

# Comparing Oral Medications for Adults With Type 2 Diabetes

## CLINICIAN'S GUIDE

### CLINICAL ISSUE

Controlling blood glucose levels for people with type 2 diabetes often requires several strategies. The clinical approach begins with lifestyle modifications, including increased physical activity and diet control. Weight loss usually improves blood glucose levels for people with type 2 diabetes. However, many also need oral medications or insulin.

There is a large body of clinical evidence that can help inform decisions about hypoglycemic medications. This guide summarizes evidence from both observational studies and controlled trials that compare the effectiveness and safety of oral hypoglycemics.

Standard oral hypoglycemic regimens include single drugs (monotherapy) and combinations of two or three drugs from different classes, such as metformin and a sulfonylurea. Choosing among available oral hypoglycemics requires consideration of their benefits as well as their adverse effects and cost. The dose and price of the drugs reviewed in the comparative studies are listed on the back page.

This guide does not address insulin, combining oral medications with insulin, older first-generation sulfonylureas, or the new drug class of DPP-IV inhibitors. It does not cover using oral hypoglycemics for type 1 diabetes or gestational diabetes. It also does not review the evidence about the effectiveness of diet, exercise, and weight loss.

**SOURCE** The source material for this guide is a systematic review of 216 research studies. The review, *Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults With Type 2 Diabetes* (2007), was prepared by the Johns Hopkins Evidence-based Practice Center. The Agency for Healthcare Research and Quality (AHRQ) funded the systematic review and this guide. The guide was developed using feedback from clinicians who reviewed preliminary drafts.

### CLINICAL BOTTOM LINE

Based on studies that compare oral hypoglycemics, we know that:

- As single agents, all second-generation sulfonylureas, thiazolidinediones (TZDs), metformin, and repaglinide work well to reduce hemoglobin A1c (HbA1c) levels by about 1 percentage point on average.

**LEVEL OF CONFIDENCE:** ● ● ○

- Combination therapies reduce HbA1c about 1 percentage point more than monotherapies.

**LEVEL OF CONFIDENCE:** ● ● ○

- People taking sulfonylureas, TZDs, and repaglinide gain about 2–10 lbs. Metformin does not cause weight gain.

**LEVEL OF CONFIDENCE:** ● ● ○

### CONFIDENCE SCALE

The confidence ratings in this guide are derived from a systematic review of the literature. The level of confidence is based on the overall quantity and quality of clinical evidence.

**HIGH** ● ● ● There are consistent results from good quality studies.

**MEDIUM** ● ● ○ Findings are supported, but further research could change the conclusions.

**LOW** ● ○ ○ There are very few studies, or existing studies are flawed.

## COMPARING EFFECTIVENESS

### HbA1c

#### Single Agents

Most oral hypoglycemics work equally well at lowering blood glucose, as measured by hemoglobin A1c (HbA1c). They lower HbA1c about 1 percentage point on average (i.e., HbA1c can go from 8 percent to 7 percent after a medication is started).

**LEVEL OF CONFIDENCE:** ● ● ○

Evidence is insufficient to compare the effectiveness of alpha-glucosidase inhibitors and nateglinide with the other oral hypoglycemics.

#### Combining Oral Hypoglycemics

Combinations of oral hypoglycemics will lower HbA1c about 1 percentage point more than monotherapy.

- Combining metformin and a sulfonylurea reduces HbA1c more than using metformin or a sulfonylurea alone.

**LEVEL OF CONFIDENCE:** ● ● ●

- Combining a TZD with metformin or a sulfonylurea reduces HbA1c more than using metformin or a sulfonylurea alone.

**LEVEL OF CONFIDENCE:** ● ● ○

- Evidence from comparative studies is insufficient to determine how well other combinations of oral hypoglycemic drugs work to lower HbA1c.

### Weight

Metformin monotherapy did not affect the weight of participants in placebo-controlled trials. In randomized trials comparing metformin with other oral hypoglycemics, people taking oral hypoglycemics other than metformin gained 2–10 lbs.

**LEVEL OF CONFIDENCE:** ● ● ○

Evidence is insufficient to determine the effects of alpha-glucosidase inhibitors and nateglinide on weight.

### HDL

Most oral hypoglycemics have very little effect on high density lipoprotein (HDL).

- Pioglitazone increases HDL by about 3–5 mg/dl compared with metformin and sulfonylureas.

**LEVEL OF CONFIDENCE:** ● ● ○

- Pioglitazone increases HDL by about 1–3 mg/dl more than rosiglitazone, which also raises HDL.

**LEVEL OF CONFIDENCE:** ● ● ○

### LDL

Most oral hypoglycemics have a small effect on low density lipoprotein (LDL).

- Metformin monotherapy decreases LDL by about 10 mg/dl when compared with sulfonylurea monotherapy.

**LEVEL OF CONFIDENCE:** ● ● ○

- The combination of metformin and a sulfonylurea decreases LDL by about 8 mg/dl when compared with sulfonylurea monotherapy.

**LEVEL OF CONFIDENCE:** ● ● ○

- Both rosiglitazone and pioglitazone increase LDL, but rosiglitazone has a greater effect. Rosiglitazone increases LDL by 10 mg/dl more than pioglitazone.

**LEVEL OF CONFIDENCE:** ● ● ○

## AGENTS & ACTIONS

Drug Class	Drug Name	Brand Name	Mechanism of Action
Biguanides	Metformin	Glucophage®	Inhibit glucose production by the liver
Sulfonylureas (second-generation)	Glimepiride Glipizide Glyburide	Amaryl® Glucotrol® Diabeta®, Glynase PresTab®, Micronase®	Increase insulin secretion by pancreatic beta cells
Meglitinides	Repaglinide Nateglinide	Prandin® Starlix®	Increase insulin secretion by pancreatic beta cells
Thiazolidinediones (TZDs)	Pioglitazone Rosiglitazone	Actos® Avandia®	Increase glucose uptake by skeletal muscle
Alpha-glucosidase inhibitors	Acarbose Miglitol	Precose® Glyset®	Inhibit carbohydrate absorption in the small intestine

## ASSESSING RISKS

### Hypoglycemia

Sulfonylureas and repaglinide cause similar rates of hypoglycemia. It occurs in about 14 percent of people taking a sulfonylurea and 12 percent of people taking repaglinide.

Sulfonylureas are more likely to cause hypoglycemia than metformin or TZDs. People taking sulfonylureas have about a 7-percent higher risk of hypoglycemia.

The risk of hypoglycemia increases with combination therapy. People taking a combination of oral hypoglycemics have about an 11-percent higher risk than people on monotherapy.

### Lactic Acidosis

Lactic acidosis is relatively uncommon. In one year, about 1 of 10,000 people who are generally healthy (without significant pulmonary, renal, or hepatic dysfunction) and taking any oral hypoglycemic will develop lactic acidosis. The rate of lactic acidosis is similar for metformin and other oral hypoglycemics.

### Cardiac Problems

TZDs are 1–2 percent more likely to exacerbate congestive heart failure than the other oral hypoglycemics. In August 2007, the Food and Drug Administration strengthened the warning about the risk of heart failure with TZDs. These drugs are not recommended for people with symptomatic heart failure.

The risk of ischemic cardiovascular events with TZDs has received considerable attention. It is still unknown whether TZDs are more likely than other oral hypoglycemics to increase the risk of myocardial infarction.

## Gastrointestinal Problems

People who take metformin have more gastrointestinal (GI) problems, including diarrhea, nausea, and gas, than those who take TZDs or sulfonylureas. GI problems are about 10 percent more common for people taking metformin than for people taking other oral hypoglycemics.

Fewer people have GI problems when metformin is combined with a sulfonylurea or a TZD than when metformin is used alone. When metformin was studied in combination with other agents, a lower dose of metformin was used.

### Edema

TZDs are 5–10 percent more likely to cause peripheral edema than the other oral hypoglycemics.

### Anemia

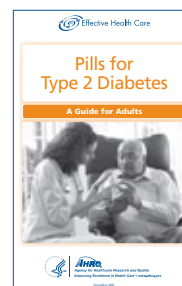
TZDs are about 3 percent more likely to cause anemia (hematocrit drop of 1–3 percent) than the other oral hypoglycemics.

## STILL UNKNOWN

Most studies of oral hypoglycemics last 1 year or less and focus on short-term outcomes. There is insufficient evidence from comparative studies to determine whether oral hypoglycemics differ in their effects on long-term outcomes, such as cardiovascular disease, retinopathy, kidney disease, and neuropathy. Better postmarketing studies and research that includes long-term assessments would help address this critical need.

It is not known whether the safety and effectiveness of oral hypoglycemics for adults with type 2 diabetes vary among people of different genders, races, ethnicities, or age groups, or those who have coexisting medical conditions.

## RESOURCE FOR PATIENTS



*Pills for Type 2 Diabetes: A Guide for Adults* is a companion to this Clinician's Guide. It can help people talk to their health care professional about oral medications for

type 2 diabetes. It provides information about:

- Types of oral diabetes medications.
- Benefits, risks, and price.

## FOR MORE INFORMATION

For electronic copies of the consumer's guide, this clinician's guide, and the full systematic review, visit this Web site: [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)

### For free print copies call:

The AHRQ Publications Clearinghouse  
(800) 358-9295

*Consumer's Guide*,  
AHRQ Pub. No. 07(08)-EHC010-2A

*Clinician's Guide*,  
AHRQ Pub. No. 07(08)-EHC010-3

AHRQ created the John M. Eisenberg Center at Oregon Health & Science University to make research useful for decisionmakers. This guide was prepared by Bruin Ruge, M.D., Theresa Bianco, Pharm.D., Valerie King, M.D., Sandra Robinson, M.S.P.H., Martha Schechtel, R.N., and David Hickam, M.D., of the Eisenberg Center.

## Dose and Price of Oral Hypoglycemics

Drug Name <sup>1</sup>	Brand Name	Dose <sup>2</sup>	Price for 1-Month Supply <sup>3</sup>	
			Generic	Brand
<b>BIGUANIDES</b>				
Metformin	Glucophage®	500 mg daily	\$20	\$30
		500 mg bid	\$40	\$60
850 mg bid		\$70	\$95	
1000 mg bid		\$85	\$120	
	Glucophage XR®	1000 mg daily	\$45	\$60
		2000 mg daily	\$90	\$115
<b>SECOND-GENERATION SULFONYLUREAS</b>				
Glimepiride	Amaryl®	1 mg daily	\$10	\$15
		2 mg daily	\$20	\$25
		4 mg daily	\$35	\$45
		8 mg daily	\$75	\$85
Glipizide	Glucotrol®	5 mg daily	\$10	\$15
		10 mg daily	\$20	\$30
		10 mg bid	\$40	\$60
		20 mg bid	\$75	\$125
	Glucotrol XL®	5 mg daily	\$10	\$15
		20 mg daily	\$50	\$65
Glyburide	Diabeta®, Micronase®	2.5 mg bid	\$30	\$35
		5 mg daily	\$25	\$30
		5 mg bid	\$45	\$65
		Glynase PresTab®	1.5 mg daily	\$10
		3 mg daily	\$20	\$35
		6 mg bid	\$60	\$115
<b>THIAZOLIDINEDIONES (TZDs)</b>				
Pioglitazone	Actos®	15 mg daily	NA	\$115
		30 mg daily	NA	\$190
		45 mg daily	NA	\$205
Rosiglitazone	Avandia®	2 mg bid	NA	\$145
		4 mg daily	NA	\$110
		8 mg daily	NA	\$200
<b>MEGLITINIDES (taken before meals)</b>				
Repaglinide	Prandin®	0.5 mg tid	NA	\$130
		1 mg tid	NA	\$130
		4 mg tid	NA	\$265
Nateglinide	Starlix®	60 mg tid	NA	\$130
		120 mg tid	NA	\$135
<b>ALPHA-GLUCOSIDASE INHIBITORS (taken with meals)</b>				
Acarbose	Precose®	25 mg tid	NA	\$80
		50 mg tid	NA	\$85
		100 mg tid	NA	\$105
Miglitol	Glyset®	25 mg tid	NA	\$75
		50 mg tid	NA	\$85
		100 mg tid	NA	\$95
<b>COMBINATIONS</b>				
Glyburide/metformin	Glucovance®	2.5 mg/500 mg bid	\$65	\$75
		5 mg/500 mg bid	\$65	\$75
Glimepiride/rosiglitazone	Avandaryl®	2 mg/4 mg daily	NA	\$120
		4 mg/4 mg daily	NA	\$120
Metformin/rosiglitazone	Avandamet®	500 mg/4 mg bid	NA	\$220
		1000 mg/2 mg bid	NA	\$130
Metformin/pioglitazone	Actoplus Met®	500 mg/15 mg bid	NA	\$180
		850 mg/15 mg bid	NA	\$180

<sup>1</sup> These drugs were evaluated in the systematic review.

<sup>2</sup> Doses are representative of those used in the research studies.

<sup>3</sup> Average Wholesale Price from *Drug Topics Red Book*, 2007.

XL/XR = extended release,  
bid = twice a day,  
tid = three times a day,  
NA = not available as generic.