Antihyperglycemic Medications

Overwhelmed with Too Many Options?

Karen Beer, PA-C, MSPAS, RD, LD, CDE

KEYWORDS

- Sulfonylurea • Biguanide • Thiazolidinedione (TZD)
- Dipeptidyl peptidase (DPP)-4 inhibitor
- Sodium glucose cotransporter (SGLT)-2 inhibitor
- Glucagon-like peptide (GLP)-1 receptor agonist • Basal insulin • Prandial insulin

KEY POINTS

- Metformin, along with diet and exercise, is the first-line treatment in newly diagnosed type 2 diabetes mellitus.
- Glucagon-like peptide (GLP)-1 receptor agonists, sodium glucose cotransporter (SGLT)-2 inhibitors, dipeptidyl peptidase (DPP)-4 inhibitors, and thiazolidinediones (TZDS) have been suggested as alternatives to metformin monotherapy.
- Patients with type 1 diabetes mellitus must be started on insulin, either multiple daily injection (MDI) or insulin pump therapy.
- Insulin is the most potent glucose-lowering agent. It has no dose ceiling and is effective in most patients. It is required for many patients with type 2 diabetes mellitus at some point in the course of their disease process.

INTRODUCTION

The number and types of medications available to treat diabetes grow each year. There are currently 9 classes of oral medications, 2 types of injectable medications, and a variety of insulins. Which medication to prescribe a patient with poorly controlled diabetes becomes more challenging as new medications enter the marketplace. Fortunately, 2 excellent resources exist. The American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) provide guidance for medication selection. The ADA publishes new guidelines annually: the *Standards of Medical Care*, which appear each year in the January issue of *Diabetes Care*. The AACE publishes the periodically updated type 2 algorithm, most recently published in the January 2016 issue of *Endocrine Practice*.

Oregon Medical Group, 974 Cabriole Court, Eugene, OR 97401, USA
E-mail address: kbeer@oregonmed.net

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Barriers to patient adherence to diabetic regimens include several factors that relate directly to the medications themselves: complexity, multiple daily dosing, cost, and side effects. Where possible, providers should collaboratively select medication regimens with patients to minimize these obstacles. In addition, providers should take into consideration efficacy, weight, comorbidities, risk of hypoglycemia, and patient preference. The goal is blood glucose reduction with minimal side effects, especially hypoglycemia.[1,2]

Severe hypoglycemia is strongly associated with a variety of adverse clinical outcomes, including vascular events and death. It is not known whether hypoglycemia is a cause of these events or a marker of vulnerability to such events. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial, risk factors for severe hypoglycemia were older age, longer duration of diabetes, higher creatinine levels, lower body mass index, lower cognitive function, use of 3 or more oral glucose-lowering medications, history of smoking or microvascular disease, and assignment to the intensive glucose control group.[3]

Metformin, diet, and exercise are considered first-line treatments for patients with newly diagnosed type 2 diabetes mellitus. After 3 months, if hemoglobin A_{1c} targets are not reached, additional medication(s) may be chosen from any of the following: sulfonylureas, TZDs, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 receptor agonists, or basal insulin. Each new class of noninsulin medications, when added to metformin, lowers hemoglobin A_{1c} approximately 0.9% to 1.1%.[1] The AACE now considers GLP-1 receptor agonists, SGLT-2 inhibitors, DPP-4 inhibitors, α-glucosidase inhibitors, sulfonylureas, glinides, and TZDs as acceptable alternatives to metformin as initial therapy.[2]

Insulin is often the last medication to be added, but insulin initiation should not be delayed in patients who do not achieve glycemic targets. For patients with hemoglobin A_{1c} greater than 9.0% and symptoms (polyuria, polydipsia, and weight loss) at diagnosis, initial treatment with insulin is preferable.[1]

BIGUANIDE: METFORMIN

Metformin is the preferred initial pharmacologic agent for type 2 diabetes mellitus, unless contraindicated. Metformin activates AMP-kinase to reduce hepatic glucose production. It is safe, efficacious, and inexpensive; promotes modest weight loss; and may lower risk of cardiovascular events and death.[1,2] Advantages of metformin include low cost, a long safety profile, absence of hypoglycemia and, based on results of the United Kingdom Prospective Diabetes Study (UKPDS), reduction in cardiovascular events.[1,2,4] Disadvantages of metformin include gastrointestinal side effects (diarrhea, nausea/vomiting, and flatulence), vitamin B_{12}, deficiency, and a low risk of lactic acidosis. Vitamin B_{12} levels should be monitored in patients on this medication and supplements advised when deficiency is identified.[2] Contraindications to use of metformin include chronic kidney disease, acidosis, hypoxia, and dehydration.[1]

Metformin should be started at 500 mg, once or twice per day with meals, and titrated by 500 mg weekly to 1000 mg twice per day with meals to minimize gastrointestinal side effects. Gastrointestinal side effects may limit maximal dosing.[5] If gastrointestinal side effects appear, patients may revert to the highest previously tolerated dose. Modestly greater effectiveness is seen at doses up to 2500 mg/d. Metformin has been shown to lower hemoglobin A_{1c} approximately 1% compared with placebo after 3 months. Gastrointestinal side effects may be lessened by using extended release products.

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