

## FROM THE EDITOR

## New Diabetes Drugs: Ready for Prime Time?

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Turn on any TV in America between 6 and 8 pm, and you will learn a lot about diabetes. At least you will see a lot about diabetes. There seems to be an abundance of new drugs. Better drugs. Drugs that don't require injection. Drugs that don't cause hypoglycemia. Drugs that facilitate weight loss. Drugs to ask your doctor about. New GLP1 analogues, DPP4 inhibitors, and SGLT2 inhibitors seem to be emerging daily, with many more of each of these in various stages of research and development. Two older drugs (cosevelam and bromocriptine) were repurposed as diabetes drugs. Newer insulin preparations are on the way. How is a primary care physician to sort the options and find the high value for patients? Does the barrage of new drugs really add value to the armamentarium of diabetes treatments? With the sudden flood of new drugs to the market, it is important that prescribers critically ask, "Where do these new drugs fit in my care of patients?"

As diabetes program chief at the Louis Stokes Cleveland VAMC, clinician-educator in our internal medicine residency program, and former ACCORD (Action to Control Cardiovascular Risk in Diabetes) principal investigator, I am often called upon to bring clarity to the dizzying array of new diabetes drugs on the market today.

GLP1 and DPP4 inhibitors are drugs that leverage the recently discovered incretin hormonal system to lower glucose. They potentiate "first phase" insulin release from the pancreas after a meal, slow gastric motility and absorption of glucose thereby limiting postprandial glucose excursions, increase satiety through central (direct brain effects) and peripheral mechanisms, and decrease insulin resistance in the periphery. Weight loss is potentiated by the GLP1 agents but not by DPP4s. There is evidence that they may pre-

serve beta cell mass as well. A1C lowering in clinical trials has been 0.5% to 0.8% with the earliest of these drugs; however, recent trials of a newer GLP1 analogue taken once weekly demonstrated as much as a 1.5% A1C reduction in those who tolerated it. Side effects including nausea and emesis have led to discontinuation in as many as 30% of patients in some trials. Concerning questions regarding side effects such as pancreatitis, pancreatic cancer, and C-cell carcinoma of the thyroid are still under investigation.

SGLT2 inhibitors are drugs that block the reuptake of filtered glucose in the proximal tubule of the nephron. They potentiate the glycosuria that occurs in hyperglycemia states. By doing so, they are said to potentiate weight loss and lower glucose. A1C lowering is in the range of 0.5%, and side effects include urinary tract and genital (yeast) infections in 10% to 12% of patients with no previous infection (and up to 30% of patients with previous infections) as well as increased urinary frequency, electrolyte imbalances, dehydration, and renal effects. It is hard to understand how these drugs will improve the lives of patients who already are experiencing these symptoms as part of their diabetes.

Cosevelam (a bile acid sequestrant) and bromocriptine (a dopamine agonist) received FDA approval for diabetes treatment in 2009. While they remain on the list of "diabetes therapies," their limited effect on A1C (approximately 0.5%), poorly understood mechanism of action, and side effects (e.g. nausea for both as well as fatigue, vomiting, headache, and dizziness for bromocriptine) raise many questions for those who set the standards for approval of diabetes drugs. What is a diabetes drug? Should there be a minimal requirement for A1C lowering before drugs are FDA approved? How do we define effectiveness? Is "any" glucose

lowering enough? Who should be judging this and advocating for patients on these issues?

To be sure, we have learned much about diabetes physiology from the development of these new drugs. Their proponents offer great hope for beta cell preservation, weight loss (or the avoidance of weight gain), decreased hypoglycemia, and possible improved cardiovascular outcomes. But amidst all of these promises, what is truly known about improving clinical outcomes for patients with diabetes? The *proven* targets still are A (A1c reduction, aspirin), B (blood pressure control), and C (cholesterol lowering)—plus smoking cessation, which still eclipses all other interventions in terms of attenuating the cardiovascular risk in patients with diabetes. Since 2008, the FDA has required cardiovascular outcome studies of all new diabetes drugs prior to approval. What have these shown? *No demonstrable effect* on cardiovascular outcomes to date. It seems they "just" lower glucose in those who take them—and not by much. The average A1C lowering with each of these agents is 0.5% to 0.8%. Compare that to metformin (1% to 2%) secretagogues (1% to 1.5%), TZDs (1%), and insulin (the sky's the limit!). What does that mean for the patient whose A1C is greater than 9%? The Endo Society and the AACE guidelines recommend "initial triple therapy." Now compare costs: up to \$10 per month for generics versus an average of \$300 per month for each newer agent. Can we afford this? *Should we afford this?*

How can primary care physicians navigate the complexity of diabetes care in this era of uncertainty? Here are some suggestions:

1. Understand the controversies over the newer diabetes drugs.

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- Understand the uncertainties. Learn about newer drugs as they emerge, and develop your own list of priorities. Ask probing questions, and define for yourself and your patient how you assign value to these newer agents. Is the highest priority to avoid hypoglycemia, limit financial burden, or lower A1C? Do you believe in the theoretical benefits of the newer agents?
2. Understand clinical guidelines, research, and position papers as they emerge, and ask yourself if they are applicable to the patient you are seeing.
  3. Set individualized glucose targets for your patient, and liberalize your glycemic targets when they exhibit hypoglycemia or experience advanced complications of diabetes.
  4. Include diabetes education and dietary management as part of your care plan. These are effective tools to prevent hypoglycemia and promote lifestyle change.
  5. Don't give up on home glucose testing. Taking secretagogues or insulin without testing is like driving with a blindfold on. Most importantly, take the time to review the glucose logs or meter downloads with patients to reinforce health behaviors and inform your treatment decisions.
  6. Educate your patients on goals of treatment (ABCs), and set individualized goals.
  7. Change your targets for treatment when the evidence suggests new strategies are better or old strategies are not effective.

Lastly, as advocates for our patients, we need to understand the potential clinical value these drugs add before we decide. Comparative effectiveness trials are needed to inform this discussion.

The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) Trial is sponsored by the National Institute for Diabetes and Digestive and Kidney Disease and is now enrolling patients at more than 40 sites in the United States. The 6,000 participants with recent onset diabetes (i.e. duration less than five years), age over 30 at diagnosis, and baseline hemoglobin A1C of 6.8% to 8.5% will be randomly assigned to the sulfonylurea glimepiride, the DPP-4 inhibitor sitagliptin, the GLP-1 agonist liraglutide, or the basal insulin glargine when metformin monotherapy fails to maintain A1C less than 7%. Patients will be followed for up to seven years and will benefit from close monitoring and free diabetes medications during the course of the study. Aside from glucose management in the trial, all other medical care will continue to be managed by the patient's primary care physician. To learn more about the GRADE Trial or to refer patients, see <https://grade.bsc.gwu.edu>.

As primary care physicians, we are uniquely situated to identify patients early in the course of their diabetes who are eligible for clinical trials. We are aware of the high burden diabetes places on our patients and the need for comparative effectiveness trials to inform our recommendations to patients. We should continue to learn about new therapies as they emerge and ask appropriate questions in order to guide our patients toward value-based decisions regarding diabetes management. We should demand improvements in the drug approval system that set minimal expectations for the value added by emerging therapies prior to their adoption.

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