ACP Updates Guideline on Oral Pharmacologic Treatments for Type 2 Diabetes Mellitus

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Evidence rating system used? Yes

Literature search described? Yes

Guideline developed by participants without relevant financial ties to industry? No

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Diabetes mellitus is the seventh leading cause of death in the United States. The most common form is type 2, which affects about 25.8 million Americans. Type 2 diabetes increases with age—nearly 27 percent of U.S. adults older than 65 years have the disease. In 2007, the costs associated with diabetes reached $174 billion in the United States. Most persons diagnosed with diabetes take more than one class of medication to treat complications such as hyperglycemia and retinopathy; 58 percent take only oral medications, and 14 percent take oral medications and insulin.

The American College of Physicians (ACP) has published an updated guideline on the oral pharmacologic management of type 2 diabetes. Recommendations are based on a systematic evidence review of head-to-head comparisons of oral pharmacologic treatments for type 2 diabetes, and an evidence report sponsored by the Agency for Healthcare Research and Quality.

Recommendations

When lifestyle modifications, including diet, exercise, and weight loss, do not adequately improve hyperglycemia in patients diagnosed with type 2 diabetes, physicians should add oral pharmacologic therapy.

Initiating oral pharmacologic therapy is important for managing type 2 diabetes effectively. Because there are no data on the best time to add oral therapies to lifestyle modifications, other factors such as the patient's life expectancy and preferred method of receiving medications, the presence or absence of microvascular and macrovascular complications, and the risk of adverse events related to glucose control should be considered to avoid placing an unacceptable burden on the patient. An A1C level less than 7 percent based on individualized assessment is a reasonable goal for many, but not all, patients. The A1C goal should be set after assessing risk of comorbidity, complications from diabetes, life expectancy, and patient preferences.

Physicians should prescribe metformin (Glucophage) as the initial pharmacologic therapy to treat most patients with type 2 diabetes.

Unless contraindicated, metformin is considered the preferred choice for patients with type 2 diabetes. Evidence shows that metformin is the most effective pharmacologic agent as monotherapy and in combination with other medications. It is more effective than other pharmacologic agents in reducing glycemic, low-density lipoprotein cholesterol, and triglyceride levels, and it does not cause weight gain. Metformin has been associated with slightly lower all-cause mortality and cardiovascular mortality compared with sulfonylureas. In addition, it is associated with fewer hypoglycemic episodes, and is less expensive than other pharmacologic agents.

Metformin is contraindicated in patients with impaired kidney function, decreased tissue perfusion or hemodynamic instability, liver disease, alcohol abuse, heart failure, and any condition that may lead to lactic acidosis. It is also associated with an increased risk of adverse gastrointestinal effects.

Other diabetes medications may also cause adverse effects. Sulfonylureas and meglitinides are associated with an increased risk of hypoglycemia. Thiazolidinediones are associated with an increased risk of heart failure, but there is no conclusive evidence that they increase ischemic cardiovascular risk. Physicians and ▶

Table 1. Key Findings and Strength of Evidence for Long-Term Outcomes of Treatments for Type 2 Diabetes Mellitus

Comparison	*All-cause mortality*	*Cardiovascular mortality*	*Cardiovascular and cerebrovascular morbidity*	*Nephropathy and neuropathy*
Monotherapy vs. monotherapy				
Metformin (Glucophage) vs.				
TZD	Neither favored, low	Neither favored, low	Unclear, low	Favors pioglitazone,* moderate
Sulfonylurea	Favors metformin, low	Favors metformin, low	Unclear, low	Unclear, low*; insufficient†
DPP-4 inhibitor	Unclear, low	Insufficient	Insufficient	Insufficient
Meglitinide	Unclear, low	Unclear, low	Unclear, low	Insufficient
GLP-1 agonist	Insufficient	Insufficient	Insufficient	Insufficient
TZD vs.				
TZD	Insufficient	Insufficient	Unclear, low	Insufficient
Sulfonylurea	Neither favored, low	Unclear, low	Unclear, low	Unclear, low*
DPP-4 inhibitor	Insufficient	Insufficient	Insufficient	Insufficient
Meglitinide	Insufficient	Insufficient	Insufficient	Unclear, low*
GLP-1 agonist	Unclear, low	Insufficient	Unclear, low	Insufficient
Sulfonylurea vs.				
DPP-4 inhibitor	Insufficient	Insufficient	Insufficient	Insufficient
Meglitinide	Unclear, low	Unclear, low	Unclear, low	Insufficient
GLP-1 agonist	Insufficient	Insufficient	Insufficient	Insufficient
DPP-4 inhibitor vs.				
Meglitinide	Insufficient	Insufficient	Insufficient	Insufficient
GLP-1 agonist	Insufficient	Insufficient	Insufficient	Insufficient
Monotherapy vs. combination therapy				
Metformin vs.				
Metformin plus TZD	Unclear, low	Unclear, low	Unclear, low	Insufficient*; unclear, low†
Metformin plus sulfonylurea	Neither favored, low	Unclear, low	Favors metformin, low	Insufficient
Metformin plus DPP-4 inhibitor	Unclear, low	Unclear, low	Unclear, low	Insufficient*; unclear, low†
Metformin plus meglitinide	Unclear, low	Unclear, low	Unclear, low	Insufficient

DPP = dipeptidyl-peptidase; GLP = glucagon-like peptide; TZD = thiazolidinedione.

continued

**—Key finding for nephropathy.*

†—Key finding for neuropathy.

patients should discuss adverse events before selecting a medication regimen.

When lifestyle modifications and monotherapy do not adequately control hyperglycemia, physicians should add a second agent to metformin to treat patients with persistent hyperglycemia.

All dual-therapy regimens reviewed by the ACP were more effective than monotherapies in reducing A1C levels by approximately one additional percentage point. Although some evidence suggests that the combination of metformin and another agent tends to be more effective than any other monotherapy or combination therapy, there is no good evidence to support one particular combination therapy over another.

Combination therapies are associated with an increased risk of adverse effects compared with monotherapy. Although generic sulfonylureas are the least expensive second-line therapy, evidence suggests that

Table 1. Key Findings and Strength of Evidence for Long-Term Outcomes of Treatments for Type 2 Diabetes Mellitus *(continued)*

Comparison	*All-cause mortality*	*Cardiovascular mortality*	*Cardiovascular and cerebrovascular morbidity*	*Nephropathy and neuropathy*
Combination therapy vs. combination therapy				
Metformin plus another agent vs.				
Metformin plus TZD	Unclear, low	Unclear, low	Unclear, low	Conclusion unclear for nephropathy and neuropathy, low
Metformin plus sulfonylurea	Unclear, low	Unclear, low	Unclear, low	Insufficient
Metformin plus meglitinide	Unclear, low	Insufficient	Insufficient	Insufficient
Metformin plus DPP-4 inhibitor	Unclear, low	Unclear, low	Unclear, low	Insufficient
Metformin plus GLP-1 agonist	Insufficient	Unclear, low	Insufficient	Insufficient
Metformin plus basal insulin	Insufficient	Unclear, low	Unclear, low	Insufficient
Metformin plus premixed insulin	Unclear, low	Unclear, low	Insufficient	Insufficient
TZD plus another agent vs.				
Metformin plus TZD	Insufficient	Insufficient	Unclear, low	Insufficient
Metformin plus sulfonylurea	Unclear, low	Insufficient	Unclear, low	Insufficient
Metformin plus meglitinide	Unclear, low	Insufficient	Insufficient	Insufficient
Metformin plus DPP-4 inhibitor	Insufficient	Insufficient	Insufficient	Insufficient
Metformin plus GLP-1 agonist	Insufficient	Insufficient	Insufficient	Insufficient
Metformin plus basal insulin	Unclear, low	Insufficient	Insufficient	Insufficient
Metformin plus premixed insulin	Unclear, low	Insufficient	Unclear, low	Insufficient

DPP = dipeptidyl-peptidase; GLP = glucagon-like peptide; TZD = thiazolidinedione.

**—Key finding for nephropathy.*

†—Key finding for neuropathy.

Adapted with permission from Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. *2012;156(3):W-43.*

adverse effects are generally worse with combination therapies that include a sulfonylurea. Some patients with persistent hyperglycemia may also need insulin therapy.

A comparison of pharmacologic therapies for the treatment of diabetes is included in *Table 1.* ■

Answers to This Issue's CME Quiz

Q1. C
Q2. B
Q3. B, D
Q4. B
Q5. C
Q6. A, B, C, D
Q7. B
Q8. A, D
Q9. A, B, C
Q10. A, C, D
Q11. D