Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus

You should be offering psychosocial care to all patients with diabetes, says the ADA. Here are the specific recommendations.
The American College of Physicians (ACP) recently updated its clinical practice guideline on oral pharmacologic treatment of type 2 diabetes. The guideline was last updated in 2012, before the FDA-approved sodium–glucose cotransporter-2 (SGLT-2) and dipeptidyl peptidase-4 (DPP-4) inhibitors. The new guideline—which is endorsed by the American Academy of Family Physicians—evaluates those new medications, as well as metformin, thiazolidinediones (TZDs), and sulfonylureas, and makes 2 overarching recommendations.

1. **ACP recommends metformin as first-line pharmacologic treatment for adults with type 2 diabetes**

Nonpharmacologic therapy includes dietary modifications, regular exercise, lifestyle modifications, and weight loss. Prescribe metformin in adults with type 2 diabetes when weight loss or lifestyle modification fails. Metformin as a first-line treatment is:

- More effective than most other antidiabetic drugs
- Associated with fewer adverse effects
- Lower in cost

There are a few precautions to be aware of when considering metformin. The FDA recently updated metformin's labeling to indicate that it is safe to use in patients with mild to moderate renal impairment (eGFR >30 mL/min/1.73m2). Additionally, gastrointestinal side effects of metformin appear to be similar to those of TZDs and sulfonylureas, compared as single agents or in combination with metformin.

Metformin is contraindicated in patients with:

- Decreased tissue perfusion or hemodynamic instability
- Advanced liver disease
- Alcohol abuse
- Acute unstable congestive heart failure
- Any condition predisposing to lactic acidosis

2. **When metformin alone is inadequate, the ACP recommends adding a second oral antidiabetic agent**

Combination therapies are more effective than metformin monotherapy for reducing:

- HbA1C levels
- Weight
- Blood pressure

However, it is important to note that combination therapies are associated with an increased risk of adverse effects compared with monotherapy.

Recommended metformin add-ons include:

- Sulfonylureas
- TZDs
- SGLT-2 inhibitors (flozins)
- DPP-4 inhibitors (gliptins)

When selecting an add-on drug, arrive at a shared decision with your patient, considering benefits, adverse events, and costs. The pros and cons of each class are outlined below:
Sulfonylureas

- **Pros:**
  - Least costly of all metformin add-ons
  - More effectively reduce weight than do TZDs

- **Cons:**
  - Weight gain is common alone or in combination with other oral agents except metformin
  - Hypoglycemia risk is higher than with metformin + TZD, DPP-4 inhibitor, or SGLT-2 inhibitor (see accompanying table)

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### SULFONYLUREAS

**Risk for mild, moderate, or total hypoglycemia**

- Metformin < Metformin + sulfonylurea
- DPP-4 inhibitor (gliptin) < Sulfonylurea

**Risk for severe hypoglycemia**

- Metformin OR thiazolidinedione (TZD) < Sulfonylurea
- Metformin + DPP-4 inhibitor OR metformin + SGLT-2 inhibitor (flozin) < Metformin + sulfonylurea

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TZDs

- **Pros:**
  - More effectively lower A1C than DPP-4 inhibitors
  - Rosiglitazone has a more positive impact on short-term CVD mortality than do DPP-4 inhibitors

- **Cons:**
  - Increased congestive heart failure risk
  - Increased bone fracture risk
  - Increased bladder cancer risk

SGLT-2 Inhibitors (Flozins)

- **Pros:**
  - Favored over sulfonylureas for:
    - CVD mortality
    - Lowering A1C
    - Reducing weight
• Lowering systolic blood pressure
• Lowering heart rate
  – Favored over DPP-4 inhibitors for:
  • Reducing weight
  • Lowering systolic blood pressure

• Cons:
  – Genital mycotic infection: higher risk than for metformin alone or in combination with sulfonylurea or DPP-4 inhibitor
  – Increased bone fracture risk: Canagliflozin may be associated with increased risk for bone fracture and risk for decreased bone mineral density

DPP-4 Inhibitors (gliptins)

• Pros:
  – Favored over sulfonylureas for:
    • Long-term all-cause mortality
    • Long-term CVD mortality
    • Long term CVD morbidity
  – Favored over pioglitazone for:
    • Short-term CVD morbidity
    • More effectively reduce weight than do sulfonylureas or TZDs

• Cons:
  – Joint pain: DPP-4 inhibitors may be associated with potentially severe and disabling joint pain
  – Heart failure: Saxagliptin and alogliptin may increase risk, especially in patients with heart or kidney disease

The accompanying table lists the medication options to consider.
Important facts to help you explain to patients the importance of lowering blood glucose

- Diabetes is the 7th leading cause of death in the U.S. It is a major cause of these serious illnesses:
  - Eye disease, including blindness
  - Kidney disease
  - Nerve pain and nervous system disorders
  - Heart and blood vessel disease
  - Stroke
- More than 29 million people in the U.S. have type 2 diabetes.
- The risk of developing it increases with age; more than one-fourth of people aged >65 years have type 2 diabetes
- With the increasing prevalence of obesity in the U.S., type 2 diabetes is becoming more common in younger people

ACP guidelines do not address these areas:

- Switching patients currently taking sulfonylureas
  - For patients with adequate glycemic control and no adverse effects with sulfonylureas, continuing sulfonylurea treatment is reasonable
- Non-oral antidiabetic treatments
  - For patients with persistent hyperglycemia despite oral drugs and lifestyle interventions, insulin may be required
- When initial or add-on drugs should be started
- Particular preference for one add-on drug over another
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