Older Type 2 Drugs Are as Effective as Newer Ones

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Contributing Writer

Metformin and second-generation sulfonylureas appear to be as safe and effective as the newer, more expensive oral diabetes drugs in the treatment of type 2 diabetes in adults, according to Dr. Shari Bolen of Johns Hopkins University, Baltimore, and colleagues.

The researchers analyzed safety and efficacy data from 216 controlled clinical trials and cohort studies of oral diabetes agents, along with two systematic reviews. The studies and reviews were selected from published reports in MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials databases, and from unpublished reports from industry and the Food and Drug Administration.

"Each oral diabetes agent is associated with adverse events that counterbalance its benefits," wrote Dr. Bolen and colleagues. "Overall, metformin seemed to have the best profile of benefit to risk." The American Diabetes Association favors metformin as initial pharmacotherapy for type 2 diabetes, although the choice of therapy often depends upon patient comorbidities.

Metformin and second-generation sulfonylureas were generally as effective as newer agents in improving intermediate outcomes. As monotherapy, all oral diabetes agents had similar effects on glycemic control, with an absolute reduction in hemoglobin A_{1c} levels of about 1 percentage point. The effects on glycemic control were additive when oral diabetes agents were used in combination therapy. The various agents did not differ significantly in their effect on systolic or diastolic blood pressure.

Only thiazolidinediones improved HDL-cholesterol levels, with a relative mean increase of 0.08-0.13 mmol/L, compared with treatment with other agents. However, thiazolidinediones also increased LDL cholesterol levels by a relative mean increase of 0.26 mmol/L. Metformin improved LDL cholesterol levels by a mean decrease of 0.26 mmol/L. Other oral diabetes agents did not appear to affect LDL cholesterol levels.

Metformin treatment was not associated with weight gain, compared with other agents or placebo. Acarbose treatment also did not lead to weight gain, compared with placebo. Weight gains ranging from 1 to 5 kg were seen with most other oral diabetes medications: thiazolidinediones, repaglinide, and second-generation sulfonylureas. They found no evidence of increased risk of lactic acidosis with metformin, compared with other oral diabetes agents. Hypoglycemic episodes occurred more frequently with second-generation sulfonylureas and repaglinide than with metformin or thiazolidinediones, although there was wide variation in the risk levels reported from the different clinical trials. Gastrointestinal symptoms were most frequent with metformin treatment, ranging from 2% to 63%, a higher rate than most other agents.

In short-term randomized trials, greater risk of congestive heart failure was seen with thiazolidinediones, compared with second-generation sulfonylureas or metformin. The absolute risk of congestive heart failure ranged from 0.8% to 3.6% for thiazolidinediones and from 0% to 2.6% for other oral diabetes agents. In placebo-controlled trials and cohort studies neither second-generation sulfonylureas nor metformin showed increased risk of congestive heart failure.

Because few studies have analyzed major clinical outcomes, data were insufficient for a thorough comparison of the effects of various oral diabetes agents on cardiovascular morbidity and mortality, microvascular outcomes, neuropathy, or death from any cause. "Large, long-term comparative studies on major clinical end points, such as myocardial infarction, chronic kidney disease, and cardiovascular mortality, are needed to determine definitively the comparative effects of the oral diabetes agents, especially in light of recent controversy regarding rosiglitazone," they wrote.

In an interview, Dr. Zachary Bloomgarden of Mount Sinai School of Medicine in New York, agreed with the researchers' conclusion that the various agents have similar glucose-lowering events but challenged their conclusion that metformin is not associated with increased risk of lactic acidosis, citing toxicology evidence from numerous animal studies. The review "appears not to address much of the relevant information on this immense topic."

Dr. Bloomgarden has served as a consultant for Merck and on speaker panels for Takeda, GlaxoSmithKline, Novo Nordisk, Eli Lilly, Amylin, Merck, and Novartis. ■

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