Effective Health Care Program

Diabetes
Type 2 Diabetes

Comparing Medications for Adults With Type 2 Diabetes

Focus of Research for Clinicians

A systematic review of 166 clinical studies published between January 1966 and April 2010 examined the comparative effectiveness, benefits, and adverse effects of available monotherapy and two-drug combinations of medications for adults with type 2 diabetes (see list on page 2). The review did not cover treatment of type 1 diabetes or gestational diabetes nor does it review evidence regarding the effectiveness of diet, exercise, and weight loss. The full report, listing all studies, is available at http://www.effectivehealthcare.ahrq.gov/diabetesmeds.cfm. This summary, based on the full report of research evidence, is provided to inform discussions with patients of options and to assist in decisionmaking along with consideration of a patient's values and preferences. However, reviews of evidence should not be construed to represent clinical recommendations or guidelines.

Background Information

The management of hyperglycemia is an important focus of treatment to achieve improved macrovascular and microvascular outcomes in patients with type 2 diabetes. Controlling blood-glucose levels often requires several strategies, including weight loss if needed, dietary control, increased physical activity, and antidiabetic medications.[1]

Treatment regimens include single drugs and combinations of drugs from different classes. Choosing among the available medications requires consideration of benefits, adverse effects, mechanism of action, and cost. In 2007, the Agency for Healthcare Research and Quality published its first systematic review on the comparative effectiveness of oral medications for type 2 diabetes. The 2011 update includes newer medications and two-drug combinations.

Conclusion

Evidence on the comparative effectiveness of antidiabetic medications for long-term macrovascular and microvascular outcomes is limited. However, evidence is available on intermediate outcomes. Many antidiabetic medications given as monotherapy work equally well to lower blood glucose. Two-drug combinations decrease hemoglobin A1c (HbA1c) further. Most agents (except metformin [MET] and glucagon-like peptide-1 [GLP-1] receptor agonists) are associated with increases in weight. The risk of mild to moderate hypoglycemia varies—it is highest for second-generation sulfonylureas (SU) and is increased for some two-drug combinations over monotherapy. MET may cause gastrointestinal (GI) upset. A United States Food and Drug Administration (FDA) warning indicates that thiazolidinediones (TZD) are associated with increased risks for cardiac failure, cardiovascular events, hip and nonhip fractures, and other risks in some patients. Tables 1, 2, and 3 summarize evidence about benefits, adverse events, and long-term benefits.

[1] American Diabetes Association; European Association for the Study of Diabetes

Clinical Bottom Line *(Detailed comparisons: Tables 1–3)*

Glycemic Control (HbA1c)

- On average, many of the single agents reduce HbA1c levels by 1 percentage point (●●○ to ●●●).
- On average, two-drug combination therapies reduce HbA1c about 1 percentage point more than monotherapies (●●○ to ●●●).
- Some two-drug combinations are equally effective (●●○) and others, though less studied, show promise (●○○).

Weight

- MET monotherapy was associated with less weight gain when compared with other monotherapies or two-drug combinations (●●○ to ●●●).
- When compared to second-generation sulfonylureas (SUs), GLP-1 receptor agonists were associated with less weight gain (●●○).
- The combination MET/SU was associated with less weight gain than were two-drug combinations with TZDs (●●○).
- Some newer agents in two-drug combinations show promise for lower levels of weight gain (●○○).

Risk of Adverse Effects

- SUs and meglitinides (MEG) are more likely to cause mild to moderate hypoglycemia than monotherapy with MET, TZD, or a dipeptidyl peptidase-4 (DPP-4) inhibitor (●●○ to ●●●).
- When compared to MET monotherapy, two-drug combinations with MET increase the risk of mild to moderate hypoglycemia, except for MET/DPP-4 inhibitor combinations (●●○).
- MET is associated with more GI adverse events when compared with other single agents (●●○ to ●●●).
- TZDs are associated with a higher risk of congestive heart failure when compared with SUs (●●○). (See FDA Alerts for TZDs on page 5.)
- TZDs alone or in combination are associated with a higher risk of hip and nonhip fractures when compared with other agents (●●●).
- FDA warnings indicate that TZDs are associated with increased risks for cardiac failure, cardiovascular events, fractures, and other risks. (See FDA Alerts for TZDs on page 5.)

Strength of Evidence

High:	●●●	There are consistent results from good-quality studies. Further research is very unlikely to change the conclusions.
Moderate:	●●○	Findings are supported, but further research could change the conclusions.
Low:	●○○	There are very few studies, or existing studies are flawed.
Insufficient:	○○○	Evidence either is unavailable or does not permit estimation of an effect.

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Type 2 Diabetes Medications Studied by Class With Abbreviations

Class	*Generic Name*	*Brand Name*
Biguanides	Metformin (MET)	Glucophage®, Glucophage XR®
Second-generation sulfonylureas (SU)	Glimepiride	Amaryl®
	Glipizide	Glucotrol®, Glucotrol XL®, GITS®
	Glyburide	Diabeta®, Micronase®, Glynase Prestab®
Meglitinides (MEG)	Repaglinide (Rep)	Prandin®
	Nateglinide	Starlix®
Thiazolidinediones (TZD)	Pioglitazone (Pio)	Actos®
	Rosiglitazone (RSG)	Avandia®
Dipeptidyl peptidase-4 (DPP-4) inhibitors	Sitagliptin	Januvia®
	Saxagliptin	Onglyza®
Glucagon-like peptide-1 (GLP-1) receptor agonists	Exenatide injection	Byetta®
	Liraglutide injection	Victoza®
Insulin	NPH insulin	Humulin N®, Novolin N®
	Insulin detemir	Levemir®
	Insulin glargine	Lantus®
	70% NPH: 30% Regular	Humulin® 70/30, Novolin® 70/30
	50% lispro protamine suspension: 50% lispro	Humalog® Mix50/50™
	75% lispro protamine suspension: 25% lispro	Humalog® Mix75/25™
	70% aspart protamine suspension: 30% aspart	NovoLog® Mix 70/30

Clinical Outcomes Table 1: Benefits *(Findings followed by evidence on specific comparisons.)*

Monotherapy Versus Monotherapy	
HbA1c	Monotherapy with MET, SU, TZD, or Rep reduced HbA1c levels by about 1 percent: MET versus SU ●●● SU versus TZD ●●○ Pio versus RSG ●●○ MET versus TZD ●●○ SU versus Rep ●●○
	MET lowers HbA1c 0.4% better than do DPP-4 inhibitors. ●●○
Weight	From the 2007 report, many oral diabetes medications (TZD, SU, and Rep) increased weight by 1–5 kg; however, MET did not increase weight in placebo-controlled trials. ●●○ to ●●●
	MET maintained or decreased weight when compared with other monotherapies, as shown below: MET versus TZD, -2.6 kg ●●● MET versus SU, -2.7 kg ●●● MET versus DPP-4 inhibitor, -1.4 kg ●●○
	GLP-1 receptor agonists were associated with less weight gain, by -2.5 kg, when compared with SUs. ●●○
	SU and MEG had similar effects on body weight. ●●●
LDL	MET was associated with lower LDL levels when compared with: SU, by -10.1 mg/dL ●●● RSG, by -12.8 mg/dL ●●○ Pio, by -14.2 mg/dL ●●○ DPP-4 inhibitors, by -5.9 mg/dL ●●○
HDL	Pio was associated with higher HDL levels when compared with: MET, by 3.2 mg/dL ●●● RSG, by 2.3 mg/dL ●●○ SU, by 4.3 mg/dL ●●○
	MET was associated with HDL levels similar to those of: SUs ●●● RSG ●●○
TG	MET was associated with lower TG levels when compared with: RSG, by -27 mg/dL ●●○ SU, by -8.6 mg/dL ●●○
	Pio was associated with lower levels of TG by -27.2 mg/dL when compared with MET. ●●●
	TG levels for SU and MEG were similar. ●●○
Monotherapy Versus Combination Therapy	
HbA1c	Two-drug combination therapies were more effective than monotherapy, reducing HbA1c by an additional 1 percent. MET versus MET/SU ●●● MET versus MET/TZD ●●● MET versus MET/DPP-4 inhibitors ●●○
Weight	MET had a more favorable effect on weight when compared with these combination therapies: MET/TZD, by -2.2 kg ●●● MET/SU, by -2.3 kg ●●●
LDL	MET/RSG was associated with higher levels of LDL, by 14.5 mg/dL, when compared with MET. ●●●
HDL	When compared with MET monotherapy: MET/RSG was associated with higher HDL levels by 2.8 mg/dL. ●●● MET/DPP-4 inhibitor was associated with similar levels of HDL. ●●○ MET/Pio was associated with higher levels of HDL. ●○○
TG	MET was associated with lower TG levels, by -14.5 mg/dL, when compared with MET/RSG. ●●●

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Combination Therapy Versus Combination Therapy (Continued from previous page.)	
HbA1c	MET/SU and MET/TZD were associated with similar HbA1c levels. ●●○
	Several other combinations had similar efficacy at reducing HbA1c: MET/TZD versus MET/Rep ●○○ MET/TZD versus MET/sitagliptin ●○○ MET/TZD versus MET/GLP-1 receptor agonist ●○○ MET/SU versus MET/DPP-4 inhibitor ●○○ MET/GLP-1 receptor agonist versus MET/basal insulin ●○○
Weight	MET/SU had a more favorable effect on weight when compared with these combinations: TZD/SU, by -3.2 kg ●●○ MET/TZD, by -0.9 kg ●●○
	MET/GLP-1 receptor agonists had a more favorable effect on weight, by about -1.9 to -12.3 kg, when compared with the following combinations: MET/SU ●○○ MET/TZD ●○○ MET/basal insulin ●○○ MET/DPP-4 inhibitor ●○○
	MET/DPP-4 inhibitors had a more favorable effect on weight, by about -1.5 to -2.5 kg, when compared with: MET/TZD ●○○ MET/SU ●○○
LDL	MET/SU was associated with lower levels of LDL, by about -13.5 mg/dL, when compared with MET/RSG. ●●○
HDL	When compared with the combination of MET/SU: MET/Pio was associated with 5-mg/dL higher levels of HDL. ●●○ MET/RSG was associated with 2.7-mg/dL higher levels of HDL. ●●○ SU/Pio was associated with higher levels of HDL. ●○○
TG	When compared with the combination of MET/SU: MET/Pio was associated with lower levels of TG. ●●○ MET/RSG was associated with similar levels of TG. ●●○

DPP-4 inhibitors = dipeptidyl peptidase-4 inhibitors; GLP-1 receptor agonists = glucagon-like peptide–1 receptor agonists; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MEG = meglitinides; MET = metformin; Pio = pioglitazone; Rep = repaglinide; RSG = rosiglitazone; SU = second-generation sulfonylureas; TG = triglycerides; TZD = thiazolidinediones.

Clinical Outcomes Table 2: Adverse Events *(Findings followed by evidence on specific comparisons.)*

Monotherapy Versus Monotherapy	
Mild to moderate hypoglycemia	The risk of mild to moderate hypoglycemia for SU alone was: 4.6-fold higher than MET ●●● 3.9-fold higher than TZD ●●● higher than with DPP-4 inhibitors ●●○
	When compared with MET monotherapy: MEG was associated with a 3-fold increase in hypoglycemia ●●○ TZD was associated with a similar risk of hypoglycemia ●●○
GI adverse events	MET was associated with more GI adverse events than were: TZD ●●● SU ●●○ DPP-4 inhibitors ●●○
	TZDs and SUs were associated with similar rates of GI adverse events. ●●●
Liver injury	Rates of liver injury for TZDs were low (range, 0% to 0.9%) and were similar to: SUs (range, 0% to 1%) ●●● MET (range, 0.8% to 2.2%) ●●○
Hip/nonhip fractures	TZDs were associated with higher rates of bone fractures when compared with MET. ●●●

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Clinical Outcomes Table 2: Adverse Events *(Findings followed by evidence on specific comparisons.)*

Monotherapy Versus Monotherapy (Continued from previous page.)	
CHF (see FDA alert below)	Rates of CHF were higher for TZDs than for: SUs ●●○
	There were no long-term trials that provided a robust assessment of the comparative safety of the DPP-4 inhibitors and GLP-1 receptor agonists with respect to the risk of heart failure. ○○○
Severe lactic acidosis	While the risk of severe lactic acidosis was low for MET, SU, and MET/SU, individuals with significant renal, liver, or cardiovascular disease were excluded from the studies. ●●○
Monotherapy Versus Combination Therapy	
Mild to moderate hypoglycemia	When compared with MET monotherapy: MET/SU was associated with an increased risk. ●●○ MET/TZD was associated with an increased risk. ●●○ MET/DPP-4 inhibitor was associated with a similar risk. ●●○
GI adverse events	If the dose of MET was higher in the monotherapy arm than in the combination component, MET monotherapy was associated with more GI adverse events than these combinations: MET/SU ●●○ MET/TZD ●●○
Hip/nonhip fractures	MET/TZD was associated with higher rates of bone fractures than was MET. ●●●
Combination Therapy Versus Combination Therapy	
Mild to moderate hypoglycemia	MET/SU was associated with higher levels of hypoglycemia than were these combinations: MET/TZD ●●● MET/GLP-1 receptor agonist (liraglutide) ●●○
	MET/basal insulin combinations were associated with lower rates of hypoglycemia than were MET/premixed insulin combinations. ●●○
GI adverse events	MET/SU was associated with more GI adverse events than was SU/TZD. ●●○
Hip/nonhip fractures	Combination therapy with a TZD was associated with higher rates of bone fractures than was MET/SU. ●●●

CHF = congestive heart failure; DPP-4 inhibitors = dipeptidyl peptidase-4 inhibitors; GI = gastrointestinal; GLP-1 receptor agonists = glucagon-like peptide–1 receptor agonists; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MEG = meglitinides; MET = metformin; Pio = pioglitazone; Rep = repaglinide; RSG = rosiglitazone; SU = second-generation sulfonylureas; TG = triglycerides; TZD = thiazolidinediones.

FDA Alerts for TZDs

According to FDA boxed warnings, TZDs may cause or exacerbate CHF in some patients and are contraindicated in patients with serious or severe heart failure. In 2010, the FDA placed additional prescribing restrictions on rosiglitazone use for type 2 diabetes in response to data that suggested an elevated risk of cardiovascular events, including myocardial infarction and stroke. In 2011, the FDA released a Safety Announcement that the use of pioglitazone for more than one year may be associated with an increased risk of bladder cancer (for more information visit www.fda.gov).

Gaps in Knowledge

- Studies are needed to address the efficacy of treatments for hyperglycemia in patients with type 2 diabetes who have varying levels of underlying cardiovascular and renal disease, who come from different ethnic groups, or who have variant forms of type 2 diabetes.
- Additional comparative studies are needed, including comparisons of newer medications, combinations with basal or premixed insulin and MET or other oral agents, and additional two-drug combinations.
- Sufficient data on event rates are needed to analyze major clinically important outcomes, adverse events, and long-term complications of type 2 diabetes.

Clinical Outcomes Table 3: Long-Term Benefits *(Findings followed by evidence on specific comparisons.)*

Studies examining long-term benefits were limited. Only low levels of evidence were available for long-term outcomes (except as noted below for Pio, which may provide benefit for renal function), making it difficult to draw conclusions.

Monotherapy Versus Monotherapy	
All-cause mortality	MET was associated with a lower risk of all-cause mortality when compared with SU. ●○○
	There was insufficient evidence for all other comparisons, including: DPP-4 inhibitor comparisons ○○○ RSG versus Pio combinations ○○○ Oral agent/insulin combinations ○○○ GLP-1 receptor agonist comparisons ○○○ All other combination therapy comparisons ○○○
Cardiovascular mortality	MET was associated with a slightly lower risk of cardiovascular mortality when compared with SU. ●○○
	MET was associated with rates of cardiovascular mortality similar to those of TZDs. ●○○
Cardiovascular and cerebrovascular morbidity	MET versus TZD was inconclusive. ●○○
Nephropathy	Pio lowered the albumin-to-creatinine ratio better than MET, likely indicating less nephropathy. ●●○
Retinopathy	Evidence was insufficient for all comparisons. ○○○
Monotherapy Versus Combination Therapy	
Cardiovascular mortality	MET alone was slightly favored over MET/RSG. ●○○
	Evidence was insufficient for all other comparisons. ○○○
Cardiovascular and cerebrovascular morbidity	MET alone was favored over MET/RSG for risk of fatal and nonfatal ischemic heart disease. ●○○
	Evidence was insufficient for all other comparisons. ○○○
Combination Therapy Versus Combination Therapy	
Cardiovascular mortality	Evidence was insufficient for all comparisons of combination therapies. ○○○
Cardiovascular and cerebrovascular morbidity	Evidence was insufficient for all comparisons of combination therapies. ○○○

The abbreviations used in this table are defined at the bottom of Table 2.

Average Wholesale Prices for Diabetes Medicines

Drug Type			*Price for 1-Month Supply*	
Generic	*Brand*	*Dose*	*Generic*	*Brand*
Biguanides				
Metformin	Glucophage®	500 mg once a day	$25	$35
		500 mg twice a day	$50	$70
		500 mg three times a day	$75	$105
		850 mg once a day	$40	$60
		850 mg twice a day	$80	$115
		850 mg three times a day	$120	$175
		1,000 mg once a day	$45	$70
		1,000 mg twice a day	$90	$140
	Glucophage XR®	500 mg once a day	$25	$35
		1,000 mg once a day	$50	$70
		1,500 mg once a day	$75	$105
		2,000 mg once a day	$100	$140
Second-Generation Sulfonylureas				
Glimepiride	Amaryl®	1 mg once a day	$15	$20
		2 mg once a day	$25	$35
		4 mg once a day	$40	$60
		8 mg once a day	$80	$120
Glipizide	Glucotrol®	5 mg once a day	$15	$25
		10 mg once a day	$25	$40
		10 mg twice a day	$50	$80
		20 mg twice a day	$100	$160
	Glucotrol XL®	5 mg once a day	$15	$25
		20 mg once a day	$65	$90
Glyburide	Diabeta®, Micronase®	2.5 mg twice a day	$40	$45
		5 mg once a day	$30	$40
		5 mg twice a day	$60	$80
	Glynase PresTab®	1.5 mg once a day	$9	$30
		3 mg once a day	$18	$45
		6 mg twice a day	$72	$145
Meglitinides				
Repaglinide	Prandin®	0.5 mg three times a day	NA	$255
		1 mg three times a day	NA	$255
		4 mg three times a day	NA	$505
Nateglinide	Starlix®	60 mg three times a day	NA	$195
		120 mg three times a day	NA	$200
Thiazolidinediones				
Pioglitazone	Actos®	15 mg once a day	NA	$180
		30 mg once a day	NA	$275
		45 mg once a day	NA	$300

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Average Wholesale Prices for Diabetes Medicines *(Continued from previous page.)*

Drug Type			*Price for 1-Month Supply*	
Generic	*Brand*	*Dose*	*Generic*	*Brand*
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors				
Sitagliptin	Januvia®	100 mg once a day	NA	$230
Saxagliptin	Onglyza®	2.5 mg–5 mg once a day	NA	$220
Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists				
Exenatide	Byetta®	Injection of 5 mcg twice a day	NA	$300
		Injection of 10 mcg twice a day	NA	$330
Liraglutide	Victoza®	Injection of 0.6 mg once a day	NA	$160
		Injection of 1.2 mg once a day	NA	$315
		Injection of 1.8 mg once a day	NA	$470

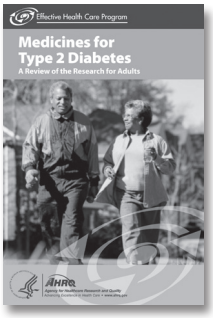
These prices are the Federal median price for generic medicines and the average wholesale price for brand name medicines rounded to the next $5. These prices come from *Red Book: Pharmacy's Fundamental Reference*, 2011 Edition.

XR/XL = extended release NA = not available as a generic

What To Discuss With Your Patients

- Establishing a goal for HbA1c and strategies to help accomplish that goal, including weight loss, exercise, and consistent use of medication.
- Strategies to increase adherence, including creating a medication schedule, addressing the costs of medications, and reporting adverse effects in a timely manner.
- The need for regular glucose testing and routine blood tests for HbA1c.
- What side effects to expect from the chosen medicines, and when to contact you if side effects occur.

Resource for Patients



Medicines for Type 2 Diabetes, A Review of the Research for Adults is a companion to this clinician research summary. It can help people talk to their health care professionals about medications for type 2 diabetes. It provides information about:

- Types of diabetes medications.
- The benefits and risks of medications.
- Costs of medications.

Ordering Information

For electronic copies of *Medicines for Type 2 Diabetes, A Review of the Research forAdults*, this clinician research summary, and the full systematic review, visit www.effectivehealthcare.ahrq.gov/diabetesmeds.cfm. To order free print copies, call the AHRQ Publications Clearinghouse at 800-358-9295.

Source

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