Advancements in Diabetes Seminar
Trends in Diabetes Medication Management

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Christopher Lamer:

Professionally, I started working at Cherokee Indian Hospital a number of years ago and went on to work with the patient education program, the Office of Information Technology and now I've been very privileged to be able to work with division of diabetes treatment and prevention. My talk today is on trends in diabetes medication management and I'm a pharmacist, but by no means an expert. If to air as human, I am a super human and often make mistakes. So please if I say something that you catch as incorrect or disagree, would you please bring it up. I assume, I don't want to give out any bad information and hopefully I won't.

So we can get started with the slides. There are the objectives. Just to jump right into it, diabetes is a progressive disease where the ability to secrete insulin diminishes over time. The first thing that goes is the ability to make enough insulin recover postprandial blood sugars. Next, there's a reduction in basal insulin release, and eventually the pancreas stops secreting insulin completely. As time goes on, so does the risk of diabetes complications. Now there's no set time frame for how fast this decline occurs. I have some years up there but they're just really estimations. It is really individualized and it will vary by patient. We try to slow this progression with various treatments and recommendations. The primary treatment is improved nutrition and increased physical activity, and it's important to know that this life style interventions are not one kind of things. They are a life-long change and should always be incorporated to the patient's treatment plan.

When lifestyle is not able to compensate for the failing pancreas, non-insulin medications can be initiated. But I mentioned, eventually the pancreas will no longer be able to secrete insulin, exogenous insulin or insulin shots are going to be required. Now this doesn't mean that insulin is only used as last line therapy. It's an effective treatment at any point after a diagnosis with diabetes, it can always be considered as part of the patient's treatment plan.

There have been many changes in diabetes management over the past ten years. If we look back to 2007, we used to focus on sugar, pressures and lipids and had very clear cut goals for A1c, blood pressure LDL, and if you were over 40, you received an aspirin. Research had

shown us that this approach is not practical or safe for any every patient. And if we look at A1c, hypoglycemia is a serious concern for people and it could lead to increased risk of morbidity, cardiovascular events and death. While most people should have a treatment target of less than seven, treatment goals have to be individualized per the patient.

Lower blood pressure targets in people with diabetes not demonstrate consistent improvements or cardio vascular risk reduction compared to targets of less than 140 over 90, but may carry an increased risk of side effects from adding on medications or of hypotension. The JNC 8 or Joint National Committee 8 of Hypertension Guidelines recommends that for blood pressure, we should treat every patient to goal blood pressure of less than 140 over 90 except for the elderly, in which case it's 150 over 90. There's still a lot of on-going debate but the American Heart Association, American College of Cardiology recommends that this focus on 10-year risk for cardiovascular disease prediction and prescribes statins were indicated rather than targeting LDLs less than a 100 and non-LDL less than 130 as a secondary target. And finally, aspirin is no longer indicated for people with diabetes based on age alone. Newer recommendations with a term of 10-year cardiovascular risk, while presence of risk factors prior to prescribing, this table here today gives some guidance on why we want to look at individualized targets for A1c.

Just a couple of examples, during pregnancy, there's a faster turnover of red blood cells. And the hemoglobin A1c maybe under represented. So, for this reason, A1c should be a secondary target with glucose being the primary and should ideally be less than 6.5% to reduce the risks of congenital abnormalities. In the early disease when somebody has just been diagnosed with pre-diabetes or diabetes and the patient engaged primarily in lifestyle management, maybe taking metformin, and can have a treatment target of about 6.5%.

As the disease progresses and you start to add medications on, then most people tend to have an A1c target of 7%. As we get older, now we could develop more chronic diseases. Complex adults have a target of less then 8% and very complex adults, those who have end-stage illness, end-stage heart failure, oxygen-dependent lung disease, or on dialysis or cancer, may have a target of less then 8.5% because the risk of going to low in these patients is worse than being a little on the higher side.

Treatment algorithms were pretty straight forward back in 2007 as well. Metformin was the first line medication. Sulfonylureas are effective and cheap, but they were always considered second line because they carry the risk of hypoglycemia and weight gain. And that if the patient did not want to go on insulin like most people do, the thiazolidinediones were third line therapy if you had them on formulary because of their higher cost.

Today, we have more medication options to help manage blood glucose for people with Type 2 Diabetes. All these medications provide more options but also greater complexity. Ten years ago, we could have a talk about diabetes in just under 30 minutes focusing on the medications, but now, to talk about diabetes medications in less than an hour is difficult thing to do.

Treatment algorithms like the one from 2007 don't fit very well for every patient. Decisions must be individualized based on the patient's age, how long they've had diabetes, how the patient reacts to certain medications, other co-morbid diseases they may have and other medications that they may be taking because of risks of drug interactions. But fortunately, we do have some guidance on what medications to choose.

The American Diabetes Association recommends a step one that we give metformin for most patients. Either alone or with another medication based upon the patient's A1c as first line therapy along with lifestyle management. If the patient's A1c is less than 9%, metformin and lifestyle therapy may help to bring the A1c down to goal alone, since the former low of A1c by the 1% to 2%. If the A1c is a little higher between 9% and 10%, they recommend starting metformin with a second agent, because it may be necessary to have two drugs to bring the A1c down enough to reach the target. And if the patient's A1c is greater than or equal to 10%, the patient is going to require insulin therapy with or without other medications so we get the blood glucose under control. Insulin should also be initiated if the patient has signs or symptoms of ketonuria or if the patient cannot take oral medications due to drug interactions or problems with the parallelizing of the medication.

Metformin has a really good safety profile and beneficial effects on lipids. Unlike insulin, metformin may reduce weight by a few kilograms. Because of it's mechanisms of action, decreasing hepatic glucose production, decreasing intestinal glucose absorption and increasing insulin sensitivity, metformin does not cause hypoglycemia when used alone.

There are some side effects associated with metformin use. It may cause taste disturbances such as a loss of taste or a metallic taste in the mouth of some people. Although reported in literature for a number of years, this has been the first year I think that the ADA noted that metformin may possibly interfere with the absorption of Vitamin B12 resulting in B12 deficiency after years of metformin therapy. There's no specific guidance on addressing this. So there's nothing to say that after 5 years you check a B12 level or anything, it's all sort of individualized. But monitoring the B12 level maybe performed in patients specially those who have anemia or peripheral neuropathy. Again, it appears to occur in some patients after many years of therapy between 5 and 10.

The most common side effect of metformin is GI upset. Bloating, pain, gas, nausea and diarrhea. These effects are cause by direct stimulation of the GI tract. To reduce the GI side effects, try to start metformin slowly with meals and increase the dose slowly over time. There are two formulations of metformin, a regular release and an extended release. The extended release was developed to in theory cause fewer GI side effects. However, if you have a patient who's taking one and it's been tolerated, it's not recommended to switch because if you do switch, there could, those GI side effects could come back.

Lactic acidosis occurred with an older biguanine called phenformin, which was pulled from the market in 1977. Because of the dangers observed with phenformin, the FDA was very hesitant

to study and release metformin. There are a number of contraindications and cautions added to the package insert to reduce the possibility of people developing lactic acidosis. These cautions have included severe renal dysfunction and conditions that can lead to poor renal functions such as congestive heart failure, hypoxia and surgery. The recommendations used to be that you stop metformin when serum creatinine was less than 1.5 in men or 1.4 in women, which is roughly an eGFR of around 60 mls per minute.

Based on the results of numerous studies demonstrating the safety of metformin in patients with reduced kidney function yet, they recently updated the package inserts. New guidelines require monitoring of the eGFR and discontinuing if the GFR is less than 30. Metformin should be started if the GFR is between 30 and 45, but if the patient is already taking it, it can be continued cautiously. eGFR should be monitored annually unless the patient is at risk of declining renal function, in which case more often than one.

These are the revised contraindications and cautions for metformin therapy. If contraindicated, in severe renal failure and acute or chronic metabolic acidosis such as DKA or diabetic ketoacidosis, you might temporarily hold metformin during procedures involving contrast media. Contrast media can insult the kidneys and lead to acute renal failure and this typically occurs about one to two days after administration. So metformin should be discontinued on the day of contrast media. Once the serum creatinine is returned to normal, after two days, metformin can be restarted. Since lactate is cleared by the liver, you only use with caution in people with who have liver dysfunction or those who use alcohol.

If your initial therapy, and this is initial therapy and an appropriate dose, doesn't achieve A1c targets after about three months. The American Diabetes Association recommends moving on to step two which is adding another agent. Second line treatment can consist of either insulin, sulfonylurea, thiazolidinedione, GLP-1 agonist, DPP-4 inhibitors or SGLT2 inhibitors. And the selection of agent is based on the patient's goals, their willingness to use injectable medications, the cost of the medications, side effects and the risk profile.

Some glucose lowering medications are not listed, such as the Alpha-glucosidase inhibitors, the glutenides, bile acid sequestrants, dopamine agonists, bromocriptine and amylinomimetics. These medications do lower blood glucose levels but do not seem to provide as much benefit to the majority of patients as those are listed on this table right here.

I'm going to spend the next few minutes going over the various medications, the classes of the medication themselves. The first are the sulfonylurea. They stimulate the pancreas to make it insulin. These agents require a functioning pancreas in order to work. If the pancreas cannot make insulin such as in a patient of a Type 1 Diabetes, these medications won't have any effect. If the pancreas is still functioning, even if not at 100%, the sulfonylurea will bind with the receptor on the potassium channel and stimulate the release of insulin. These drugs can decrease the A1c by about 1% to 2%, but since they do increase insulin, patients can expect to have some weight gain. There's also a risk of hypoglycemia especially with elderly people,

those who are very sensitive to therapy or when they're used in combination with other medications.

The sulfonylureas have been around for a really long time. They were first developed during World War II. These drugs were called the first generations sulfonylureas and include Tolazamide, Tolinase, Acetohexamide, Chlorpropamide and Carbutamide. They are not used too much these days because the second generation sulfonylureas such as Glyburide and Glipizide became available in the mid 60s. These drugs are more potent, they're more predictable, and they cause fewer side effects.

Glimepiride was released as a third generation sulfonylurea and it's claim to fame is it reduces the risk of exercise induced hypoglycemia. One of the differences with dosing of this agents, Glimepiride is it is dosed once daily, whereas, the Glyburide or Glipizide as your dose gets higher, you typically go to a twice a day dosing. Glipizide is the sulfonylurea that has been chosen to be on the IHS National Core Formulary. Glyburide which many sites have used in the past has two metabolites that are also active and stimulate insulin release. These metabolites may build up in people who have mild renal dysfunction. Therefore, Glyburide should be discontinued or used with caution in people who have a GFR of less than 60 mls per minute.

All the sulfonylureas lower A1c to a similar extent, although there may be differences in adverse effects or risk of hypoglycemia, with the first generations having the greater risk. And you should never need to combine two sulfonylureas together.

The next group of drugs are the thiazolidinediones. The exact mechanism of action of these drugs is not known, but it's believed that they stimulate PPARy activity and promote adipose tissue to convert from what they call a visceral to a more stable subcutaneous adipose tissue. Visceral adipose tissue is highly lipolytic and breaks down into free fatty acids which can increase triglycerides and promote insulin resistance. It also releases things called adipokines and cytokines which may increase inflammation.

The thiazolidinediones lower A1c by 1% to 2% and they also cause weight gain. They appear to have no effect on cardiovascular disease in patients with Type 2 Diabetes. However, in the recent study called, "The Irish Trial," Pioglitazones have shown some cardiovascular protection in people without diabetes and a history of stroke or TIA. Despite this finding, TZDs have not demonstrated consistent cardio protective results. So, important effects that you need to be aware of are that the thiazolidinediones may stimulate ovulation in woman who are previously anovulatory due to reduced insulin resistance. Because of this some unexpected pregnancies have occurred after starting therapy.

TZDs can also cause fluid retention for an unknown mechanism in the vasculature. This may unmask an underlying risk for developing heart failure, resulting in the symptoms and diagnosis of heart failure sooner than if not prescribed a TZD. Patients who have heart failure

should be monitored very closely. Bone fractures have been observed during post mortem surveillance in recent clinical trials. In general, the TZDs have been associated with various forms of cancer prevention. However, new data suggest that Pioglitazone may increase the risk of bladder cancer. But there are conflicting results. Some studies show that it does, some show that it doesn't, so the actual extent is not completely known. But I think the literature is weighing more on the side of the risk that it may be. Both Rosiglitazone and Pioglitazone had been associated with macular edema which is another important reason for regular eye exams especially when they are in need of medication. The dosages of thiazolidinediones are pretty comparable in regards to effects on A1c and Pioglitazone is a thiazolidinedione on the National Core Formulary.

The next group of drugs are the GLP-1 agonist or the Glucagon-like peptide-1 Agonist. GLP-1 is predominantly released from the intestines and causes the alpha cells of the pancreas to stop producing glucagon. They also stimulate the beta cells to increase insulin production. There are four GLP-Agonists on the market, exenatide which comes as a daily or weekly dose, liraglutide, albiglutide, and dulaglutide.

There is a GLP-1 Agonist with the brand name of Saxenda. Saxenda is liraglutide that's not indicated for the treatment of diabetes. Instead, this medication is marketed for weight loss and people who have a BMI greater than or equal to 30 or greater than or equal to 27 at least one weight related condition such as diabetes hypertension or dyslipidemia. About the only difference is between Saxenda and Victoza is that Saxenda can be dosed higher, up to 3 milligrams per day and Victoza has a maximum dose of 1.8 milligrams per day. None of the GLP-1 agonists are included on the IHS National Core Formulary.

These agents work by suppressing glucagon's secretion to lower blood glucose and slow gastric emptying. This combined effect can reduce A1c by about 1%, resulting in weight loss of about 4 kg. Although, early stages have not shown a cardiovascular effect with the GLP-1 Agonist, two recent studies shown some improvements in reducing cardiovascular end points. The leader trial showed a decrease in first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke with liraglutide. Similar results were demonstrated with another study usign a drug called Semaglutide, which is in phase 3 clinical trials.

GI side effects are the most common side effect that occurs with these agents and they often subside over time. Injecting the medication after a meal can help. All of the GLP-1 agonists are considered Pregnancy Category C and albiglutide should be discontinued within one month of a planned pregnancy. So, this is something to talk about with females and in bearing years. None of these agents have been evaluated during breastfeeding and should be aborted if possible. All of these agents are administered subcutaneously and are available as a pen. Dosing for each agent is listed on the table here.

Exenatide, the Byetta formulation, and liraglutide are administered daily, while Exenatide in the Bydureon formulation and the other agents are administered weekly. So, the weekly dose does bring up a good question about how to address missed doses.

So, here we have H.S. who's a middle-aged man with type 2 diabetes who is diagnosed just over six years ago. He's been taking albiglutide 50 milligrams every Mondays for about nine months. He calls you on Thursday and says, "Oh, I forgot to take my medication on Monday, and is it okay for me to take it now or should I just wait until next Monday?" Well, if you told H.S. to wait, don't worry, you didn't kill him. But the best answer is to tell him to go ahead and take it today and then continue taking it Monday on his normal schedule. Weekly doses present a new problem when people miss a dose. Taking an extra dose could result in a higher concentration, while missing a dose can drop the steady state concentration. For the GLP-1 medications that are dosed weekly, the rule is to take the dose if you remember it and if it was in within three days of the next dose. So, since H.S. isn't due for his next dose until Monday, three days prior would be Friday. So, H.S. should take his dose today and then again the next one on his regular scheduled Monday.

What about switching the day that you're taking your medication? Let's say you no longer like taking it on Monday, you want to take it on a different day. You can change the day as long as it's four days after the last dose. So, if you take a dose on Monday, you can switch your next dose to Friday, Saturday or Sunday. If you want to switch to Tuesday it will be a two-step process, you would switch to Friday, Saturday, Sunday and then your next dose would be, you would take it down to Tuesday.

GLP-1 is rapidly inactivated by dipeptidyl peptidase-4 or DPP-4 and that brings us to the next group of drugs called the DPP-4 inhibitors. The DPP-4 inhibitors block DPP-4 and help prolong the duration of natural GLP-1. Not the GLP-1 agonist, but naturally occurring GLP-1 which is often reduced in type 2 diabetes. These agents result in a small A1 decrease of about half of a percent. And there's no effect on weight. So, there is no weight loss but there's also no weight gain. Unlike the GLP-1 agonist, DPP-4 inhibitors rely on the body's ability to make GLP-1. However, the ability to take them by mouth instead of an injection makes them more enticing to some people.

Although it may seem that combining a GLP-1 agonist with the DPP-4 inhibitor may be a great combination, the combination to date has not shown improved outcomes and may further increase adverse effects. DPP-4 inhibitors are not recommended in combination with GLP-1 agonists to A1C lowering effects.

There are four agents on the market including sitagliptin, saxagliptin, alogliptin and linagliptin. Headache, nasopharyngitis and your upper respiratory tract infection are the most common side effects, so they are pretty mild. Most marketing reports however have indicated that there may be associated cases of pancreatitis. Arthralgia or joint pain has occurred in a number of people and can happen at anytime. There are a couple of cases where patients with

suspected arthralgia discontinued their DPP-4 inhibitors and felt better but had recurrence of the arthralgia after they restarted the DPP-4 inhibitors. And heptic failure has occurred with Alogliptin. These medications do appear to be safe during pregnancy but they are secreted in breast milk. The effects in breast milk are not known.

Saxagliptin is the DPP-4 inhibitor on the National IHS Core Formulary. It's dosed to 5 milligrams a day unless the patient has a GFR less than 50 mls per minute, or is taking medication that strongly inhibits cytochrome P450 enzymes such as ketoconazole. The FDA issued a warning that Saxagliptin and Alogliptin may increase the risk of developing heart failure. If you look at the literature, it says it's a 20% increased risk, but breaking it down it comes out to be that there are 27 patients out of a thousand who develop heart failure on placebo and 35 patients out of a thousand who develop heart failure on Saxagliptin. So, there is a statistically significant increase but it's not a dramatic increase.

Next group of drugs are the SGLT2 inhibitors. They are the newest class of drugs to lower glucose and they work in the kidney. Almost all the glucose that reaches the kidney gets reabsorbed by the sodium-glucose transport protein or SGLT. Glucose is carried by capillaries, the red color there, blood vessels to the kidney where it gets filtered by the nephron. Most, about 90% of the glucose gets reabsorbed in the proximal tubule and returned to the bloodstream. The 10% that isn't reabsorbed by SGLT2 gets reabsorbed 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. There are three sodium-glucose transport protein inhibitors or SGLT2 inhibitors approved by the FDA: canagliflozin, dapagliflozin and empagliflozin. And I'm sorry for my pause but I had to think about how to pronounce these drugs before I say them. There's actually a website that I found that tells you how to say drug names and kind of interesting. I had found out I had mispronounced a whole lot of drugs.

There are no SGLT2 inhibitors included on the National Core Formulary at this time. All three of these are oral agents and they can be taken once a day. They should not be used in patients with renal failure. Canagliflozin and empagliflozin should not be used if the GFR is less than 45, and dapagliflozin should not be used with if the eGFR is less than 60. SGLT2 inhibitors lower A1C by about 1% and may reduce weight by 2 to 3 kilograms. There are also reports that they lower the systolic blood pressure by about 3 to 5 millimeters of mercury.

They have a number of adverse effects, adverse risks including renal damage, genital mycotic infections and pruritus, polydipsia, polyuria. So, obviously, if it's making you pee up a lot more sugar, you're going to be peeing out a lot more water as well which makes you have to go to the bathroom more and also makes you more thirsty. And also in some cases we do volume depletion. And there have been a small increase in the number of lower extremity amputations in some of the canagliflozin studies. The cause of this is not known. Another risk is for ketoacidosis which is more commonly found on people with type 1 diabetes and elevated blood glucose. But they can occur in people with type 2 diabetes and control blood glucose for

taking the SGLT2 inhibitors. Patients should be instructed to immediately report any symptoms of difficulty breathing, nausea, vomiting, abdominal pain, confusion or unusual fatigue or sleepiness. Some post-marketing adverse events that have been found with these agents include bone fractures and fall risk with canagliflozin, bladder cancer with dapagliflozin, and ostealgia with empagliflozin.

Two studies, the EMPA-REG and CANVAS, suggest that these drugs may reduce death from cardiovascular disease. In both studies, patients were at risk or had cardiovascular disease and type 2 diabetes. Those who received an SGLT2 inhibitor had lower rates of cardiovascular death -- which is the slide over there to the left, lower all cause of mortality and lower rate of hospitalization for heart failure. I'm showing these two graphs to highlight that the benefits occurred independent of A1C lowering. The graph on the right shows that over time, the A1C lowering effect wasn't very different from the placebo group. So, you see that the A1C drop was a little bit lower like when the study started and over time, it kind of went back up. It wasn't that different from the placebo group. So, the cause of the cardiovascular benefit seems to be independent of the A1C. This independent effect that empagliflozin has, has lead to the FDA to provide a new indication for empagliflozin to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and cardiovascular disease.

The EMPA-REG study also showed the empagliflozin, they also lower the UACR and help protect the kidneys, which kidney failure is another complication of type 2 diabetes. The CANVAS study using canagliflozin showed reductions in the UACR specially those who had elevated microalbumin, however, these changes were not significant.

And then the last group of drugs to talk about, basal insulin, you know, there's been many changes with insulin over the past 10 years as well, as well as the integration of insulin in the management strategies for type 2 diabetes. The focus here is on basal insulin which suppresses overnight hepatic glucose production and lowers fasting blood glucose. Up until about the year 2000, NPH was the only available basal insulin on the market. Today, we have a number of longer acting insulins that lower blood glucose and A1C, with less incidents of hypoglycemia and weight gain.

Before getting into discussions about different types of insulin, I just want to take a moment to discuss what makes it different. Now, we have the onset of insulin, when the insulin peaks, the duration of action and the concentration. In the past, almost all insulins were U-100. Today, there are U-100, U-200, U-300 and U-500 insulins. Increased concentration means more units of insulin are contained in each millimeter. In the U-100 vile, there are 100 units in each milliliter. In the U-200, there is twice as much, 200. U-300 contains 300, and U-500 contains 500 units in one milliliter. So, if a patient receives 0.5 milliliters of a U-100 insulin, which is 50 units and you withdraw 0.5 milliliters from U-500 insulin, you just gave them 250 units of insulin, 200 more than they are supposed to get.

So, why are there these different concentrations of insulin? Well, there's a number of purposes for the increased concentrations. You can give a larger dose with one injection versus having to give two or more injections, you have the ability to store more insulin in insulin pins making it more convenient for patients. And this increased concentration has been shown to extend the duration of action of some insulin.

Now, getting into the insulins, NPH has an average duration of action ranging from 12 to 16 hours. Therefore it can requires twice daily dosing to provide full basal insulin coverage, it peaks from between 4 to 12 hours after the dosage is administered. This could result in low blood sugar levels during peak times. Although NPH doesn't mimic natural basal insulin, it may be a reasonable choice among patients who have insulin resistance or may benefit by its peak and duration. NPH still remains a commonly prescribed insulin based on its lower cost and the familiarity of clinicians having using it. Long-acting insulins can often be injected once daily as lower fasting glucose levels with lowers risks of hypoglycemia and less weight gain at NPH level. There are two long-acting insulin products: Glargine which was FDA approved in 2000 and Detemir. Both agents can last 24 hours although sometimes, especially at lower doses, they may not and they may need to be taken twice a day. Newer ultra-long-acting insulin products provide steady insulin levels over 24 or more hours. Insulin Glargine is a concentrated version of the long acting insulin Glargine and Degludec is a new insulin. Whoops I was behind there.

Glargine U300 is three times as concentrated as Glargine. After injection, it is a slowly released providing a very long duration of action up to about 36 hours. This long duration of action assures that there is a consistent basal release of insulin without a peak so there's less risk of hyperglycemia and weight gain is compared to NPH or long-acting insulin. Glargine U300 is only available as a pen and it cannot be mixed with other insulins.

Degludec insulin has a very long half-life and duration of action at about just 46 hours. There's similar efficacy when the doses are measured between 8 and 40 hours. So, if a patient has taken a dose in the morning, they can take it one day at night and there will be no effect on their basal insulin levels. Degludec is only available as a pen and it also cannot be mixed with other insulins.

All right, so bringing you all back to Step 2; that was a quick review of some of the commonly used medications for Type 2 diabetes. In addition to knowing how the medications work alone, you also need to consider how they may work with other medications that the patient is taking. All of these agents are good add-ons to metformin therapy. Some such as the SGLT2 inhibitors may find increased synergy with metformin based upon their mechanism of actions. Others may have an added effect on the A1C lowering.

Although we know how medications were effective with majority of people based on clinical trial data, there are still many factors that affect the medication's effectiveness, poverty, food insecurity, chronic stress, availability of medications and resources, vis-à-vis side effects and

tolerability, many of these which are out of our control as clinicians. But it's still important to take the time and listen to patients to help them find the medication that may best fit their lifestyle and need.

Then this brings us to Step 3, which is adding on another agent if the A1C is not controlled after three months of therapy on a treatment level base of medication. But, before adding medication, it's always important to ask the patient if they're taking it regularly, because drugs don't work if people don't take them.

We'll talk a little bit about medication adherence now. The data for the nation shows us that people do not take their medications as prescribed. If we look at the hundred prescriptions for chronic medications, only 88 get filled at the pharmacy. Of those, 76 get taken by the patient and of those, less than half, pick up a refill and continue the therapy. So, what's the data like in the Indian Health Service? While we have two adherence-shares related measures and I don't want to get into the details of it because they're kind of confusing. The first one is called proportion of coverage and it looks at the number of days the patient has their medications, not necessarily when they're taking them, but when they have them in their possession.

In this example, the blue box shows the base the patient has the medication and the red part of the arrow shows the days where the patient did have the medications. The total days must be greater than 292 to count as the patient having good medication adherence. So, in talking about good medication adherence, we're talking about patients taking their medications five days out of the week at least. So, that's still not great, but that's what the measure looks at.

The second measure is called the gap-in therapy and it looks at people who go from 30 days or more between the time they run out of their medications until the time they get the next prescription filled. Here, we can look at the data from 2015. The proportion of days covered in blue is less than 50%. We want that number to be higher. This is telling us that a large number of our patients who were prescribed these medications don't have enough of it at home to take it daily for most days. Again, this doesn't measure actual adherence. We don't know how many people are actually taking the medication, but out of 50% who do have the medication, we know that probably there's a number of people who don't take it. Likewise, the gap-in therapy is just over 50%, more than half of the patients prescribed with diabetes medications, go 30 or more days between running out and getting a new prescription.

Blood pressure medication shows similar results. And here, the slide shows adherence of statin medications. This is looking at the proportion of days covered over the past couple of years from 2011 to 2015 and we can see that this information hasn't really changed much. The proportion of days covered remains under 50% and the gaps-in therapy remain just around just 50%.

These measures have been reviewed by IHS Sites, by pharmacists across IHS and other workgroups, and unfortunately they appear to be accurate. We do continue to test and

evaluate them and we're looking for ways to improve medication adherence. There are no magic bullets for addressing medication adherence, but the first step is to be aware and consider it in every patient. Don't be afraid to ask about adherence and take up simple approach to improving it, and you can see some of the things listed here on how to improve medication adherence, but I won't get into them today.

Moving on to Step 4 and we've reached that point where the patient is no longer secreting insulin and oral diabetes medications or oral and injectable medications just don't seem to be doing the trick anymore, we need to move on to the addition of Bolus and Basal insulin. The addition of bolus insulin and basal that started already may be required to cover fasting and meal time glucose.

When patients are beginning insulin therapy with basal insulin, we generally recommend that you continue with all the other oral medications. But what do you do when the patient begins using basal and bolus insulin therapy? Should you continue all the medications or stop them? There are no strict rules on what should be done and there have been few studies that evaluate the benefits of continuing or discontinuing medications. Metformin is generally recommended to be continued because it has many, many beneficial effects.

Sulfonylureas and meglutinides work to increase insulin production from the pancreas. If you know the pancreas has gone kaput and it's no longer producing insulin and you're getting insulin, then there's really not a need to have the sulfonylureas around, so these agents should just be discontinued if not needed.

Thiazolidinedione have been used with and added to insulin therapy to reduce insulin resistance, and in some studies, the Thiazolidinedione have reduced the amount of insulin a person needs to achieve their glycemic targets. On the other side, the combination of insulin and thiazolidinedione may increase the risk of edema and weight gain. So, these drugs should be used with caution when the benefits outweigh the risks of the side effects.

Some of the newer agents such as the SGLT2 inhibitors, DPP4 inhibitors and GLP1 agonists may be used with insulin and may contribute to positive health outcomes. But the impact of the combination with insulin especially over the long term is less clear.

The Division of Diabetes Treatment and Prevention has created a number of algorithms that help manage diabetes. They're not in-depth guides, but they're meant to be at a glance cards at the point of care. The left side specifically contains clinical practice recommendations and the right side has drug information for dosing and monitoring. You can print and hold this card and it fits nicely into a lab coat. And one that's missing right now is the glucose card and we're currently in -- the Division of Diabetes Treatment and Prevention is, currently in the process of updating that card in hopes to have it available in the very near future.

So, just to recap the trends, I hope that you got something useful from my presentation today. I focused on the medications used to treat Type 2 diabetes, but it's very important to remember that our objectives in addition to providing excellent clinical care, are also to provide compassion, understanding, support and to listen to our patients to know how to better serve them. To learn more about living with Type 2 diabetes from a patient perspective, I strongly recommend that you read a copy of the book "Using Our Wit and Wisdom to Live Well With Diabetes" by Barbara Mora. It provides a personal perspective while living with diabetes that you just can't get from a text book or a journal article. And with that, I'm going to end my presentation and am happy to take any questions that anybody may have or any clarifications that may be needed.

Jan Frederick:

Thank you Chris. For our participants, if you have questions, now is your chance to type those into the chat. While you're doing that, I'm going to invite Dr. Ann Bullock, the Director of the Division of Diabetes to add any additional remarks that she would like to, Dr. Bullock?

Dr. Bullock:

Thanks Jan. Thanks Dr. Lamer for an excellent presentation, wonderful and fast, succinct tour through the major drug classes for glucose lowering and associated issues. So thank you very much for that. As Chris was making clear, none of those recommendations relate to pregnancy and women who are or could become pregnant. It's just in general for diabetes care. Also there are FDA restrictions on the use of medications for children as well. So this is for your general, adult patients with diabetes.