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.1 The vast majority of those individuals have type 2 diabetes, caused by a relative insulin deficiency superimposed on a background of insulin resistance.2

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 β-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.3,4 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%.4 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.4,5 Weight loss occurring during initiation of metformin occurs even without change in energy expenditure.4

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.6 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.3

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.3 Patient compliance may be better with the sustained-release formulation of metformin rather than immediate-
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. 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 ≥ 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.

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.

**Sulfonylureas**

Sulfonylureas include several medications that act on β-cells to increase insulin release. They bind to the sulfonylurea receptor on the surface of the β-cell and inhibit potassium efflux, thus depolarizing the β-cells and facilitating insulin release. First-generation agents (e.g., acetohexamide, chlorpropamide, and tolbutamide) have largely been replaced by second-generation sulfonylureas (e.g., glyburide, glipizide, and gliclazide) because of improved safety profiles.

Because sulfonylureas act by stimulating insulin release from β-cells, patients with insufficient numbers of β-cells, such as those with type 1 diabetes, pancreatectomy 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, ~ 1.5 percentage points.

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.

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. 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 ≥ 2 kg after initiation of these medications.

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.

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 replaglinide exert their effects by binding to the sulfonylurea receptor and inducing depolarization of the β-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 ~ 1–1.5 percentage points.

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. This may make glinides more attractive medications for individuals who are predisposed to hypoglycemia, such as elderly...
patients. Because of their chemical
dissimilarity to sulfonylureas, 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 sulfonylureas, which
are available in generic formulat-
ions. Their need for frequent dosing
may also adversely affect patient
compliance.

**Thiazolidinediones**
The thiazolidinediones rosi-
litazone 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 ele-
ments in promoter regions to affect
the transcription of as many as
100 genes. They may act to stimu-
late production of proteins such as
adiponectin, which increase insulin
sensitivity.\(^{14,15}\) They may also act
by blocking transcription of other
proteins responsible for insulin
resistance or inflammation.\(^{14,16}\)

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 rosigli-
taxone is to lower glucose levels, and
especially fasting glucose. The usual
reduction of AIC expected from
these medications is 0.5–1.4 percent-
age points.\(^{6}\)

Patients using thiazolidinedi-
diones require hepatic monitoring.
These agents can be associated,
although rarely, with hepatotoxicity.
Therefore, patients should undergo
hepatic function tests before initia-
tion of the medications and regularly
thereafter. Thiazolidinediones
should be discontinued for eleva-
tion in hepatic enzymes greater than
three times the upper limit of nor-
mal. Thiazolidinediones may also
cause an increase in bone loss, which
could lead to fracture.\(^{17}\)

In addition to its glucose-
lowering effects, pioglitazone may
also improve lipid profiles, possibly
because of its partial PPAR\(\alpha\) activ-
ity (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
cautions should be exercised for any
patients who may be predisposed
to developing edema. Use of diuret-
ics 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,\(^{18}\) 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 ampu-
tation, acute coronary syndrome,
coronary artery bypass graft or
percutaneous coronary interven-
tion, and leg revascularization.
There was, however a reduction in
the composite of all-cause mortality,
nonfatal myocardial infarction, and
stroke. A recent meta-analysis\(^{19}\) 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 weak-
nesses. 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 polysac-
charides are poorly absorbed from
the gastrointestinal tract, the effect
of these drugs is to slow the absorp-
tion of carbohydrate after a meal. Slower
absorption of carbohydrate may
limit postprandial hyperglycemia in
patients with limited \(\beta\)-cell reserves.
Clinically, an AIC reduction of
0.5–0.8 percentage points is typical.\(^{6}\)

The primary side effects of
\(\alpha\)-glucosidase inhibitors are flatu-
ence and other gastrointestinal
symptoms. Impaired absorption
of carbohydrate leads to increased
arrival of carbohydrate in the
colon, which can cause consider-
able gas production, diarrhea, and
abdominal pain. Some studies have
demonstrated a potential improve-
ment in risk of cardiovascular
disease in patients with impaired
blood glucose tolerance, although more
research is required to confirm this.
It is also noteworthy that discontinu-
ation of the drug because of side
effects (primarily gastrointestinal) in
such trials was 24%,\(^{20}\)

\(\alpha\)-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. A1C reduction in patients with type 2 diabetes in a recent clinical trial 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. 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.

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 modifications, 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.

REFERENCES


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