taking sulfonylureas. This data suggests that a longer duration of sulfonylurea use maybe associated with a decline in C-peptide and therefore, the ability to secrete insulin.

A more recent, clear trial, published in 2014 suggested that there are no differences in quality-adjusted life years, which includes time to insulin dependence between adding a sulfonylurea as a second agent or another newer medication as a second binding agent. So there's some conflicting information out there but what we do know is that using sulfonylurea as a second line agent no worse than any other medication to date as long as it fits in with the treatment and it's being tailored to the patient's needs.

These agents stimulate insulin release and can decrease A1C by about one to two percent. Meglitinides are basically shorter acting sulfonylureas. They are only taken right before a meal and since they're not always constantly stimulating the pancreas to make insulin, they lower A1C a little bit less at about 1.6 to 1.8 maximally. Since all these agents increase insulin, patients can expect weight gain. Any medications that increase insulin, including insulin itself, will cause weight gain because you're now able to utilize glucose for building storage.

Sulfonylureas have been around for a very long time. They were first developed in East Germany during World War II. Samples are smuggled out to West German pharmaceutical companies who tested and began making a first generation sulfonylurea chlorpropamides marketed as orinase. Other first generation agents are cycloheximide, chlorpropamide and carbutamide. That little tank was supposed to have rolled out a little while ago.

Second generation sulfonylureas such as glyburide and glipizide became available in the mid-1960s. These agents were more potent, more predictable and cause fewer side effects. Glimepiride was released as a third generation sulfonylurea to reduce the risk of hypoglycemia. Specifically, in theory, exercise induced hypoglycemia because it is associated with the K1 receptor much more rapidly than even the second generation sulfonylureas. All of the sulfonylureas lower A1c to a similar extent. Although there may be differences in the adverse effects or the risk of hypoglycemia, with the first generation agents having a greater risk because they had prolonged durations of action and are less predictable and they peaked more differently. You should never need to combine two different sulfonylureas. If the patient is on one sulfonylurea, that's all they're going to be needing.

This table shows the meglitinide dosing, and there are two meglitinides available, repaglinide and nateglinide. Again, these are dosed only before meals and have a shorter duration of action. As you can see here, they only last for about two to three hours.

So we're back to HS. He's still taking his albiglutide, 50 milligrams weekly, metformin, 2 grams twice a day and glyburide, 5 milligrams twice a day. After walking back from the local bar, his wife noted that he was acting funny. Well, it was more funny than usual. He was sweating and he had the shakes. He laid down, had a snack and felt better after a bit. But she's concerned about what happened. Well, odds are likely that he had a hypoglycemic event related to a couple of possible factors. There was some increased physical activity of him walking home. He possibly had some alcohol consumption at the bar and he's taking glyburide which could've enhanced the effects and lowered the blood sugar and caused his feelings of hypoglycemia. We really would need to know more such as when and what he ate to be certain of what's going on. But we do know that medications can cause hypoglycemia.

The risk is minimal with medication such as those on the left, especially when they're used alone. But when we combine them with sulfonylureas and insulin, the risk of hypoglycemia increases. The greatest risk of hypoglycemia is with regular and NPH insulin, due to their longer duration of action and the fact that they peak. Now, that's not to say they cannot be used safely. In fact, with some patients, the delay in prolonged peaks may be beneficial.

There are different categories of hypoglycemia. Basically, by the numbers, hypoglycemia is when the blood glucose is less than 70, but this is an arbitrary number. Some people may be fine when their blood glucose is less than 70, while someone else maybe feeling hypoglycemic at episodes with greater blood glucose levels.

Severe hypoglycemia is defined as when the patient needs the assistance of another person. This can be a medical emergency and life-threatening. Glucagon injections or glucose are the preferred treatments. Symptomatic hypoglycemia, what HS likely had, is when the patients have symptoms of hypoglycemia but they manage it themselves. A common recommendation is to use the 15/15 rule, which is to take 15 grams of glucose and recheck the blood sugar in 15 minutes to see if it's back to normal values.

Asymptomatic hypoglycemia occurs when the patient has no symptoms. This is sometimes referred to as hypoglycemia unawareness. It can lead to increased risk of severe hypoglycemia. There are several factors that can cause asymptomatic hypoglycemia, such as medications. Beta blockers for example can mask the jittery feelings that the patient may be used to. Having a long duration of diabetes or alcohol, less recognition of what's happening, and possibly less glucose response from the liver. It's a little bit more common in type 1 diabetes, especially where people are being treated very aggressively, and they're used to having low blood sugars. If a patient does have asymptomatic hypoglycemia, avoiding low blood sugars for a few weeks may help people regain their symptoms. And again, that's in cases where people are being treated aggressively.

We also have a category of nocturnal hypoglycemia, which happens at night, and the patient may not know about it but they'll wake up feeling tired, sweaty or like they had a terrible sleep. If patients report these symptoms, they should be instructed to wake up from their sleep in the middle of the night and check their blood sugar to find out what's going on, and then to correct the problem.

There is also something called pseudo hypoglycemia, which occurs when blood glucose levels appear to be normal or even high. People who have very high blood glucose levels for a prolonged time may get used to that level. Aggressive treatment or lowering the blood glucose too quickly may make them feel that they're hypoglycemic and they feel terrible. In this case, lowering the blood glucose more slowly and over time can help prevent this from happening.

Just like treating people with diabetes, managing hypoglycemia is an individualized process. The main goal is to find out and to correct the cause of hypoglycemia and determine any future risk. This may involve any number of changes including modification of the treatment plan or if hypoglycemia is chronic and worrisome to even raising the A1C target if warranted.

All right, our next group of drugs are the biguanides. There is only one. Metformin is the only drug in the biguanide class. The actual method of action for metformin is unknown, but is believed to reduce hepatic glucose production, decreased glucose absorption and unproven for sensitivity. This results in an A1C decrease of about 1% to 2% and some weight loss. Metformin can also lower triglyceride levels.

The most common side effect is GI upset which we come across as bloating, pain, gas, nausea and diarrhea. These effects are caused by direct stimulation of the GI tract. To reduce GI side effects, metformin should be taken with meals and doses increased slowly. On average, about 500 milligrams per week.

There are two formulations of metformin, the regular release and the extended release. The extended release was marketed to cause fewer side effects than the regular release metformin. But if one formulation is being tolerated, you don't want to recommend switching over to another formulation unless you have to, because there may be GI side effects when we do that switch. The body gets used to one formulation and switching them over can cause it to come back.

The maximum dose of metformin regular release is 2,500 milligrams, and the maximum dose of the XR formulation is 2,000 mg. After the regular release formulation was made available, newer studies show that max benefit from metformin was around 2,000 milligrams. So, the lower max dose of the XR was just based upon positive outcomes coming out from around 2,000 versus going any higher and both formulations are equally efficacious.

In addition to the GI upset, metformin can cause metallic taste in the mouth and decrease Vitamin B12 levels. Lactic acidosis is the most concerning potential side effect and this even delayed metformin from clinical trials due to previous experience with another biguanide called phenformin. Although metformin was discovered a long time ago, I think back in the '30s, phenformin was discovered in 1957 and marketed in 1958. It was effective but associated with approximately 64 cases of lactic acidosis per 100,000 patient years and in comparison, metformin may casually be associated with up to three cases.

Still, lactic acidosis is a serious condition and half of the cases is fatal. So in 1977, phenformin was pulled from the market. Because of that risk and the fear around Phenformin, the FDA was hesitant to release metformin, and included numerous contraindications that hopefully prevent any cases of lactic acidosis. Today, metformin is the most widely used medication for diabetes and numerous clinical trials have been performed with it. And many people also have been saying that you know, some of these earlier restrictions about lactic acidosis are not appropriate anymore. We know more about the medication, we know that it's safer.

Lactic acidosis is rare. The amino acid lactate is converted to glucose by the liver. Since metformin may block gluconeogenesis and therefore increase the concentrations of lactate, also called lactic acid, contraindications for metformin therapy are targeted to reduce the risk of developing lactic acidosis. Metformin is excreted, unchanged in the urine so severe renal function and conditions that can lead to poor renal functions such as congestive heart failure, hypoxia, surgery, may put the patient at risk of development of lactic acidosis.

The FDA recently updated the package inserts based on studies showing that metformin use is safe in mild to moderate renal impairment. New guidelines require monitoring the eGFR. Now this is different because in the past, the guidelines looked at a serum creatinine, and the levels for serum creatinine were greater than 1.5 in men or 1.4 in women. Now, they're saying that you need to look at the eGFR which is based upon in our system, the MDRD formulation. Metformin is contraindicated when the eGFR is less than 30. If the patient has an eGFR between 30 and 45, metformin should not be started. But if the patient is already taking it, you can continue the metformin, but continue it cautiously. The eGFR should be monitored annually unless you feel the patient is at risk of declining renal function. In which case, looking at it more often is warranted. Since metformin can cause acidosis, it's contraindicated in other cases of patients with acute or chronic metabolic acidosis including diabetic ketoacidosis.

You want to temporarily hold metformin during processes involving iodinated contrast media. Contrast media can insult the kidneys and potentially to acute renal failure. This insult or temporary damage done to the kidneys usually occurs about one to two days after the contrast media is administered. The recommendation is that you discontinue metformin on the day of contrast media. Metformin has a short half-life of about six hours. So, after about a day, only about 12% of the drug is still going to be remaining. So that's a very slow low amount for causing any problems. Continue to monitor serum

creatinine and you can restart metformin once it's returned to normal. Since lactate is cleared by the liver, caution should be used in people with liver dysfunction or those who use alcohol.

The next group of drugs are the thiazolidinediones and their use has gone up and down over the past 15 to 20 years. Rosiglitazone was released by GlaxoSmithKline in '99 and was bringing in $2.5 billion in 2006. In 2007, The New England Journal of Medicine published a meta-analysis that associated rosiglitazone with acute myocardial infarction. Sales dropped drastically, I think at around $10 million. And eventually, rosiglitazone was pulled from the European market. Between November 2011 and 2013, the FDA restricted the prescribing of rosiglitazone to certified doctors and the medication can only be dispensed from specialized mail-order pharmacies. As concerns over rosiglitazone induced myocardial infarction increased, sales dropped. Meanwhile sales for pioglitazone increased with $2.4 billion in 2008. In 2013, the FDA lifted the restriction after a study called the RECORD trial showed that there was not an increased risk of heart attack associated with rosiglitazone.

So the exact mechanism of these agents are not known but it's believed that they stimulate PPAR gamma and promote adipose tissue to convert from visceral to a more stable or subcutaneous adipose tissue. Visceral adipose tissue is highly lipolytic. It breaks down into free fatty acids and these free fatty acids can increase triglycerides and they can also promote insulin resistance. They also release a different kind of cytokines which may increase inflammation. TZDs can lower A1C by 1% to 2%, decrease triglycerides and because they increase utilization of insulin they also cause weight gain. Increases in LDL have been observed but this is believed to be a result of transitioning from a more atherosclerotic small dense LDL particle to a less atherogenic, big buoyant LDL.

The dosages of these agents are comparable in regards to their effects on A1C. They are listed there on the table, but many people recommend a max dose of pioglitazone of 30 milligrams and rosiglitazone of 8 milligrams. And you can go higher on these doses, but overall, there doesn't seem to be much benefit going to a higher dose over 30 or 8.

In addition to the risks on the previous slide, thiazolidinediones by reducing insulin resistance, may cause women who are anovulatory to stimulate ovulation and unexpected pregnancies have occurred after starting therapy, so this is something to think about when prescribing these medications. Top concern, TZDs can cause fluid retention through an unknown mechanism in the vasculature. This may unmask an underlying risk for developing heart failure resulting in symptoms and diagnosis of heart failure sooner. Patients who have heart failure should be monitored very closely if prescribed the thiazolidinediones because of the fluid increase. Bone fractures have been observed in both post-marketing surveillance and in recent clinical trials.

In general, the TZDs have been associated with various forms of cancer prevention. That's not to say that they treat cancer or prevent cancer, but there has been less incidence of cancer among some patients on TZDs compared to placebo in some clinical trials. But there's a new data that suggests that pioglitazone may increase the risk of bladder cancer. Again, there's conflicting results on this, but this is one of the recent studies published.

Another new study called the IRIS trial discovered benefits of pioglitazone therapy in preventing secondary strokes and heart attacks and people without diabetes who had a stroke. The study found that 28 strokes or heart attacks may be prevented for every 1,000 patients who take pioglitazone for up to five years. And the reason for this is there's an association linking insulin resistance and strokes. It has been identified that thiazolidinediones may offer some protection. So maybe at some day in the future, we see people being prescribed thiazolidinediones without diabetes but who had a stroke for this prevention.

The final class of drugs to discuss are the latest agents and are those that are designed the lower blood glucose, sodium-glucose co-transporter 2 inhibitors. There are already three of these that are approved by the FDA; canagliflozin, dapagliflozin and empagliflozin. These are oral agents and they're

taken once a day. It's been recommended that they not be used in patients with renal disease. Canagliflozin and empagliflozin should not be used if the eGFR is less than 45 and dapagliflozin should not be used if the eGFR is less than 60. It is also interesting because these medications are using eGFR as their guideline and that makes it much easier for us to figure out whether the patient is across that line or not because the eGFR is reported in our system. Oral medications continue to use the Cockcroft-Gault equation which must be calculated.

So, almost all of the glucose that reaches the kidneys gets reabsorbed by SGLT. Glucose is carried by capillaries to the kidneys where it is filtered by the nephrons. Most, 90% of the glucose gets reabsorbed in the proximal tubule by SGLT2. The 10% that isn't absorbed gets absorbed by SGLT1. If we block SGLT2 with an inhibitor, much of the glucose can pass through the nephron and be released in the urine thereby lowering blood glucose levels.

SGLT2 inhibitors lower A1C about at 1%. They also cause some modest weight reduction of 2 to 3 kilograms. There are also reports that they may lower the systolic blood pressure by 3 to 5 millimeters of mercury. They have a number of adverse risks including renal damage, genital mycotic infections, enteritis, polyuria, polydipsia, nausea, volume depletion and there can be increases in LDL by up to 5% although this significance is not known.

Post-marketing activities or findings have found that some people who have had bone fractures and fall risk increases with canagliflozin within the fall risk possibly related to orthostatic hypotension. Bladder cancer has been associated with dapagliflozin and arthralgia has occurred with empagliflozin. Another risk with these agents is for ketoacidosis, more commonly found on people with type 1 diabetes but it can occur in people with type 2 diabetes who are on SGLT2 inhibitors. The proposed mechanism by ketoacidosis with SGLT2 inhibitors is that when the glucose gets excreted in the urine, it could result in a normal type of blood glucose level if the patient has good control. Lower glucose results in less insulin release in pancreas. The body still requires energy since it isn't getting it from insulin and glucose entering the cells. So adipose tissue breaks down into free fatty acids, which gets oxidized to become ketones. Increased ketones results in acidosis. Ketoacidosis is a medical emergency and can be life- threatening. Patients should be instructed to immediately report any signs of ketoacidosis such as difficulty of breathing, nausea, vomiting, abdominal pain, confusion, unusual fatigue or sleepiness.

There are some additional possible benefits that may occur with SGLT2 inhibitors. Two studies suggest that these agents may reduce death from cardiovascular disease. However, in both studies, patients who are on an SGLT2 inhibitor also had lower A1C values than the placebo group. It is theorized that a combination of SGLT2 inhibitors and DPP-4 inhibitors maybe able to work together to help reduce kidney damage by lowering urine albumin excretion. However, clinical studies have not been performed to determine whether this is the case or not.

There's no one size fits all approach to managing the treatment for someone who has diabetes. All treatment plans must be individualized based on the person's wants and their needs. I just want to point out a few statements that came from the latest ADA standards of care; metformin remains the preferred initial medication for people who have type 2 diabetes. Adding a second treatment is recommended if the A1C is not controlled after max dose of a first drug for three months. They do not have a recommendation on what medication should be selected next. It really needs to be individualized to the patient.

As stated early on in the presentation, insulin is often a requirement for people with long standing diabetes. And I take this opportunity, just to let you know that a new glucose treatment algorithm is being developed by the Division of Diabetes Treatment and Prevention and will be made available under DDTP's website in the near future. The link to the algorithm is on the bottom of the slide, but also if you go to the DDTP website and look on the left-hand side, you can see a link to the treatment algorithms there under the clinical tools heading.

Anyway, just a few more minutes. So I'm going to run through these next slides really, really fast. So please forgive me if you don't catch all of this. You know, one of the most important things that talk about medications is that they aren't going to work if people aren't going to take them. And when we look at medication adherence across the country, if there's a 100 prescriptions written, 88 get filled in the pharmacy, 76 get taken and less than half get refilled after the prescription runs out.

So what's it look like in the Indian Health Service? Well, we have two quality measures in the CRS that take a high-level view on medication adherence. They are called the proportion of days covered and gaps in therapy. Proportion of days covered, illustrated with an image: if the brown arrow is 365 days in a year and the orange box, the yellow-orange boxes are the days that the patient has their medications. If we add up the number of days that they have their medications and it's greater than 80% or greater than 292 days, they're considered to be adherent to their medication.

Gaps in therapy looks at people who have 30 days between having their medication run out and getting their next fill of that medication. When we look at the results for diabetes, we could see in the yellowish color the proportion of days covered is below 50% meaning that over half of our patients are not taking their medications at least 292 days out of the year. And about 50% of people -- well, just over 50% of people go for more than 30 days without taking their medications. Now this isn't really telling us exactly what their adherence is. This is telling us whether they have their medication or not. So, of those 50% of patients who actually have their medications for that time period, we don't really know if they're taking them.

We have similar results with cardiovascular medications, beta-blockers, ACE-inhibitors and ARBs, calcium channel blockers and statins. And when we look at this information, these slides, it's data from 2015. If we look at the data from 2011 to 2015 and this is just looking at the statins, we can see that there really hasn't been much change over the years and the proportion of days covered between 2011 and 2015, less than half of patients have access to the medications throughout the entire time period.

So medications adherence is a real concern for us. We can address this in a number of different ways, but one is the SIMPLE approach; simplify the regimen, impart knowledge and education, modify patient beliefs, right communication and trust, leave the bias, and of course, evaluate adherence. Don't be afraid to ask people if they're taking their medicines, or if you don't think they are, don't be afraid to ask them why they aren't.

This is this just the way that I remember to take my medications. I was actually -- I take an allergy pill in the morning and eye drops at night, and you would think being a pharmacist, part of the health ed. program and a proponent for medication adherence that I'd be pretty good about taking my own medicines. Well, I'm not. And in fact, actually, I had to sit down and think with myself and say, "Okay, what do I need to do in order to take them?" And so, I have a clock in my bathroom that I look at whenever I go in there and usually, the first thing in the morning and last thing at night. And by associating my medicines with something that I do everyday, I see them and I now take them pretty regularly. I'm not advocating that everybody needs a Lego Stormtrooper alarm clock in their bathroom, but it is just to get the point that everybody has something that they do that help remind them to take their medications regularly.

There's a lot of places that you can go to, to get information about medication adherence. There's just two resources here. Script Your Future has a lot of patient-oriented tools, and the National Diabetes Education Program has a wealth of adherence information including clinical data, statistics, tools for patients, and tools for clinicians.