
7. Oral Diabetes Drugs

The combination of progressive beta-cell dysfunction and increasing insulin resistance leads to the need for pharmacologic therapy to control hyperglycemia in most patients with type 2 diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) showed that fewer than 25% of persons treated with diet and exercise were able to maintain hemoglobin A1C levels of <7% after 3 years, and fewer than 10% achieved this goal after 9 years.

The goal of pharmacotherapy is to achieve target hemoglobin A1C and fasting and postprandial glucose values within a few months. This is achievable if medications are prescribed early and at adequate dosages. The two major categories of oral diabetes drugs are insulin secretagogues and insulin sensitizers that enhance insulin action. Information about oral hypoglycemic drugs is provided in **Table 7-1**.

When does a patient need to start oral therapy?

If the fasting plasma glucose level remains greater than 126 mg/dL or the hemoglobin A1C value remains above 7% after lifestyle changes (medical nutrition therapy and exercise) have been in place for 4 to 6 weeks, pharmacologic therapy with an oral agent should be initiated.

What do I need to teach my patients about oral medications?

- At the initial visit, describe the progressive nature of type 2 diabetes and stress that oral medications are part of the continuum of care for many patients with diabetes. These agents should *not* be characterized as a sign of patient failure or an indication that the diabetes is worse.

- Provide written information about the medication name, dosage, and timing with food intake and when to take the medication for maximum effectiveness.
- Because of financial or other concerns, many patients choose to take one of their oral medications but not others. Therefore, stress the action and synergistic nature of multiple medications.
- Ask that patients contact you about side effects rather than stopping the medication.
- Provide instructions on how to handle forgotten and missed doses.
- Ask patients to get a first-alert bracelet because of potential hypoglycemia and hyperglycemia issues.
- Provide patients with *Keeping Track of Your Pills* in Chapter 7 of the *Diabetes Care Guide Toolkit* to help them remember to take their medications and *Your Wallet-Sized Medical Record* (in the same chapter of the toolkit) to keep a record of their physician's name, their medical conditions, any allergies they have, and their medications. (Remind them that because the latter tool will contain confidential information, they should be careful who has access to it.)

Insulin Secretagogues

Insulin secretagogues stimulate pancreatic secretion of insulin, which in turn decreases hepatic glucose production and enhances the uptake of glucose by muscle. There are two classes of secretagogues: sulfonylureas and non-sulfonylurea secretagogues.

Sulfonylureas

- *Mechanism of action:* Stimulate insulin secretion from the pancreas.

Table 7-1. Oral Hypoglycemic Drugs

Drug	Duration	Comments
Secretagogues: Sulfonylureas—1st generation		These medications have been largely replaced by 2nd generation sulfonylureas. Because they are cleared hepatically, these medications should be avoided in patients with abnormal liver function.
Tolbutamide	10–12 hours	
Tolazamide	12–24 hours	
Chlorpropamide	>24 hours	
Secretagogues: Sulfonylureas—2nd generation		Consider using in patients starting oral therapy who have normal hepatic/renal function and in patients already on an insulin sensitizer who need additional glucose lowering. Avoid using in patients with impaired renal function (creatinine clearance <60 mL/min) or who are elderly. There is a risk of hypoglycemia for those who skip meals.
Glyburide	12–24 hours	
Glipizide	12–24 hours	
Glimepiride	24 hours	
Nonsulfonylurea secretagogues		Consider using in patients with modest postprandial hyperglycemia and in patients who have irregular timing of meals. These agents can be used in patients with renal impairment.
Repaglinide	4–6 hours	
Nateglinide	4 hours	
Biguanides		Good first-line agent for overweight or obese patients. Consider using in patients already on a secretagogue who need additional glucose lowering. Avoid in patients with renal or hepatic impairment or New York Heart Association (NYHA) class III or IV heart failure.
Metformin	12–18 hours	
Metformin extended release	24 hours	
Alpha-glucosidase inhibitors		Consider using in patients who have primarily postprandial hyperglycemia. Avoid in patients with gastrointestinal disease or hepatic or renal insufficiency. May be used in combination with sensitizers or sulfonylurea secretagogues but not nonsulfonylurea secretagogues.
Acarbose	2–3 hours	
Miglitol	2–3 hours	
Thiazolidinediones		These agents are used as monotherapy in patients on a secretagogue or metformin. Avoid in patients with abnormal hepatic function or NYHA class III or IV heart failure. They may cause weight gain and/or peripheral edema.
Rosiglitazone	Days–weeks	
Pioglitazone	Days–weeks	
Dipeptidyl peptidase IV inhibitors		This drug is used as monotherapy or in conjunction with metformin or thiazolidinediones in patients with type 2 diabetes for whom diet and exercise or their current drug regimen is insufficient as treatment.
Sitagliptin	24 hours	

- **Dosing:** Typically dosed twice daily with the exception of glimepiride, which is taken once daily. The maximum effective dosage of sulfonylureas is usually half the maximum dosage listed on the package insert.
- **Efficacy:** Lower fasting and postprandial glucose levels. Lower A1C value by to 1 to 2 percentage points.
- **Benefits:** The UKPDS showed a 25% decrease in microvascular complications and a 12% reduction in all diabetes-related endpoints in patients who were treated with sulfonylureas, with or without insulin.
- **Adverse effects:** Can cause weight gain and hypoglycemia. These medications are metabolized by the liver and cleared by the kidney

(with the exception of glimepiride, which is excreted both renally and hepatically) and should therefore be used cautiously in patients with impaired hepatic or renal function. Glyburide has an active metabolite and can cause prolonged hypoglycemia in cases of renal failure. Sulfonylureas should be used at low dosages in the elderly, who may have a decreased glomerular filtration rate even with a normal serum creatinine concentration. Caution should also be used with patients who tend to skip meals, as these medications stimulate insulin secretion in a glucose-independent manner.

Nonsulfonylurea Secretagogues

- *Mechanism of action:* Rapidly stimulate insulin secretion from the pancreas.
- *Dosing:* Taken before meals. If a meal is skipped, the medication is not taken.
- *Efficacy:* Lower postprandial blood sugar. Lower A1C by 0.5 to 2 percentage points.
- *Benefits:* Rapid onset of action and short duration of action. Lower risk of hypoglycemia and less weight gain compared with sulfonylureas. Repaglinide is cleared hepatically and may be used in patients with renal impairment. A good option for patients who have erratic timing of meals.
- *Adverse effects:* Metabolized by the liver so should be used with caution in patients with impaired hepatic function.

Insulin Sensitizers

Agents that enhance insulin action work through several mechanisms. They may inhibit glucose absorption, inhibit hepatic gluconeogenesis and glycogenolysis, or increase glucose uptake in fat and muscle. These medications fall into three categories: biguanides (metformin),

thiazolidinediones (TZDs), and alpha-glucosidase inhibitors.

Biguanides (Metformin)

- *Mechanism of action:* Inhibits hepatic gluconeogenesis and to a lesser extent glycogenolysis. Also enhances insulin sensitivity in muscle and fat.
- *Dosing:* Typically given twice daily in divided doses (breakfast and supper). Can be given three times daily with meals. The extended form can be given once daily.
- *Efficacy:* Lowers the level of fasting and postprandial blood sugars. Lowers A1C value by 1 to 2 percentage points.
- *Benefits:* Does not cause hypoglycemia when used as monotherapy and can cause weight loss. Macrovascular benefits: In the UKPDS, the risk of a myocardial infarction decreased by 39% among overweight patients treated with metformin. Diabetes prevention: A 31% reduced incidence of diabetes occurred among persons with impaired glucose tolerance who were treated with metformin in the Diabetes Prevention Program (DPP).
- *Adverse effects:* Lactic acidosis is a rare but potentially fatal adverse effect of metformin. The risk of lactic acidosis is increased if baseline renal function is abnormal or if an acute insult is affecting the kidneys, such as dehydration, major surgery, chronic heart failure, or administration of radiocontrast agents (e.g., during computed tomographic scanning or cardiac catheterization). Metformin should not be prescribed if the serum creatinine is >1.5 mg/dL in men or >1.4 mg/dL in women. Twenty-four hour creatinine clearance should be assessed in the elderly (age >80 years) prior to prescribing metformin. The renal clearance of metformin is decreased approximately 30% when the creatinine clearance is below 60 mL/min. Additional side effects include nausea, abdominal pain or cramping,

diarrhea, and a metallic taste. Starting with a small dosage followed by dosage escalation can minimize these side effects.

Thiazolidinediones

- *Mechanism of action:* Enhance insulin sensitivity in muscle and fat by increasing the expression of glucose transporters.
- *Dosing:* Taken once or twice daily.
- *Efficacy:* Lower the level of fasting and postprandial blood sugar. Lower A1C values by 1 to 2 percentage points. Typically, 8 to 12 weeks are needed to achieve maximum therapeutic effect, and the effects taper over weeks after the medication is discontinued.
- *Benefits:* Do not cause hypoglycemia when used as monotherapy. Salutary effect on lipid parameters: lower the level of triglycerides, raise the HDL cholesterol level, and increase the LDL cholesterol particle size. Reduce levels of inflammatory cytokines associated with cardiovascular risk and may improve endothelial dysfunction.
- *Adverse effects:* Can cause modest to significant weight gain, largely because of fluid retention, and may also cause peripheral edema. These effects are generally less pronounced at lower dosages. These medications should be avoided in patients with New York Heart Association functional class III or IV heart failure. The agent troglitazone was withdrawn from U.S. market due to hepatotoxicity. The U.S. Food and Drug Administration (FDA) no longer issues a black box warning to regularly monitor the levels of transaminases in persons taking pioglitazone or rosiglitazone; however, baseline transaminase levels should be checked before these medications are started. If these levels are >2.5 times normal, these agents should not be used.

Alpha-Glucosidase Inhibitors

- *Mechanism of action:* Competitively block the enzyme alpha-glucosidase in the brush borders of the small intestine, resulting in absorption of carbohydrates in the mid and distal small intestine (delayed absorption).
- *Dosing:* Taken before meals that contain carbohydrates. If a meal is skipped, the medication is not taken.
- *Efficacy:* Lower postprandial hyperglycemia. Lower A1C values by 0.5 to 1 percentage points.
- *Benefits:* Macrovascular disease: The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial showed a nearly 50% reduction in the incidence of cardiovascular events among persons with impaired glucose tolerance who were treated with acarbose.
- *Adverse effects:* Should not be used in people with severe hepatic or renal impairment or in those with gastrointestinal disease. Gastrointestinal side effects can be severe and include bloating, abdominal cramps, diarrhea, and flatulence.

Novel Therapies—Dipeptidyl Peptidase IV Inhibitors

These oral medications inhibit dipeptidyl peptidase IV (DPP IV)—the enzyme that degrades endogenously secreted incretins, including glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide. Higher levels of these incretin hormones lead to increased insulin secretion and suppression of glucagon secretion. Sitagliptin (Januvia) was the first DPP IV inhibitor to be approved by the FDA for use as monotherapy or in combination with metformin or TZDs. A decision from the FDA regarding approval of vildagliptin, another DPP IV inhibitor, is expected in 2007 (after publication of the *ACP Diabetes Care Guide*).

Sitagliptin

- *Mechanism of action:* Inhibits degradation of DPP IV, leading to increased insulin secretion and decreased glucagon secretion.
- *Dosing:* 100 mg taken once daily, with or without meals.
- *Efficacy:* Lowers A1C by 0.7%–1.4%. Has a greater effect on postprandial than fasting glucose levels.
- *Benefits:* Is weight neutral. The mechanism of action involves glucose-dependent insulin secretion. When used as monotherapy or in combination with insulin sensitizers (metformin or TZDs), this drug does not cause hypoglycemia.
- *Adverse effects:* Metabolized in the liver but excreted largely unchanged in the urine. Dosage needs to be reduced by 50% to 75% in patients with renal insufficiency. Most common adverse effects include nasopharyngitis and headache.

How should I choose an agent for a patient starting oral therapy?

Consider whether a patient is relatively more insulin deficient or insulin resistant when choosing an initial oral agent. Persons with central obesity, even those who are only modestly overweight, are typically insulin resistant. Insulin sensitizers are a good choice for initial pharmacotherapy for these patients: for example, metformin 500 mg once or twice daily or a TZD at the lowest dosage, depending on the degree of hyperglycemia when pharmacotherapy is started.

Sulfonylureas may be used in combination with insulin sensitizers when pharmacotherapy is started if significant hyperglycemia (A1C value >9%) and concern about starting a sensitizer at a higher dosage are factors. Lean persons tend to be relatively more insulin deficient than resistant and may benefit less from insulin

sensitizers. For them, it is reasonable to try a sulfonylurea with the understanding that if that fails, insulin treatment will most likely be needed. Some persons have primarily postprandial hyperglycemia without significantly elevated fasting blood sugar levels. In them, it is reasonable to consider either an alpha-glucosidase inhibitor or a nonsulfonylurea secretagogue at meals.

A major problem with diabetes management is that physicians too often start patients on an initial low dosage of a sensitizer or secretagogue and fail to titrate the medication after a few months, despite no improvement in glycemic control. Inertia on the part of physicians to start and accelerate pharmacotherapy leads to suboptimal treatment of hyperglycemia. For example, after the initial 3 months of pharmacotherapy, if the A1C value decreases from 9% to 8.3%, physicians will too often “leave things alone” and recheck laboratory values in another 3 to 6 months. Clinician inertia can leave patients with A1C values above target for months or years. Starting pharmacotherapy is just the first step, and active management with medication titration should be pursued by both the patient and the physician.

Starting, Titrating, and Adding Oral Agents

The natural history of type 2 diabetes includes progressive beta-cell failure and insulin resistance. Increasing the dosages of existing medications and adding new classes of medications are generally the rule for patients with type 2 diabetes: the UKPDS showed that more than 70% of patients fail to maintain a hemoglobin A1C value below 7% with diet or one oral agent.

The dosage of an oral agent should be increased every 4 to 8 weeks until fasting and postprandial glucose levels are at target. You can base these adjustments on home monitoring values you obtain by calling patients between visits. After 3 months, plasma glucose and hemoglobin A1C levels should be measured. If these levels

continue to be elevated, the dosage of the initial oral agent should again be increased and/or a second oral agent with a complementary mechanism of action should be added. It is not always necessary to titrate a medication to its maximal dosage before starting a second agent. Increasing the dosage of a sulfonylurea above half the maximum recommended dosage provides little additional therapeutic benefit. Similarly, patients taking 2000 mg of metformin daily are unlikely to get much additional benefit from increasing the dosage to 2550 mg/d (the maximum recommended dosage).

Combination therapy can generally lower the hemoglobin A1C by an additional 0.6 to 2.0 percentage points. The FDA has approved several combinations of oral agents:

- A sulfonylurea with metformin, a TZD, or an alpha-glucosidase inhibitor
- A nonsulfonylurea secretagogue with metformin
- Metformin with a TZD or an alpha-glucosidase inhibitor

Several of these are available as combination products. These may be helpful to reduce the number of pills a patient needs to take; however, dosing and titration options are less flexible with combination products.

Special considerations in prescribing oral diabetes drugs are summarized in **Table 7-2**.

Helping Patients Succeed with Oral Therapy

What facts about each oral medication do my patients need to know?

Sulfonylureas:

- How to prevent, recognize, and treat hypoglycemia.

Table 7-2. Special Considerations When Prescribing Oral Diabetes Drugs

Elderly patients (age >80 years): Sulfonylureas can cause prolonged hypoglycemia in elderly patients, primarily because of renal insufficiency or the skipping of meals; glyburide in particular should be used with caution in elderly patients because it is cleared renally and has an active metabolite. Metformin should be used with caution in elderly patients and avoided if creatinine clearance is abnormal (<60 mL/min).

Renal impairment (creatinine clearance <60 mL/min): Metformin and alpha-glucosidase inhibitors should be avoided. Glyburide dose should be lowered.

Hepatic impairment: Thiazolidinediones and metformin should be avoided.

Congestive heart failure (decompensated or New York Heart Association class III or IV): Thiazolidinediones and metformin should be avoided.

Pregnancy: No oral drugs are approved by the Food and Drug Administration (FDA) for use in pregnancy. NPH insulin, regular insulin, and the rapid-acting insulin analogues aspart and lispro are endorsed by the American Diabetes Association (ADA) for use in pregnancy but are not formally approved by the FDA. Glulisine, the third available short-acting insulin analogue, has not been studied in pregnancy and is not endorsed by the ADA. Similarly, neither of the long-acting insulin analogues (glargine and detemir) has been studied or endorsed by the ADA for use during pregnancy.

- May cause weight gain. Refer for medical nutrition therapy if this is a concern for the patient.

Nonsulfonylurea secretagogues:

- Greatest effect is on postprandial glucose levels.
- Take just before or up to 30 minutes prior to meals. If meal is omitted, do not take medication.
- How to prevent, recognize and treat hypoglycemia.

Metformin:

- Greatest effect is on fasting blood glucose levels.
- Take with largest meal (usually supper) to reduce nausea and metallic taste.
- Can cause weight loss.
- Diarrhea is common but should decrease with time. If diarrhea persists, may need to reduce the dosage or switch to another medication.
- When to discontinue for surgical or contrast dye procedures.

TZDs:

- May take 2 to 12 weeks to become effective, so be patient.
- Fluid retention may cause swelling and modest weight gain (edema).
- Blood tests need to be done as prescribed to monitor liver function.
- When used with a sulfonylurea or insulin, may necessitate a lower dosage of those agents.

Alpha-glucosidase inhibitors:

- Take with the first bite of your meal.
- If you skip a meal, do not take this medication.
- Main side effects are bloating, gas, and diarrhea.

Sitagliptin

- Is weight neutral.
- In patients with renal insufficiency, dosage reduction is necessary.

What should I ask my patients about their oral medications at each visit?

Some questions to ask patients at each visit about their oral medications include:

- Are you having any side effects?
- Are you having trouble paying for any of your medications?
- About how often do you miss taking your medications?

- Are you taking any vitamins or herbal or natural products?
- Do you have difficulty taking your medications? What specific problems have you encountered? How have you tried to solve this problem? What other options do you think may be effective?
- How well do you think your treatment plan is working to manage your diabetes?
- Do you have any questions about your medications?
- How can I help most?

What tips can I provide to help patients remember to take oral medications?

The following tips can be shared with patients to help them remember to take their medications:

- Take at the same time each day.
- Take when you do other routine activities (e.g., eat meals, get ready for bed).
- Store in a pill container with days of the week (see *Keeping Track of Your Pills* in Chapter 7 of the toolkit).
- Keep a dose in a purse, briefcase, or pocket.
- Create a reminder system for doses that are especially hard to remember—for example, a watch with an alarm clock, an electronic reminder through your computer at work, or a sticky note where you will be sure to see it at the appropriate time.

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