

# Diabetes Treatment: Oral Agents

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**Editor's note:** This article is the third in an eight-part series reviewing the fundamentals of diabetes care for physicians in training. This series is an updated adaptation of a 12-part series published in *Clinical Diabetes* between 2006 and 2009. The previous series, and earlier installments of this one, can be found online at the journal Web site (<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 19 million people in the United States may have diabetes.<sup>1</sup> The vast majority of those individuals 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 changes or incorporate them into their treatment regimen. Unfortunately, most patients are unsuccessful in controlling type 2 diabetes through lifestyle modification alone and also 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. 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 type 1 diabetes. Oral agents are also not tested or approved for use in patients who are pregnant.

## Metformin

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

Metformin exerts its effects primarily by decreasing hepatic glucose output and has a comparatively minor effect in increasing insulin sensitivity. Isotope studies suggest that 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 those 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 A1C levels. The degree of clinical effect varies among patients, but most patients experience an A1C reduction of ~1.5 percentage points.<sup>6</sup> Because metformin exerts its effects primarily by impairing hepatic gluconeogenesis, it is an antihyperglycemic agent rather than a hypoglycemic agent such as insulin or the sulfonylureas. As a result, the incidence of hypoglycemia with metformin is quite low. Metformin has additional effects of modest reduction in plasma triglyceride concentrations because of decreased very-low-density lipoprotein production.<sup>3</sup>

The most commonly reported adverse reaction to metformin therapy is gastrointestinal upset, including nausea, vomiting, anorexia, and diarrhea. Most patients starting on metformin experience significant mild weight loss, 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 may be better with the sustained-release formulation of metformin rather than immediate-

release formulations, which 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 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, and 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 not sufficient to control glucose levels.<sup>6</sup>

### 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 (e.g., acetohexamide, chlorpropamide, and tolbutamide) have largely been replaced by second-generation sulfonylureas (e.g., glyburide, glipizide, and glimipiride) because of improved safety profiles.

Because sulfonylureas act by stimulating insulin release from  $\beta$ -cells,

patients with insufficient numbers 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 sulfonylureas, insulin release may be augmented both in the fasting state and postprandially.

Although potencies can vary among the sulfonylureas, as a class, they tend to lower A1C to an extent similar to metformin,  $\sim$  1.5 percentage points.<sup>6</sup>

The major detrimental effect of these agents is hypoglycemia. Because different sulfonylureas possess different pharmacotherapeutic profiles, there are differences in risk of hypoglycemic episodes among the various agents within the class. Glyburide appears to pose a higher risk of inducing hypoglycemia than other sulfonylureas, possibly because of its number of active metabolites and high affinity for the sulfonylurea receptor.<sup>10</sup>

Patients using sulfonylurea medications must be cautioned about 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> Hypoglycemia may be recurrent, especially in patients with impaired renal function. Most of these drugs are renally excreted and therefore must be used with great caution in patients with renal insufficiency.

Weight gain is a disadvantage of sulfonylurea therapy. Many patients experience an increase of  $\geq$  2 kg after initiation of these medications.<sup>6</sup>

There has also been some question about the possibility that sulfonylurea medications may increase risks of coronary artery disease. The University Group Diabetes

Program study found an increased association between 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>

Some patients having an allergy to sulfonamide medications exhibit cross-reactivity with sulfonylureas. Therefore, these drugs are contraindicated in such patients. However, there may also be cross-reactivity with other drugs, such as carbonic anhydrase inhibitors, loop diuretics, and thiazide diuretics.

Low cost is an advantage of sulfonylurea medications, which are available in less expensive generic formulations. A recent consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes considered sulfonylurea medications to be second-line agents.

### Glinides

Like sulfonylureas, the glinides nateglinide and repaglinide exert their effects by binding to the sulfonylurea receptor and inducing depolarization of the  $\beta$ -cells. However, the way they bind to the sulfonylurea receptor differs from that of sulfonylureas. They also have shorter half-lives than sulfonylureas and therefore 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 have a lower propensity toward hypoglycemia. One study comparing nateglinide to glyburide found a more than twofold increase in the number of episodes of hypoglycemia in patients receiving glyburide and metformin compared to patients using nateglinide and metformin, despite similar lowering of A1C.<sup>13</sup> This may make glinides more attractive medications for individuals who are predisposed to hypoglycemia, such as elderly

patients. Because of their chemical dissimilarity to sulfonyleureas, they are not contraindicated in patients with sulfonamide allergy.

Cost is a major disadvantage of this medication class, however. Glinides are considerably more expensive than sulfonyleureas, which are available in generic formulations. Their 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 such as adiponectin, which increase insulin sensitivity.<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, including PPAR $\alpha$ , PPAR $\delta$ , and PPAR $\gamma$ . PPAR $\gamma$  receptors are the major target of thiazolidinediones and 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, and especially fasting glucose. The usual reduction of A1C expected from these medications is 0.5–1.4 percentage points.<sup>6</sup>

Patients using thiazolidinediones require hepatic monitoring. These agents can be associated,

although rarely, with hepatotoxicity. Therefore, patients should undergo hepatic function tests before initiation of the medications and regularly thereafter. Thiazolidinediones should be discontinued for elevation in hepatic enzymes greater than three times the upper limit of normal. Thiazolidinediones may also cause an increase in bone loss, which could lead to fracture.<sup>17</sup>

In addition to its glucose-lowering effects, pioglitazone may also improve lipid profiles, possibly because 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 an 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 for 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,<sup>18</sup> 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. A recent meta-analysis<sup>19</sup> sug-

gested that use of rosiglitazone may be associated with an increase in the risk of myocardial infarction and death from cardiovascular causes, but this study had significant weaknesses. More research is needed regarding the safety and efficacy of thiazolidinediones in the setting of cardiac disease.

### $\alpha$ -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 polysaccharides are poorly absorbed from the gastrointestinal tract, the effect of these drugs is to slow the absorption of carbohydrate 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 percentage points is typical.<sup>6</sup>

The primary side effects of  $\alpha$ -glucosidase inhibitors are 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 research is required to confirm this. It is also noteworthy that discontinuation of the drug because of side effects (primarily gastrointestinal) in such trials was 24%.<sup>20</sup>

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

### Dipeptidyl Peptidase-4 Inhibitors

Dipeptidyl peptidase-4 (DPP-4) 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), 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 its half-life after secretion into the blood is very short. The use of a DPP-4 inhibitor increases the 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<sup>22</sup> was a modest 0.5–1 percentage point. However, the reduction in patients with higher initial A1C levels may have been greater.

Weight neutrality is a major advantage of the DPP-4 inhibitors; they cause no significant weight gain in patients compared to placebo. The risk of hypoglycemia in clinical studies of DPP-4 inhibitors has also been similar to placebo, and there have been few drug interactions.<sup>22</sup> The dosage of these agents should be reduced in the setting of renal insufficiency.

DPP-4 inhibitors are approved for monotherapy and for use with metformin and thiazolidinediones. In the United States, the DPP-4 inhibitors sitagliptin and saxagliptin have been approved for use, and a third agent, vildagliptin, is available in other countries. The A1C-lowering effects of sitagliptin and saxagliptin appear to be similar.<sup>22,23</sup>

Cost is a major limiting factor with DPP-4 inhibitors and undoubtedly will keep insurance companies from covering these medications

until more data are available. Weaker potency is another limitation that will limit their usefulness, especially given their elevated price.

### Conclusions

The crux of type 2 diabetes control lies in lifestyle. The vast majority 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 help patients control the disorder.

Our therapeutic armamentarium to treat diabetes has grown considerably in the past decade. As a result, physicians must overcome more therapeutic dilemmas in successfully treating their type 2 diabetic patients. As our therapeutic armamentarium has grown, so has the number of studies demonstrating important information about the most appropriate use of these agents. Many pharmaceutical agents cause side effects that could result in serious morbidity if administered to unsuitable patients. Knowledge of the benefits, risks, strengths, and limitations of these pharmaceutical tools is essential to providing optimal care of patients with type 2 diabetes.

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