Type 2 Diabetes Mellitus: ACP Releases Updated Recommendations for Oral Pharmacologic Treatment

Key Points for Practice

- Metformin should be the first medication prescribed for diabetes when an oral agent is required.
- Combination treatment is superior to metformin alone for decreasing A1C levels, weight, and blood pressure.
- Medications should be selected based on benefits, possible harms, and cost.

From the AFP *Editors*

This series is coordinated by Sumi Sexton, MD, Associate Deputy Editor.

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CME This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz on page 431. Author disclosure: No relevant financial affiliations.

Type 2 diabetes mellitus, which occurs in up to 95% of persons with diabetes, is typically managed with lifestyle modifications (e.g., diet, exercise) and medication (e.g., oral drugs). When weight loss or lifestyle modifications are initially unsuccessful, medication is often prescribed. The American College of Physicians (ACP) previously released guidelines in 2012 regarding the effectiveness and safety of oral pharmacologic treatment for type 2 diabetes; however, new evidence has emerged and new drugs have been approved by the U.S. Food and Drug Administration. For this reason, the ACP has released updated guidelines for the management of type 2 diabetes with oral medication.

Recommendations

If glycemic control needs to be improved with medication in persons with type 2 diabetes, metformin should be prescribed because it can efficiently lower glycemic levels, is linked to losing weight and fewer occurrences of hypoglycemia, and is generally less expensive than other options. It is contraindicated in persons with decreased tissue perfusion, hemodynamic instability, advanced liver disease, alcohol abuse, acute unstable congestive heart failure, and conditions that can result in lactic acidosis.

Because combination treatment has been shown to be superior to metformin alone for decreasing A1C levels, weight, and blood pressure, adding a sulfonylurea, thiazolidinedione, or sodium glucose cotransporter-2 (SGLT-2) or dipeptidyl peptidase-4 (DPP-4) inhibitor can be considered when additional oral treatment is being discussed. The choice of drug should be based on a conversation with the patient about benefits, possible harms, and cost *(Table 1)* on page 473.

Sulfonylureas have the lowest cost but are associated with a greater risk of hypoglycemia and weight gain. SGLT-2 inhibitors are preferred to sulfonylureas and DPP-4 inhibitors based on their lesser effects on systolic blood pressure and weight, they are also preferred to sulfonylureas based on cardiovascular mortality, A1C, and heart rate. DPP-4 inhibitors are preferred over sulfonylureas with regard to long-term all-cause and cardiovascular mortality, as well as cardiovascular morbidity, and over sulfonylureas and thiazolidinediones with regard to weight gain.

It should be noted that combination therapy is associated with more adverse effects vs. treatment with metformin alone. Each drug has its own associated adverse effects, including increased risk of gastrointestinal issues with metformin, hypoglycemia with sulfonylureas, heart failure with thiazolidinediones, and genital mycotic infection with SGLT-2 inhibitors. Saxagliptin (Onglyza) and alogliptin (Nesina), both DPP-4 inhibitors, are associated with a greater risk of heart failure, especially in those who already have heart or kidney disease.

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Table 1. Comparative Efficacy, Adverse Effects, and Costs for Add-on Oral Therapies to Metformin

Comparative efficacy vs. other combinations with metformin (quality of evidence)	*Comparative harms vs. other combinations with metformin/class adverse effects and FDA warnings*	*Agents*	*Fair price for a 60-day supply**	*Adverse effects*
Sulfonylureas				
Sulfonylurea plus metformin favored for weight vs. TZD plus metformin (moderate)	Higher risk for hypoglycemia than with metformin combinations with TZD, DPP-4 inhibitor, or SGLT-2 inhibitor	Glipizide (Glucotrol), 5 mg	$9	Diarrhea, gas, jitteriness, dizziness, uncontrollable shaking, red or itchy skin, rash, hives, and blisters
		Glimepiride (Amaryl), 4 mg	$14	Dizziness and nausea
		Glyburide, 5 mg	$13	Nausea and upper abdominal fullness
		Glyburide (micronized, 6 mg)	$10	Nausea and upper abdominal fullness
TZDs				
TZD plus metformin favored for short-term CVD mortality (rosiglitazone [Avandia] only) (low) and A1C vs. DPP-4 inhibitor plus metformin (moderate)	TZDs increase risk for congestive heart failure	Pioglitazone (Actos), 30 mg	$30	Headache; muscle, arm, or leg pain; sore throat; and gas
	May also be associated with increased risk for fracture or bladder cancer	Rosiglitazone, 2 mg	$174	Headache, runny nose and other cold symptoms, sore throat, and back pain
DPP-4 inhibitors				
DPP-4 inhibitor plus metformin favored for long-term all-cause mortality, long-term CVD mortality, and CVD morbidity vs. sulfonylurea plus metformin (low)	FDA warns that sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta), and alogliptin (Nesina) may be associated with potentially severe and disabling joint pain	Alogliptin, 25 mg	$346	Headache, stuffy or runny nose, sore throat, and joint pain
		Linagliptin, 5 mg	$728	Headache and joint pain
		Saxagliptin, 5 mg	$746	Sore throat, headache, and joint pain
DPP-4 inhibitor plus metformin favored for short-term CVD morbidity vs. pioglitazone plus metformin (low)		Sitagliptin, 100 mg	$830	Stuffy or runny nose, sore throat, headache, diarrhea, nausea, and joint pain
DPP-4 inhibitor plus metformin favored for weight vs. sulfonylurea plus metformin (high) or TZD plus metformin (moderate)				
SGLT-2 inhibitors				
SGLT-2 inhibitor plus metformin favored for CVD mortality (low), A1C (moderate), weight (high), systolic blood pressure (high), and heart rate (moderate) vs. sulfonylurea plus metformin	Higher risk for genital mycotic infection than metformin alone or metformin combined with sulfonylurea or DPP-4 inhibitor	Canagliflozin, 300 mg	$888	Excessive urination, including at night; increased thirst; constipation; and dry mouth
	FDA warns that canagliflozin (Invokana) may be associated with increased risk of bone fracture and decreased bone mineral density	Dapagliflozin (Farxiga), 10 mg	$896	Excessive urination, including at night, and increased thirst
SGLT-2 inhibitor plus metformin favored for weight and systolic blood pressure (moderate) vs. DPP-4 inhibitor plus metformin		Empagliflozin (Jardiance), 25 mg	$832	Excessive urination, including at night, and increased thirst

CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4; FDA = U.S. Food and Drug Administration; SGLT-2 = sodium glucose cotransporter-2; TZD = thiazolidinedione.

**—Prices obtained from https://healthcarebluebook.com. Accessed August 3, 2017.*

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