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Pharmacologic Management of Type 2 Diabetes Mellitus: Part 2

*This two-part series of articles will address pharmacological agents, except insulin, used to manage type 2 diabetes mellitus. Part 1 covered sodium glucose co-transporter-2 inhibitors, incretin-based therapies, amylin analog, and dopamine receptor agonists. Part 2 will focus on biguanides, thiazolidinediones, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, and bile acid resins, as well as the authors' treatment recommendations. Appendix A (*http://bit.ly/2eyB4Px*) is a comprehensive table of the effectiveness and costs of various combination therapies.*

Biguanides (Metformin)

Overview

Biguanides are recommended as first-line anti-hyperglycemic oral agents for type 2 diabetes. Metformin, the only biguanide currently available in the United States, improves glucose tolerance and lowers both basal and postprandial plasma glucose.[1] Metformin does not increase body weight nor induce hypoglycemia. Long-term studies have shown weight loss, making it the recommended treatment in prediabetes along with lifestyle intervention.[2,3]

Mechanism of Action

Insulin levels remain unchanged with metformin treatment. It activates the enzyme AMP-activated protein kinase (AMPK) and reduces hepatic glucose production.[4] Although the complete mechanism of action has yet to be elucidated, metformin decreases hepatic gluconeogenesis, decreases intestinal glucose absorption, and increases peripheral glucose uptake and utilization by improving insulin sensitivity.[1] Fatty-acid oxidation is decreased by 10-20% and glucose oxidation is slightly increased.[1] A 25-30% decrease in fasting plasma glucose usually is seen with metformin treatment.[1] Additional benefits may be seen in the lipid profile because of decreases in plasma VLDL triglycerides.[1]

In adults, a dose between 1,500 mg and 2,000 mg per day shows clinically significant responses.[5] However, lower doses, such as 500 mg once daily, may be beneficial on initiation to minimize gastrointestinal symptoms such as nausea and diarrhea.[5] Metformin can be increased by 500 mg weekly to max dose of 1,000 mg twice daily (2,000 mg per day). Although the maximum daily dose is 2,550 mg, there is little benefit at doses greater than 2,000 mg.[2] Children and adolescents 10 years

EXECUTIVE SUMMARY

- The pharmaceutical armamentarium for the treatment of type 2 diabetes mellitus has expanded in recent years, and some agents were addressed in Part 1 of this series.
- Metformin is the first-line drug in the treatment of diabetes, as it does not induce hypoglycemia, and long-term studies have shown weight loss.
- Thiazolidinediones increase insulin sensitivity by decreasing hepatic glucose production and increasing glucose utilization at the adipose tissue and skeletal muscle.
- Sulfonylureas stimulate pancreatic islet cells to increase insulin secretion. They are inexpensive and efficacious.
- Meglitinides work similarly to sulfonylureas; however, their effect is glucose dependent and decreases at low glucose concentrations.
- Alpha-glucosidase inhibitors delay the absorption of glucose in the small intestine, but more than 10% of individuals will develop gastrointestinal side effects.
- Bile acid resins have a modest effect, are not recommended for use as monotherapy, and have high frequency of gastrointestinal side effects.

of age or older may be treated with 500 mg twice daily.[6] For adults, extended-release preparations are available and the same parameters should be used for a maximum dose of 2,000 mg per day. A decrease in A1c of about 1% can be expected.[7] Metformin commonly is used with secretagogues, thiazolidinediones, or insulin.[2]

Contraindications and Warnings

Metformin carries a Black Box warning for lactic acidosis.[5] Another biguanide, phenformin, was withdrawn from the U.S. market in 1977 because of the potential development of lactic acidosis.[1] However, the incidence of lactic acidosis in patients treated with metformin is essentially the same as the background incidence in patients with diabetes (3-10 per 100,000 person years).[8] Chronic kidney disease (CKD) may potentiate lactic acidosis since metformin is renally excreted. A recent systematic review showed that metformin treatment may be safe in patients with mild-to-moderate CKD.[8]

Table 1 demonstrates the updated recommendations for metformin use in renal impairment. In the 2016 Standards of Medical Care in Diabetes, the American Diabetes Association (ADA) recommended that metformin may be safe down to a GFR of 45 mL/min/1.73 m^2.[9] Excessive alcohol intake also can increase the risk for lactic acidosis.[5] Metformin should be withheld before radiographic intravascular contrast administration in patients with a GFR between 30 and 60 mL/min/1.73 m^2 and may be restarted after 48 hours if renal function is stable.[1] In the presence of any condition associated with hypoxemia, dehydration, or sepsis, metformin also should be withheld.[1] Earlier this year, the FDA announced that, after further review of the available data, metformin is safe to use even in renal disease including Stage 3 CKD. It still is not recommended for people with Stage 4 or 5 CKD.

Metformin is pregnancy category B.[5] It was not teratogenic in animals at up to six times the recommended human dose.[5] Although metformin crosses the placenta and has been found in breast milk, several observational studies and randomized trials have shown no adverse effects of its use during pregnancy.[10]

Key Studies/Trials

The Diabetes Prevention Program (DPP) research group found lifestyle intervention and metformin both were effective in decreasing the incidence of diabetes in people with prediabetes.[11] The ADA currently recommends both lifestyle intervention and metformin for the treatment of prediabetes.[9] In addition, the DPP research group has shown metformin is safe, well-tolerated, and still effective in a cohort after 10 years of treatment. Weight loss also has been observed and maintained in patients after 10 years of treatment.[3]

The UK Prospective Diabetes Study (UKPDS) found a 33% relative reduction in the risk of myocardial infarction and a 27% relative reduction of death from any cause in patients treated with metformin, even after they returned to traditional care.[12] Researchers also found treatment with metformin decreased microvascular disease.[12]

The cost is approximately $4 for 60 tablets.[13]

Practical Considerations

Metformin has significant gastrointestinal side effects, including nausea, dyspepsia, and diarrhea. These side effects can be reduced with a slow titration of the medication. This can be accomplished by starting metformin 500 mg once daily at the evening meal and maintaining that dose until side effects are no longer noticeable. Then the dose is increased to 500 mg twice daily during the morning and evening meal. This dose in maintained again until there are no noticeable side effects. The next dose is 500 mg in the morning and 1,000 mg in the evening again at meals until no side effects are noted, and then the dose is increased to 1,000 mg twice daily with meals. Alternatively, switching to the extended-release formulation can mitigate the gastrointestinal side effects if slow titration of the regular formulation of metformin is unsuccessful.

There is no additional efficacy benefit by raising the dose to 2,550 mg, but it may help a bit

Table 1. Updated Metformin Recommendations in Renal Impairment

- Obtain eGFR before initiating metformin and annually. Consider more frequent monitoring in those at higher risk for renal impairment (e.g., elderly).
- Metformin is contraindicated in patients with eGFR < 30 mL/min/1.73 m^2. If patients are taking metformin and eGFR falls below 30 mL/min/1.73 m^2, metformin should be discontinued.
- Starting metformin in patients with an eGFR between 30-44 mL/min/1.73 m^2 is not recommended. For individuals taking metformin, they may continue to take metformin while in this range.
- Hold metformin at time of or before iodinated contrast procedure if eGFR is 30-60 mL/min/1.73 m^2. Recheck eGFR 48 hours after procedure and restart if renal function is stable.

more with weight loss. If the physician would like to get to this dose, the titration schedule would use 850 mg tablets. Start with one tablet daily at the patient's biggest meal until no side effects are noted. Then the dose can be increased to 850 mg twice daily at meals and finally, when tolerated, to 850 mg three times daily.

Despite a slow titration regimen, about 18% of patients will not tolerate metformin. One option for these patients is to use liquid metformin (sold as Riomet in the United States). The suspension is 500 mg/5 mL and doses can start as low as one-fourth teaspoon daily, which is about 125 mg/dose. Metformin can be titrated up as each dose is tolerated.

It is well established that the use of metformin should continue throughout the duration of diabetes. Much of this is related to its non-glycemic benefits, including reduction in overall mortality in those who are overweight and obese. The timing of metformin initiation is also very important. *Brown et al also showed that even a three- to six-month delay in starting metformin after the diagnosis of type 2 diabetes (while many patients may be attempting therapeutic lifestyle changes) can substantially reduce the efficacy and durability of metformin therapy.*[14]

Thiazolidinediones

Overview

Rosiglitazone (Avandia) and pioglitazone are the two thiazolidinediones (TZDs) currently available in the United States. Taken orally, TZDs can be used as monotherapy or as an adjunct to other medications. From November 2011 until November 2013, the FDA required Avandia to be prescribed by certified physicians and to be purchased through a specified mail-order pharmacy because of potential for cardiotoxicity.[15] However, in November 2013, the FDA lifted these restrictions after reviewing results from the 2009 Rosiglitazone Evaluated for Cardiovascular Outcomes in type 2 Diabetes (RECORD) trial.[16] The use of this medication is extremely limited. TZDs typically reduce HbA1c by 1.0-1.5%. These agents are the most potent insulin sensitizers and provide a durable therapeutic effect. Pioglitazone has not had any of the above restrictions.

Mechanism of Action

TZDs increase insulin sensitivity by decreasing hepatic glucose production and increasing glucose utilization at the adipose tissue and skeletal muscle through activation of peroxisome proliferator-activated receptor-gamma (PPAR-gamma) on these tissues.[17,18]

Key Studies/Trials

Prior to 2007, TZDs were used widely for type 2 diabetes. This changed in 2007 when a meta-analysis associated rosiglitazone with a 43% increased risk of myocardial infarction ($P = 0.03$) as well as an increase in death from cardiovascular causes ($P = 0.06$).[19] These results prompted the FDA to further evaluate TZDs' safety and set the precedent that all new diabetes medications undergo cardiovascular safety studies.

In 2009, the RECORD trial confirmed an increased risk of heart failure and small bone fractures in women.[16] However, data were inconclusive regarding the effect on myocardial infarction and indicated it does not increase the overall cardiovascular morbidity or mortality compared to other anti-diabetic medications. A 2016 study demonstrated a lower risk of stroke or myocardial infarction in patients who received pioglitazone vs. placebo.

TZDs have been studied for non-alcoholic fatty liver disease in individuals both with and without diabetes. Both pioglitazone[20] and rosiglitazone[21] reduced hepatic steatosis compared to placebo. One study showed a reduction in the progression to fibrosis.[20] TZDs have hypoglycemia rates comparable to placebo.[17,18]

A 2015 study determined that pioglitazone was not associated with a statistically significant increase in bladder cancer.[22] However, the study's authors concluded prostate and pancreatic cancer risks associated with pioglitazone warranted further investigation to determine causality or due to chance. There continue to be conflicting results regarding the association of pioglitazone with bladder cancer.

Safety Concerns

Common Side Effects. Table 2 lists the common side effects that occur in more than 5% of patients taking TZDs.[17,18] Additional

potential side effects include urinary bladder tumors, changes in ovulation, and bone fractures. Pioglitazone should not be used in patients with active or prior history of bladder cancer.[17] Five-year interim results of a 10-year observational trial resulted in an increase in relative risk from three cases in 10,000 patients to 10 cases in 10,000 patients taking pioglitazone.[17]

In women, bone fracture incidence increased from 2.5% for placebo to 5.1% for pioglitazone.[17] This difference begins within one year of starting pioglitazone. The majority of bone fractures were non-vertebral fractures. The increased risk of fracture was not found in men taking pioglitazone.

Both pioglitazone and rosiglitazone are associated with ovulation in previously anovulatory premenopausal women.[17,18] When taking TZDs, perimenopausal women should be counseled about the increased risk of pregnancy and use of contraception. Unlike metformin, which can improve fertility and pregnancy outcomes, TZDs are category C in pregnancy and may lead to worse fetal outcomes. Rates of hypoglycemia are low with TZDs.

Renal/Hepatic Dose Recommendations. There is no need for renal dosing, although consideration should be given regarding the impact of fluid retention on renal perfusion.[17,18]

Boxed Warnings. This class of medications should not be prescribed for patients with symptomatic heart failure or established New York Heart Association (NYHA) Class III or IV heart failure.[17,18] Upon initiation of this class, patients should be monitored for heart failure signs and symptoms, such as rapid weight gain, edema, or dyspnea.[17,18] If heart failure develops, this class should be discontinued or reduced, and the heart failure should be treated per standard of care.

Table 2. Comparison of Pioglitazone and Rosiglitazone[17,18]

	Pioglitazone[17]	Rosiglitazone[18]
Boxed Warning	• Symptomatic heart failure • Heart Failure NYHA Class III or IV • Monitor for signs of developing heart failure after initiation of medication	
Common Side Effects (> 5% of patients)	• Upper respiratory tract infection • Headache • Sinusitis • Myalgia • Pharyngitis	• Upper respiratory tract infection • Headache • Injury/arthralgia
Warnings and Precautions	• Can worsen congestive heart failure • Hypoglycemia • Urinary bladder tumors • Edema • Fractures • Macular edema • Ovulation	• Fluid retention • Congestive heart failure • Dose-related edema • Weight gain • Anemia • Macular edema • Bone fractures
Strengths	15, 30, 45 mg	2, 4, 8 mg
Mean A1c Reduction (%)*	15 mg: -0.3 30 mg: -0.3 45 mg: -0.9	4 mg once daily: -0.8 2 mg twice daily: -0.9 8 mg once daily: -1.1 4 mg twice daily: -1.5
Mean Fasting Serum Glucose Reduction (mg/dL)*	15 mg: -30 30 mg: -32 45 mg: -56	4 mg once daily: -25 2 mg twice daily: -35 8 mg once daily: -42 4 mg twice daily: -55
Dosing	Limit initial dose to 15 mg in patients with NYHA Class I or II heart failure. Titrate up increments of 15 mg to a maximum of 45 mg once daily.	Initiate at 4 mg, titrate up to 8 mg. Also comes in 2 mg tablets.
Renal Impairment Adjustments	None	Discontinue if GFR < 45. May take up to 25 mg with GFR to 45.
Hepatic Impairment Adjustments	Check liver enzymes at baseline. Avoid in patients with active clinical liver disease. No hepatic dosing adjustments.	Check liver enzymes at baseline. Avoid in patients with active clinical liver disease (ALT >2.5 times upper limit of normal at start of therapy). No hepatic dosing adjustments.
Pregnancy Considerations	C	

Monitoring. Baseline liver testing, including serum alanine aminotransferase, aspartate aminotransferases, alkaline phosphatase, and total bilirubin, should occur. If abnormal, the manufacturers recommend treating the probable cause if possible and starting this class with caution. Monitoring liver transaminase is not recommended in patients without liver disease.

Medications in this class also cause a decrease in hemoglobin and hematocrit,[17,18] which may be related to increase in plasma volume associated with these medications.

The cost is approximately $20 to $100 for 30 tablets.[13]

Practical Implications

Despite widespread use in the past, prescriptions for pioglitazone and rosiglitazone have decreased substantially since the 2007 safety report. Even with the reversal of the initial concerns, use of these medications has been limited. These agents have significant warnings and contraindications that should be discussed with patients. Pioglitazone reduces triglycerides up to 40% and has been shown to reduce secondary stroke. However, they are potent insulin sensitizers and typically have a more durable effect than most other classes. Since so many type 2 diabetes patients have fatty liver disease, the effect of pioglitazone on the transaminases and slowing the progression to hepatic fibrosis are of benefit. Finally, for patients who need increasing doses of insulin, the use of a TZD may improve insulin sensitivity and allow patients to need less insulin.

Sulfonylureas

Sulfonylureas stimulate pancreatic islet cells to increase insulin secretion.[23] Since this effect depends on functioning beta cells, these medications are only used in type 2 diabetes. The main physiologic feature of sulfonylureas is that they stimulate glucose-independent insulin secretion and work maximally, regardless of the starting glucose. Although they can have good potency, this is coupled with an increase in hypoglycemia.

Three medications — glipizide, glyburide, and glimepiride — each with differing pharmacokinetics, make up the second generation of this class. Generally, sulfonylureas are safe, well-tolerated medications, with hypoglycemia being the dose-limiting side effect.

In the 1950s, tolbutamide was marketed as the first sulfonylurea. In the 1980s and 1990s, a second generation of more potent sulfonylureas, which include glipizide, glyburide and glimepiride, were released.[24] These drugs are 100 times more potent than tolbutamide on a molar basis,[25] and have a shorter half-life, which can reduce hypoglycemia rates.

Sulfonylureas are believed to cause a depolarization of the membrane of pancreatic cells by binding to ATP-sensitive potassium channel receptors.[25] The depolarization causes calcium influx, which induces insulin secretion.[25] Over time, extrapancreatic effects, such as reduction of basal hepatic glucose production and an enhanced peripheral sensitivity to insulin, also are seen.[25] Glipizide improves plasma glucose regulation and also reduces plasma concentrations of very low-density lipoproteins, triglycerides, and low-density lipoproteins. Glipizide and glyburide have mild diuretic effects but do not change the uric acid concentration.[25,26]

Second-generation sulfonylureas are administered orally then distribute within the extracellular fluid highly bound to protein.[25] Substantially metabolized in the liver and excreted in the urine and feces, the duration of action is between 12-24 hours depending on the agent.[25,26]

Glipizide is the most common sulfonylurea used as adjunctive therapy to metformin in type 2 diabetes.[27] Onset of action is 90 minutes, with a maximum dose effect at 2-3 hours.[25] Glipizide generally is well-tolerated, with the most limiting side effect of hypoglycemia. A 1-2% reduction in A1c can be expected. It is dosed once daily with a starting dose of 5 mg and adjustments in increments of 2.5-5 mg after several days if needed.[25] Dosages > 10 mg/day produce little additional benefit and may reduce beta-cell function.[25] Extended-release preparations are available. Glipizide can be administered safely in place of or in addition to insulin. If a patient is taking less than 20 units of insulin, insulin may be stopped and glipizide started. For patients taking more than 20 units of insulin, insulin units should be reduced by 50% when adding a typical starting dose of glipizide.[25] Elderly patients should be started at a lower dose and monitored closely for hypoglycemia.[25] Safety and efficacy have not been established for patients younger than 18 years of age.[25]

Unlike other second-generation sulfonylureas, glyburide may be used as an alternative to insulin in gestational-onset diabetes after 11 weeks of gestation (post-organogenesis).[26] Sulfonylureas are excreted in breast milk, so discontinuation of glyburide in breastfeeding mothers is recommended.[26]

Cardiovascular risks with sulfonylureas are controversial. The UKPDS found intensive therapy with sulfonylureas does not increase the risk of myocardial infarction or diabetes-related death when compared to conventional therapy.[28] However, the University Group Diabetes Program found increases in cardiovascular mortality with sulfonylurea treatment vs. dietary management alone or dietary management and insulin treatment.[29] The small sample size of this study has been criticized but remains the basis for a manufacturer's warning.[23,29]

The cost is approximately $10 to $20 for 60 tablets.[13]

Practical Implications

Sulfonylureas are inexpensive and efficacious. Prior to the advent of medications that provided glucose-dependent insulin secretion (incretin-based treatments, DPP-4I, and GLP-1RA), sulfonylureas were recommended as second-line treatment for diabetes, and they still are preferred as second-line on many formularies. However, high rates of hypoglycemia and weight gain have made them less desirable by major medical diabetes groups and many patients. Sulfonylureas require functional beta cells to work, thus making this class less desirable later in the disease. *Finally, the ADA has recommended that glyburide no longer be used in the treatment of type 2 diabetes because of the increased risk of side effects and hypoglycemia compared to other generic options in this class.*

Meglitinides

Overview

Meglitinides are a class of oral hypoglycemic medications that effectively lower postprandial glucose. This class contains two medications, nateglinide and repaglinide, which lower A1c levels by 1.6-1.9%.[30] They can be used in combination with metformin or thiazolidinediones.[30,31] Meglitinides work similarly to sulfonylureas; however, the effect of these medications is glucose dependent and decreases at low glucose concentrations.[24]

Repaglinide binds to a site on the beta cells of the pancreas and closes ATP-dependent potassium channels. Like sulfonylureas, meglitinides are not effective without functioning beta cells.[30] Repaglinide has a rapid onset, with maximum effect at one hour and a half-life of one hour. The initial dose is 0.5-2 mg preprandially up to four times per day. Initial dose is A1c dependent.[32]

Nateglinide works similarly to repaglinide but has a higher specificity for potassium channels of the beta cells of the pancreas vs. potassium channels in the vasculature.[31] There is some evidence of earlier peaking insulin levels with nateglinide than with repaglinide.[31]

Meglitinides have a category C rating in pregnancy. Since no studies have been done in pediatric patients, they are not recommended for use in children.[30-32]

The cost is approximately $30 to $50 for 90 tablets.[13]

Practical Implications

This class of medications still has glucose-independent insulin secretion, which increases the risk of hypoglycemia. However, the short half-life makes them more appealing for patients who have isolated postprandial hyperglycemia. Just as with sulfonylureas, there must be enough functioning beta cells for these medications to be efficacious. One niche for the meglitinides is patients who are normally well-controlled but who need a medication for high-carb meals that cause postprandial hyperglycemic spikes. Some patients like the flexibility of having these medications on an as-needed basis.

Alpha-Glucosidase Inhibitors

Overview

Alpha-glucosidase inhibitors (AGIs) approved for use in the United States include acarbose and miglitol. Taken orally, this class of medications often is used adjunctively with other common diabetes classes, including biguanides, insulin, and sulfonylureas. These agents have had limited use in the United States because of common side effects, including gastrointestinal discomfort, flatus, and diarrhea. As a monotherapy agent at maximum doses (100 mg tid with meals), acarbose can reduce the A1c as much as 1%.[24] There was no statistically significant difference in A1c reduction between patients taking 50 mg three times per day and 200 mg three times per day, with the range from 0.77-0.86% reduction.[24]

Dosing

The initial dosage is 25 mg three times daily with the first bite of the meal.[24] Although the effect on HbA1c was the same with acarbose dosing higher than 50 mg three times daily, the occurrence of side effects increased.[23] Dose increases are recommended at four- to eight-week intervals based on postprandial blood glucose levels.[24]

Mechanism of Action

AGIs delay the absorption of glucose in the small intestine, causing a decrease in postprandial blood glucose and insulin levels.[33] In a dose-dependent fashion, this medication inhibits gastrointestinal enzyme alpha-glucosidases, which converts complex polysaccharide carbohydrates into monosaccharides and results in a smaller rise of postprandial blood glucose.[34]

Key Studies/Trials

A meta-analysis of 41 studies demonstrated that AGIs have a beneficial effect on hemoglobin A1c reduction, fasting, postprandial blood glucose, and post-load insulin, but little positive effect on cholesterol.[33] In the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial, acarbose reduced the risk of new onset type 2 diabetes, cardiovascular events, and hypertension in patients with impaired glucose tolerance.[35]

Safety Concerns

Contraindications. AGIs are contraindicated in patients with inflammatory bowel disease, colonic ulceration, partial intestinal obstruction, digestive or absorption disorders, diabetic ketoacidosis, and liver cirrhosis. These agents are pregnancy category B but should not be used while breastfeeding, as they are excreted in the milk.

Common Side Effects. More than 10% of individuals will develop gastrointestinal upset such as abdominal pain, flatulence, bloating, or diarrhea. These symptoms typically return to pretreatment levels over time.[34,36]

Renal/Hepatic Dose Recommendations. Manufacturers recommend avoiding AGIs in patients with kidney disease, as this medication has not been studied if serum creatinine > 2 mg/dL. Below 2 mg/dL, there are no renal dose adjustments in the package insert.[34,36] Individuals with cirrhosis should not take this medication.

Risk of Hypoglycemia. Although the risk of hypoglycemia is low when this medication is given as monotherapy, the risk of hypoglycemia increases when given in combination with a sulfonylurea or insulin. *Special consideration should be given when treating hypoglycemia related to AGIs. Oral glucose (dextrose) absorption is not inhibited by AGIs like sucrose (cane sugar). The hydrolysis of glucose into fructose is inhibited by AGIs and, thus, AGIs cannot rapidly correct hypoglycemia.*[34,36]

The cost is approximately $20 to $200 for 90 tablets.[13]

Practical Implications

AGIs are unique in that they can delay the absorption of glucose in the proximal gut, which may reduce the insulin secretory burden. Acarbose treats mainly postprandial glucose, and has been shown to be moderately effective in preventing new onset type 2 diabetes in those at risk. However, it is important to instruct patients not to use fructose for the treatment of hypoglycemia while on acarbose.

Bile Acid Resins

Overview

Bile acid resins are a class of medications traditionally used to lower LDL cholesterol.[37] More recently, these agents also were shown to improve glucose as an adjunct therapy to therapeutic lifestyle changes.[38] HbA1c reduction is typically about 0.5% when added to other agents. Bile acid resins currently are not recommended for use as monotherapy in type 2 diabetes. This class of agents has a low risk of hypoglycemia and can help improve both LDL cholesterol and glucose.

Mechanism of Action

The mechanism of action is not entirely known for colesevelam, but it is believed to be related to decreased glucose absorption after meals in relation to gastrointestinal transit time. It also appears to reduce hepatic glucose production. This medication is available in 625 mg tablets or powder form (1,875 or 3,750 mg packets). The daily dose recommended for diabetes is 3,750 mg daily in divided doses.[37] Achieving this dose requires six tablets per day with ample amounts of water.[37]

Safety Concerns

Common Side Effects. Patients commonly experience gastrointestinal side effects, including nausea, constipation, and dyspepsia. Colesevelam also can raise serum triglycerides, interfere with the absorption of other medications (e.g., levothyroxine, warfarin, and others), and interfere with the absorption of fat-soluble vitamins.[37] This medication can be used in pregnancy/breastfeeding, with category B in pregnancy, but the safety in lactation is unknown.[37]

Renal/Hepatic Dose Considerations. There are no recommendations for renal or hepatic dosing. This class of medications should not be used if there is a risk of pancreatitis or GI motility or bowel obstruction.

The cost is approximately $600 for 180 tablets.[13]

Practical Implications

Although colesevelam may be attractive as it treats both hyperglycemia and hyperlipidemia, the combination of the dosing formulation, side effects, limited efficacy, and warnings has limited the use of this medication clinically.

Recommendations from the American Diabetes Association

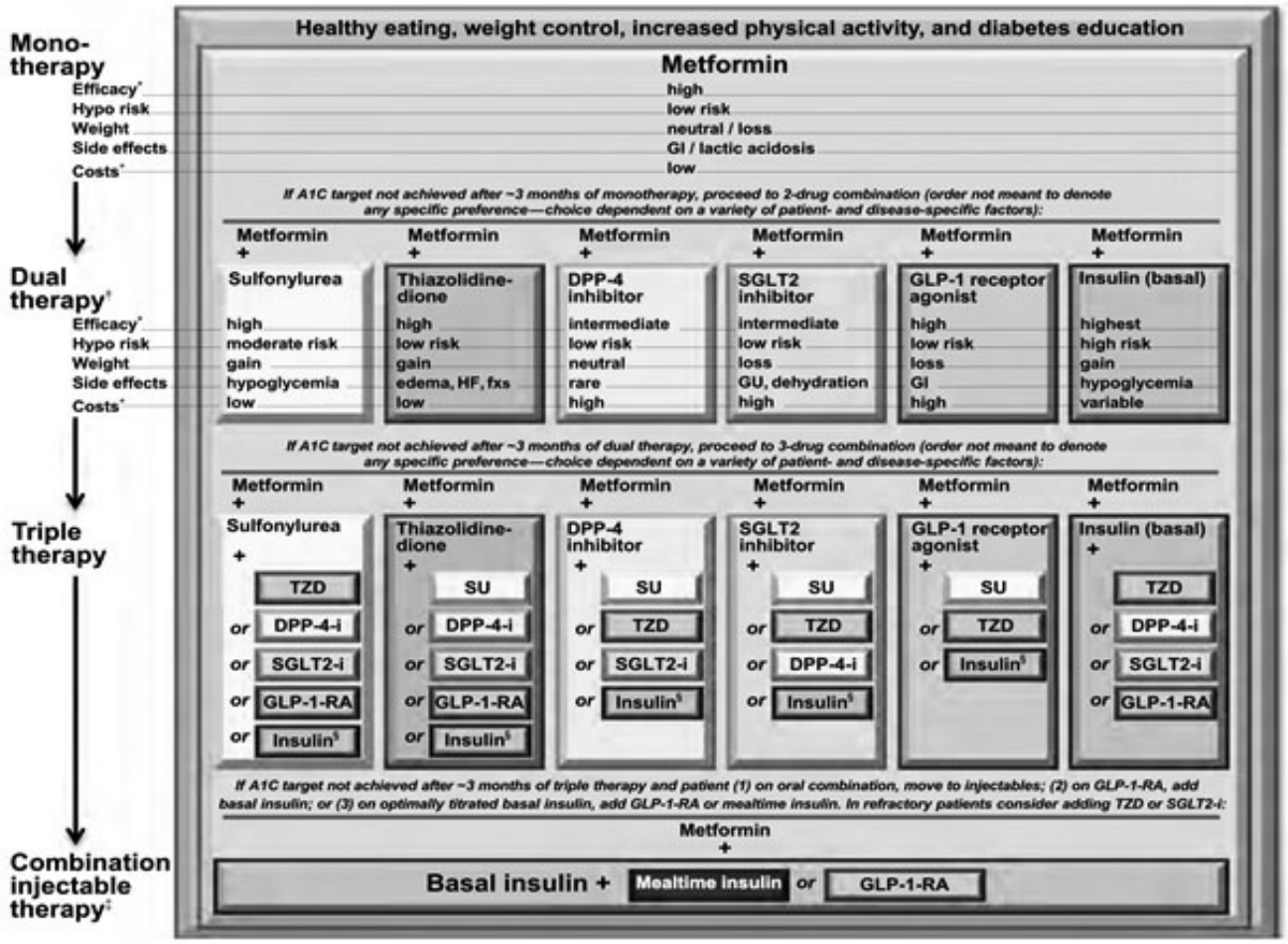
The ADA has provided a recommended algorithm for the treatment of type 2 diabetes.[39] (*See Figure 1.*) All patients should receive diabetes self-management education and support at diagnosis. Therapeutic lifestyle modification, including regular moderate physical activity and mild weight loss of about 5%, should be encouraged for all people. *In addition, the ADA recommends that pharmacologic therapy be started, with metformin as the preferred agent for most patients.* Metformin should be titrated to the highest tolerated therapeutic dose. The frequency of glucose testing is based on the intensity of the treatment and the likelihood the person may experience hypoglycemia. For those on metformin and lifestyle alone, self-monitoring blood glucose may be used to help patients know what/how daily activities affect glucose levels.

Most importantly, the treating providers should assess patients with diabetes every two to three months and titrate therapy if the glucose goals are not achieved.[39] Although major organizations agree regarding the intensity of medication titration, this is rarely achieved in routine practice.[39,40] If the guidelines were strictly followed, all patients who had not achieved glucose goals would be on insulin therapy at one year. In comparison, a study of U.S. physicians showed that patients typically will be out of control for a mean of 8.6 years before treatment is intensified to include insulin.

Authors' Treatment Recommendations

1. Always start lifestyle and metformin as an initial therapy.

Figure 1. Antihyperglycemic Therapy in Type 2 Diabetes



Source: American Diabetes Association. *Diabetes Care*, American Diabetes Association, 2012. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association. Available at: http://care.diabetesjournals.org/content/35/6/1364.figures-only. Accessed Sept. 1, 2016.

Although it is attractive to allow people to attempt therapeutic lifestyle changes at diagnosis rather than starting medications, this may not be in their best long-term interest. One study found that waiting three months after diagnosis to start metformin can reduce the failure of responding to metformin by 50%.[41]

2. Titrate metformin to the maximum tolerated dose. This usually requires slow titration. We typically start with 500 mg daily with evening meal and work up to 1000 mg twice daily, only if each previous dose was tolerated. When the immediate-release formulation is not tolerated, patients can take the extended-release metformin, which has less gastrointestinal side effects and can be taken as a single daily dose (multiple tablets).

3. Titrate therapy every three months. Both the ADA and the American Association of Clinical Endocrinologists agree that once therapy starts, patients should be assessed at least every three months; if the glucose is not at goal, therapy should be intensified.[39,40]

4. Each drug provides approximately 1% drop in A1c. Although the efficacy of the drugs all vary slightly, planning on a 1% drop per medication will allow providers to plan ahead to get the patient to goal. This is important when patients have very high A1cs. For example, patients may have a greater drop from metformin if the initial A1c was 8.5% vs. 7.5%.[41] Furthermore, early combination therapy may be much more effective than sequentially adding therapies over time.[42]

5. Initial intensive therapy with step-down therapy may be better than traditional step-up therapy. Initial combination therapy with metformin, pioglitazone, and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes.[42]

6. If a patient has an HbA1c higher than 9% despite two oral

medications, consider starting insulin therapy.

7. Use a weight-based algorithm for basal insulin therapy and let the patient control titration.

8. Consider a GLP-1RA in place of mealtime insulin.

9. Newer agents may not necessarily be more effective than older agents but they have a better nonglycemic profile (less hypoglycemia, less likely to cause weight gain, and may have cardiovascular benefit).[43]

Special thanks to Nam Vo, PharmD Candidate (2017), for his assistance in creating Appendix A. Combination Therapies: Their Effectiveness and Costs. To download a copy of Appendix A, please go to http://bit.ly/2eyB4Px.

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CME Questions

1. Which of the following is true regarding metformin?
   a. Metformin is a glucose-independent incretin.
   b. Metformin is more effective than lifestyle intervention in slowing the progression from prediabetes to diabetes.
   c. Metformin is recommended as the first-line antihypergylcemic agent for most patients with type 2 diabetes.
   d. Metformin often causes hypoglycemia.
2. What is the most serious dose-limiting side effect of sulfonylureas?
   a. Hypoglycemia
   b. Weight gain
   c. Nausea
   d. Diarrhea
3. Which of the following combinations is ***not*** recommended in the treatment of type 2 diabetes?
   a. Metformin and sulfonylurea
   b. DPP-4 inhibitor and metformin
   c. DPP-4 inhibitor and GLP-1 RA
   d. Insulin and DPP-4 inhibitor
4. When a patient is at high risk for hypoglycemia, which of the following agents have the lowest risk of hypoglycemia when used as monotherapy?
   a. Sulfonylureas (oral)
   b. Metglitinides (oral)
   c. GLP-1 RA (injection)
   d. Pramlintide (injection)
5. Which of the following is true regarding the efficacy of the oral agents for diabetes?
   a. Each oral agent will reduce A1c about 1% (0.5%-1.5%).
   b. When you add any two oral agents, the A1c reduction is additive so the sum is more than the sum of the parts.
   c. The higher the baseline A1c the greater the A1c can drop with any agent.
   d. Both a and c
6. Which of the following warning combination pairs is correct?
   a. Metformin: warning regarding lactic acidosis
   b. DPP-4 inhibitors: warning regarding pancreatitis
   c. TZDs: warning regarding pre-existing congestive heart failure
   d. All of the above

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Appendix A. Combination Therapies: Their Effectiveness and Costs

Metformin-Based Combinations		
Combination Therapy	**A1c Reduction**	**Cost**
+ Glipizide (Metaglip) 2.5 mg/250 mg	2.15[4]	$24.83-$45 per 60 tabs[1]
+ Glipizide (Metaglip) 2.5 mg/500 mg	2.14[4]	$18.87-$72 per 60 tabs[1]
+ Glipizide (Metaglip) 5 mg/500 mg	1-1.5[3]	$18.87-$45 per 60 tabs[1]
+ Glyburide (Glucovance) 1.25 mg/250 mg	1.48[5]	$5-$44.71 per 60 tabs[1]
+ Glyburide (Glucovance) 2.5 mg/500 mg	1.53[5]	$5-$33.39 per 60 tabs[1]
+ Glyburide (Glucovance) 5 mg/500 mg	1-1.5[3]	$7.20-$33.47 per 60 tabs[1]
+ Pioglitazone (Actoplus Met) 15 mg/500 mg	1-1.5[3]	$37.50-$112.96 per 30 tabs[1] $69-218.41 per 60 tabs[1]
+ Pioglitazone (Actoplus Met) 15 mg/850 mg	1.8[6]	$36-$109.67 per 30 tabs[1] $67.80-$168.62 per 60 tabs[1]
+ Pioglitazone (Actoplus Met XR) 15 mg/1000 mg	1-1.5[3]	$333.37-$349.26 per 30 tabs[1] $626.12-$659.24 per 60 tabs[1]
+ Pioglitazone (Actoplus Met XR) 30 mg/1000 mg	1-1.5[3]	$653.41-$688.36 per 60 tabs[1]
+ Rosiglitazone (Avandamet) 2 mg/500 mg (clinical studies based on a mean final dose of 7.2 mg/1799 mg)[8]	2.3[8]	$151.14-$158.54 per 60 tabs[1]
+ Rosiglitazone (Avandamet) 2 mg/1000 mg (clinical studies based on a mean final dose of 7.2 mg/1799 mg)[8]	2.3[8]	$145.11-$155.31 per 60 tabs[1]
+ Rosiglitazone (Avandamet) 4 mg/500 mg (clinical studies based on a mean final dose of 7.2 mg/1799 mg)[8]	2.3[8]	$255.14-$263.73 per 60 tabs[1]
+ Rosiglitazone (Avandamet) 4 mg/1000 mg (clinical studies based on a mean final dose of 7.2 mg/1799 mg)[8]	2.3[8]	$255.14-$263.73 per 60 tabs[1]
+ Sitagliptin (Janumet) 50 mg/500 mg	1.4[9]	$369.85-$415.80 per 60 tabs[1]
+ Sitagliptin (Janumet) 50 mg/1000 mg	1.9[9]	$367.67-$415.80 per 60 tabs[1]
+ Sitagliptin (Janumet XR) 50 mg/500 mg	0.5-1.0[3]	$194.73-$207.90 per 30 tabs[1]
+ Sitagliptin (Janumet XR) 50 mg/1000 mg	0.5-1.0[3]	$190.16-207.90 per 30 tabs[1]

Combination Therapy	A1c Reduction	Cost
+ Sitagliptin (Janumet XR) 100 mg/1000 mg	0.5-1.0[3]	$369.85-$415.80 per 30 tabs[1]
+ Saxagliptin (Kombiglyze XR) 2.5 mg/1000 mg	0.5-1.0[3]	$188.84-$203.07 per 30 tabs[1]
+ Saxagliptin (Kombiglyze XR) 5 mg/500 mg	0.5-1.0[3]	$381.72-$393.19 per 30 tabs[1]
+ Saxagliptin (Kombiglyze XR) 5 mg/1000 mg	0.5-1.0[3]	$369.79-$415.80 per 30 tabs[1]
+ Linagliptin (Jentadueto) 2.5 mg/500 mg	1.2[12]	$363.59-$393.87 per 60 tabs[1]
+ Linagliptin (Jentadueto) 2.5 mg/850 mg	0.5-1.0[3]	$363.59-$393.87 per 60 tabs[1]
+ Linagliptin (Jentadueto) 2.5 mg/1000 mg	1.6[12]	$363.59-$386.62 per 60 tabs[1]
+ Linagliptin (Jentadueto XR) 2.5 mg/1000 mg	N/A	Not yet available in pharmacies[1]
+ Linagliptin (Jentadueto XR) 5 mg/1000 mg	N/A	$375.33-$399.83 per 30 tabs[1]
+ Alogliptin (Kazano) 12.5 mg/500 mg	1.2[14]	$94.57-$212.25 per 60 tabs[1]
+ Alogliptin (Kazano) 12.5 mg/1000 mg	1.6[14]	$94.57-$184.75 per 60 tabs[1]
+ Repaglinide (PrandiMet) 1 mg/500 mg	0.5-1.0[3]	$145.54-$330.09 per 60 tabs[1]
+ Repaglinide (PrandiMet) 2 mg/500 mg	0.5-1.0[3]	$145.54-$330.09 per 60 tabs[1]
+ Canagliflozin (Invokamet) 50 mg/500 mg	0.5-1.0[3]	$395.72-$431.52 per 60 tabs[1]
+ Canagliflozin (Invokamet) 50 mg/1000 mg (clinical studies based on a maximum daily metformin dose of 1500-2000 mg/day)[16]	1.77[16]	$410.90-$433.41 per 60 tabs[1]
+ Canagliflozin (Invokamet) 150 mg/500 mg	0.5-1.0[3]	$398.07-$431.52 per 60 tabs[1]
+ Canagliflozin (Invokamet) 150 mg/1000 mg (clinical studies based on a maximum daily metformin dose of 1500-2000 mg/day)[16]	1.78[16]	$398.07-$423.18 per 60 tabs[1]
+ Dapagliflozin (Xigduo XR) 5 mg/500 mg (clinical studies based on a maximum daily metformin XR dose of up to 2000 mg/day)[17]	2.1[17]	$403.76-$423.18 per 30 tabs[1]
+ Dapagliflozin (Xigduo XR) 5 mg/1000 mg (clinical studies based on a maximum daily metformin XR dose of up to 2000 mg/day)[17]	2.1[17]	$205.93-$216.34 per 30 tabs[1]
+ Dapagliflozin (Xigduo XR) 10 mg/500 mg (clinical studies based on a maximum daily metformin XR dose of up to 2000 mg/day)[17]	2.0[17]	$409.95-$423.18 per 30 tabs[1]
+ Dapagliflozin (Xigduo XR) 10 mg/1000 mg (clinical studies based on a maximum daily metformin XR dose of up to 2000 mg/day)[17]	2.0[17]	$403.76-$423.18 per 30 tabs[1]

Sulfonylureas-Based Combinations		
Combination Therapy	**A1c Reduction**	**Cost**
Glipizide		
+ Metformin (Metaglip) 2.5 mg/250 mg	2.15[4]	$24.83-$45 per 60 tabs[1]
+ Metformin (Metaglip) 2.5 mg/500 mg	2.14[4]	$18.87-$72 per 60 tabs[1]
+ Metformin (Metaglip) 5 mg/500 mg	1-1.5[3]	$18.87-$45 per 60 tabs[1]
Glimepiride		
+ Pioglitazone (Duetact) 30 mg/2 mg	1-1.5[3]	$104.72-$589.80 per 30 tabs[1]
+ Pioglitazone (Duetact) 30 mg/4 mg	1-1.5[3]	$104.72-$589.80 per 30 tabs[1]
+ Rosiglitazone (Avandaryl) 4 mg/1 mg	1-1.5[3]	Discontinued/Off-market[2]
+ Rosiglitazone (Avandaryl) 4 mg/2 mg	1-1.5[3]	Discontinued/Off-market[2]
+ Rosiglitazone (Avandaryl) 4 mg/4 mg	2.4[18]	Discontinued/Off-market[2]
+ Rosiglitazone (Avandaryl) 8 mg/2 mg	1-1.5[3]	Discontinued/Off-market[2]
+ Rosiglitazone (Avandaryl) 8 mg/4 mg	2.5[18]	Discontinued/Off-market[2]
Glyburide		
+ Metformin (Glucovance) 1.25 mg/250 mg	1.48[5]	$5-$44.71 per 60 tabs[1]
+ Metformin (Glucovance) 2.5 mg/500 mg	1.53[5]	$5-$33.39 per 60 tabs[1]
+ Metformin (Glucovance) 5 mg/500 mg	1-1.5[3]	$7.20-$33.47 per 60 tabs[1]

DPP-4 Inhibitors-Based Combinations		
Combination Therapy	**A1c Reduction**	**Cost**
Sitagliptin		
+ Metformin (Janumet) 50 mg/500 mg	1.4[9]	$369.85-$415.80 per 60 tabs[1]
+ Metformin (Janumet) 50 mg/1000 mg	1.9[9]	$367.67-$415.80 per 60 tabs[1]
+ Metformin (Janumet XR) 50 mg/500 mg	0.5-1.0[3]	$194.73-$207.90 per 30 tabs[1]
+ Metformin (Janumet XR) 50 mg/1000 mg	0.5-1.0[3]	$190.16-207.90 per 30 tabs[1]
+ Metformin (Janumet XR) 100 mg/1000 mg	0.5-1.0[3]	$369.85-$415.80 per 30 tabs[1]
Saxagliptin		
+ Metformin (Kombiglyze XR) 2.5 mg/1000 mg	0.5-1.0[3]	$188.84-$203.07 per 30 tabs[1]
+ Metformin (Kombiglyze XR) 5 mg/500 mg	0.5-1.0[3]	$381.72-$393.19 per 30 tabs[1]
+ Metformin (Kombiglyze XR) 5 mg/1000 mg	0.5-1.0[3]	$369.79-$415.80 per 30 tabs[1]
Linagliptin		
+ Metformin (Jentadueto) 2.5 mg/500 mg	1.2[12]	$363.59-$393.87 per 60 tabs[1]
+ Metformin (Jentadueto) 2.5 mg/850 mg	0.5-1.0[3]	$363.59-$393.87 per 60 tabs[1]
+ Metformin (Jentadueto) 2.5 mg/1000 mg	1.6[12]	$363.59-$386.62 per 60 tabs[1]
+ Metformin (Jentadueto XR) 2.5 mg/1000 mg	N/A	Not yet available in pharmacies[1]
+ Metformin (Jentadueto XR) 5 mg/1000 mg	N/A	$375.33-$399.83 per 30 tabs[1]
Alogliptin		
+ Metformin (Kazano) 12.5 mg/500 mg	1.2[14]	$94.57-$212.25 per 60 tabs[1]
+ Metformin (Kazano) 12.5 mg/1000 mg	1.6[14]	$94.57-$184.75 per 60 tabs[1]
+ Pioglitazone (Oseni) 12.5 mg/15 mg	1-1.5[3]	$369.88-$401.23 per 30 tabs[1]
+ Pioglitazone (Oseni) 12.5 mg/30 mg	1-1.5[3]	$381.82-$402.27 per 30 tabs[1]
+ Pioglitazone (Oseni) 12.5 mg/45 mg	1-1.5[3]	$389.11-$408.32 per 30 tabs[1]
+ Pioglitazone (Oseni) 25 mg/15 mg	1-1.5[3]	$380.99-$400.73 per 30 tabs[1]
+ Pioglitazone (Oseni) 25 mg/30 mg	1.7[19]	$369.88-$393.29 per 30 tabs[1]
+ Pioglitazone (Oseni) 25 mg/45 mg	1-1.5[3]	$389.11-$408.32 per 30 tabs[1]

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