

# Diabetes Treatment, Part 2: Oral Agents for Glycemic Management

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**Editor's note:** This article is the fourth in a 12-part series reviewing the fundamentals of diabetes care for physicians in training. Previous articles in the series can be viewed at the Clinical Diabetes website (<http://clinical.diabetesjournals.org>).

The epidemic of type 2 diabetes in the United States and the rest of the world continues to grow rapidly; as many as 20 million people in the United States may have the disease.<sup>1</sup> The vast majority of people with diabetes have type 2 diabetes, caused by a relative insulin deficiency superimposed on a background of insulin resistance.<sup>2</sup> Most patients begin treatment with diet and exercise or incorporate them into their treatment regimen, but, unfortunately, most patients are unsuccessful in controlling type 2 diabetes through lifestyle modification alone and require pharmacotherapy.

For several reasons, oral agents are typically the first medications used in the treatment of type 2 diabetes. Because of their wide range of efficacy, safety, and mechanisms of action, it is important for clinicians to gain a broad understanding of each class of oral agents to optimize diabetes control. This article reviews the major classes of oral agents used to treat type 2 diabetes, with an emphasis on the benefits and risks of each class. It is important to note that because type 1 diabetes results from an absolute deficiency of pancreatic  $\beta$ -cells, most oral agents are not indicated in the treatment of patients with type 1 diabetes.

Oral agents are also largely not tested or approved for use in pregnancy.

## Metformin

Metformin is the sole member of the biguanide class of medications in the United States. It replaced another biguanide, fenformin, which was removed from the market because of a propensity for lactic acidosis in 1975.<sup>3,4</sup> Available in short-acting and sustained-release formulations, it is one of the oldest, and indeed one of the safest, medications used in the treatment of type 2 diabetes.

Metformin exerts its effects primarily by decreasing hepatic glucose output and has a comparatively lesser effect increasing insulin sensitivity. Isotope studies suggest hepatic glucose output is reduced primarily through inhibition of gluconeogenesis, which may be reduced by as much as 75%.<sup>4</sup> Patients using metformin also exhibit lower fasting insulin concentrations. Most patients using metformin lose weight, and as much as 88% of weight loss with metformin is loss of body fat mass. In patients with normal renal function and who are otherwise healthy, metformin does not increase plasma lactic acid levels or rate of turnover.<sup>4,5</sup> Weight loss occurring during initiation of metformin occurs even without change in energy expenditure.<sup>4</sup>

The major clinical effect of metformin is to decrease fasting glucose levels, thereby reducing hemoglobin A<sub>1c</sub> (A1C). The degree of clinical effect varies in individual patients, but most patients experience a reduction in A1C of ~ 1.5 percentage points.<sup>6</sup> Because metformin

exerts its effects primarily through impairing hepatic gluconeogenesis, it is primarily an antihyperglycemic agent, rather than a hypoglycemic agent, such as insulin or sulfonylureas. As a result, the incidence of hypoglycemia with metformin is quite low. Metformin has additional effects of modest reduction in plasma triglyceride concentrations resulting from decreased production of very-low-density lipoprotein.<sup>3</sup>

The most common reported adverse reaction to metformin therapy is gastrointestinal upset, including nausea, vomiting, anorexia, and diarrhea. Most patients beginning metformin experience significant mild weight loss, most likely as a result of these effects. The gastrointestinal side effects gradually dissipate in many patients; thus, metformin is generally started in low doses, such as 500–850 mg with breakfast and supper, and are titrated slowly to the maximum dose of 2,550 mg daily. Some patients also describe a metallic taste.<sup>3</sup> Patient compliance, owing in part to a slight decrease in gastrointestinal side effects, may be better with sustained-release metformin than with immediate-release formulations. Sustained-release formulations may be administered once or twice daily.<sup>7</sup>

Lactic acidosis is a rare but potentially fatal complication of metformin therapy. Incidence of this complication is very low: < 1 case per 100,000 treated patients.<sup>6,8</sup> Lactic acidosis can be caused by extremely high concentrations of metformin in the bloodstream or by any condition that can induce hypoxia or hepatic insufficiency, thus limiting the body's ability to metabolize lactate.

When lactic acidosis occurs, it is generally in patients who have continued using metformin despite contraindications. Exclusion criteria for metformin therapy include renal insufficiency with creatinine  $\geq 1.5$  mg/dl in men and 1.4 mg/dl in women, cardiac or pulmonary insufficiency sufficient to cause reduction in peripheral perfusion or central hypoxia, history of lactic acidosis, liver disease, alcohol abuse, or use of intravenous radiographic contrast agents.<sup>3</sup>

Because of metformin's relatively good safety profile, association with weight loss or weight neutrality, and availability as a generic formulation, it is commonly used as an initial agent in type 2 diabetes when lifestyle modification is insufficient to control glucose levels.<sup>6</sup> Recent American Diabetes Association (ADA) consensus guidelines have even suggested starting all eligible newly diagnosed type 2 diabetic patients on metformin in conjunction with efforts to modify lifestyle.

### Sulfonylureas

Sulfonylureas include several medications that act on  $\beta$ -cells to increase insulin release. They bind to the sulfonylurea receptor on the surface of the  $\beta$ -cell and inhibit potassium efflux, thus depolarizing the  $\beta$ -cells and facilitating insulin release.<sup>9</sup> First-generation agents, such as acetohexamide, chlorpropamide, and tolbutamide, have largely been replaced by second-generation sulfonylureas, such as glyburide, glipizide, and glimepiride, which have improved safety profiles. Because sulfonylureas act by stimulating insulin release from  $\beta$ -cells, patients without a sufficient number of  $\beta$ -cells, such as those with type 1 diabetes, pancreoprivic diabetes, or later stages of type 2 diabetes, do not respond to these medications. In patients who do respond to them, insulin release may be augmented both in the fasting state and postprandially. Although potencies can vary among sulfonylureas, they tend to lower A1C to a similar extent to metformin,  $\sim 1.5$  percentage points.<sup>6</sup>

Hypoglycemia is the major detrimental effect of these agents. Because different sulfonylureas possess different pharmacotherapeutic profiles, there are differences in risk of hypoglycemic episodes among the different agents. Patients using sulfonylurea medications must be cautioned regarding the signs, symptoms, and risks of hypoglycemia while using these medications.

Elderly patients may be at higher risk for hypoglycemia, and patients who frequently skip meals and experience fluctuations in activity level may not be candidates for these medications.<sup>6</sup> Glyburide appears to pose a higher risk of inducing hypoglycemia than other members of this class, possibly because it has a number of active metabolites and high affinity for the sulfonylurea receptor.<sup>10</sup> Hypoglycemia may be recurrent, especially in patients with impaired renal function. Most of these drugs are excreted by the kidney and must be used with considerable caution in patients with renal insufficiency. Glipizide is often preferred in cases where a sulfonylurea is used in the setting of renal insufficiency.

Another disadvantage of sulfonylureas is the risk of weight gain. Many patients experience an increase  $\geq 2$  kg after initiation of these medications.<sup>6</sup> There has also been some question as to the possibility that older sulfonylurea medications may increase risks of coronary artery disease. The University Group Diabetes Program study did find an increased association with tolbutamide use and risks of coronary artery events; however, this finding was not supported in the U.K. Prospective Diabetes Study.<sup>11,12</sup> It is also noteworthy that some patients with an allergy to sulfonamide medications exhibit cross-reactivity with sulfonylureas; therefore, these drugs are contraindicated in patients with sulfa allergies. There may also be cross-reactivity with other drugs, such as carbonic anhydrase inhibitors, loop diuretics, and thiazide diuretics.

An advantage of sulfonylureas, however, is cost. They are all available in generic formulations at relatively low cost to patients, which make them more appealing when cost is a major issue in medication selection. A recent consensus statement from the ADA and the European Association for the Study of Diabetes considered sulfonylurea medications to be second-line agents.

### Glinides

The glinides, nateglinide and repaglinide, exert their effects in a manner similar to sulfonylureas, by binding to the sulfonylurea receptor and inducing depolarization of the  $\beta$ -cells. However, they bind in a different manner to the sulfonylurea receptor. They also have shorter half-lives than sulfonylureas; therefore, they require more frequent dosing. They usually tend to be less potent than sulfonylureas, lowering A1C by  $\sim 1$ – $1.5$  percentage points.<sup>6</sup>

Glinides may possess a lower propensity for hypoglycemia. One study comparing nateglinide to glyburide found an increase of more than twofold in the number of episodes of hypoglycemia in patients receiving glyburide and metformin compared to patients using nateglinide and metformin, despite similar A1C-lowering effects.<sup>13</sup> This may make glinides more attractive medications in individuals who are predisposed to hypoglycemia, such as elderly patients. Because of their chemical dissimilarity from sulfonylureas, they are not contraindicated in patients with sulfa allergy.

Cost is a major disadvantage of this group of medications; they are considerably more expensive than sulfonylureas. The need for frequent dosing may also adversely affect patient compliance.

### Thiazolidinediones

The thiazolidinediones rosiglitazone and pioglitazone are insulin sensitizers. Troglitazone, another thiazolidinedione, was removed from the market in 2000 because of hepatotoxicity. These drugs

bind to peroxisome proliferator-activated receptors (PPARs) in cells, and this drug-PPAR complex (with one or more coactivators) acts on response elements in promoter regions to affect the transcription of as many as 100 genes. They may act to stimulate production of proteins that increase insulin sensitivity, such as adiponectin.<sup>14,15</sup> They may also act by blocking transcription of other proteins responsible for insulin resistance or inflammation.<sup>14,16</sup> PPARs exist in several different forms: PPAR $\alpha$ , PPAR $\delta$ , and PPAR $\gamma$ . PPAR $\gamma$  is the major target of thiazolidinediones, and these receptors are located throughout the body in many different tissues, especially adipose. PPAR $\alpha$  may be the major target for fibric acids, which act to lower triglyceride levels. The clinical effect of pioglitazone and rosiglitazone is to lower glucose levels, especially fasting glucose. Usual reduction of A1C with these medications is 0.5–1.4%.<sup>6</sup>

Patients using thiazolidinediones require hepatic monitoring because these agents have been associated with a rare side effect of hepatotoxicity. Therefore, patients should undergo hepatic function tests before initiation of these medications and regularly thereafter. Thiazolidinediones should be discontinued for elevation in hepatic enzymes of more than three times the upper limit of normal. There may also be an increase in bone loss in patients using thiazolidinediones, which could lead to fracture.<sup>17</sup>

In addition to glucose-lowering effects, pioglitazone may also improve lipid profiles, possibly as a result of its partial PPAR $\alpha$  activity (in addition to PPAR $\gamma$  agonism). Rosiglitazone appears to only act as a PPAR $\gamma$  agonist and does not tend to improve lipid profiles. Both drugs tend to cause increase in body weight and redistribution of adipose tissue from visceral to subcutaneous depots. Both drugs also cause or worsen peripheral edema and can also precipitate or worsen congestive heart failure. The incidence of heart failure

may be higher in patients who are also treated with insulin, but caution should be exercised in any patients who may be predisposed to developing edema. Use of diuretics may help control edema, but use of thiazolidinediones in patients with New York Heart Association class III or IV heart failure is contraindicated.

The PROactive Study, a prospective randomized placebo-controlled trial, did not find a significant difference in a composite endpoint of all-cause mortality, nonfatal and silent myocardial infarction, stroke, major leg amputation, acute coronary syndrome, coronary artery bypass graft or percutaneous coronary intervention, and leg revascularization. There was, however, a reduction in the composite of all-cause mortality, nonfatal myocardial infarction, and stroke.<sup>18</sup> A recent meta-analysis suggested that patients using rosiglitazone may have an increase in the risk of myocardial infarction and death from cardiovascular causes.<sup>19</sup> More study regarding the safety and efficacy of thiazolidinediones in the setting of cardiac disease is needed.

#### **$\alpha$ -Glucosidase Inhibitors**

Acarbose and miglitol are the  $\alpha$ -glucosidase inhibitors currently available in the United States. They act by inhibiting the intestinal enzyme that cleaves polysaccharides into monosaccharides. Because the polysaccharides are poorly absorbed from the gastrointestinal tract, the effect of these drugs is to slow the absorption of carbohydrates after a meal. Slower absorption of carbohydrate may limit postprandial hyperglycemia in patients with limited  $\beta$ -cell reserves. Clinically, an A1C reduction of 0.5–0.8% is typical.<sup>6</sup>

The primary side effect of  $\alpha$ -glucosidase inhibitors is flatulence and other gastrointestinal symptoms. Impaired absorption of carbohydrate leads to increased arrival of carbohydrate in the colon, which can cause considerable gas production, diarrhea, and abdominal pain. Some studies have demonstrated a potential improvement in risk of cardiovascular disease in patients with

impaired glucose tolerance, although more study is required to confirm this. It is also noteworthy that discontinuation of the drug due to side effects (primarily gastrointestinal) was 24%.<sup>20</sup>

$\alpha$ -Glucosidase inhibitors also carry a small chance of elevated liver transaminases; therefore, monitoring liver transaminases may be warranted.

#### **DPP-IV Inhibitors**

Dipeptidyl peptidase-IV (DPP-IV) inhibitors are the newest class of oral agents for the treatment of type 2 diabetes. They act by inhibiting the enzymatic degradation of glucagon-like peptide 1 (GLP-1). GLP-1 is an incretin hormone produced by the distal small intestine and released into the bloodstream. GLP-1 acts to delay gastric emptying, suppress glucagon release, and increase glucose-stimulated insulin release. It may also act to increase satiety. The resulting effect of GLP-1 is to limit postprandial hyperglycemia, but the half-life after secretion into the blood is very short. Use of DPP-IV inhibitors increases levels of endogenously produced GLP-1 and thereby decreases postprandial glucose excursions.<sup>21</sup> A1C reduction in patients with type 2 diabetes in a recent clinical trial was modest at 0.5–1%; however, the reduction in patients with higher A1C levels may have been greater.<sup>22</sup>

A major advantage of the DPP-IV inhibitors is their weight neutrality, with no significant weight gain in patients using the medication compared with placebo. Risk of hypoglycemia in clinical studies was also similar to placebo, and there are few drug interactions.<sup>22</sup> DPP-IV inhibitors are approved for monotherapy and for use with metformin and thiazolidinediones.

A major limiting factor with DPP-IV inhibitors is cost, which undoubtedly will keep insurance companies from covering the medication until more data are available. Weaker potency is another limitation that will limit their usefulness, especially given their elevated price.

Dosage should be reduced in the setting of renal insufficiency.

## Conclusion

A large portion of type 2 diabetes is a direct result of lack of exercise and excessive caloric intake. When treating patients with diabetes, the basis of treatment should focus on motivating patients to pursue a healthier lifestyle, which has a major impact on progression of the disease. Unfortunately, patients are usually not successful in controlling type 2 diabetes through dietary modification, exercise, and weight loss alone, and physicians must rely on pharmaceutical agents to control the disorder.

Our therapeutic armamentarium to treat diabetes has grown considerably in the past decade. As a result, there are more therapeutic dilemmas that physicians must overcome in the treatment of patients with type 2 diabetes. As our therapeutic armamentarium has grown, so has the number of studies demonstrating important information regarding the use of these agents. Many pharmaceutical agents possess side effects that could result in serious morbidity if administered to unsuitable patients. Knowledge of the benefits, risks, strengths, and limitations of available pharmaceutical tools will be essential in the optimal treatment of patients with type 2 diabetes.

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