In the past decade, many new medications have improved our ability to treat patients with type 2 diabetes (1). The pharmaceutical industry has played a key role in this process. Among these novel medications are newly designed insulins, thiazolidinediones (TZDs), meglitinides, orally active inhibitors of the incretin-degrading enzyme dipeptidyl peptidase-IV, and glucagon-like peptide (GLP) mimetics. Combinations of these drugs, each drug with its distinct pharmacologic mechanism of action, have increased our capacity to manage patients with diabetes.

The latter 2 drug classes mentioned enhance or mimic the effects of endogenous incretins, such as GLP hormones secreted by the gut (2–4). As with most gut peptides, GLP biological activity is exercised locally by inhibiting gastric emptying but also in the pancreas by stimulating glucose-dependent insulin secretion, promoting insulin biosynthesis, and inhibiting glucagon secretion. At the central nervous system level, GLP inhibits food and water intake, promotes satiety and weight loss, and induces nausea and vomiting. These diverse sites of action make GLP’s attractive molecules for treating diabetes.

In a randomized trial in this issue (5), we learn about use of a GLP mimic—exenatide—in combination with a TZD. The study was designed, conducted, and analyzed by employees of the manufacturer in collaboration with academicians from several institutions and “all authors participated in interpreting the data and drafting or critically reviewing the manuscript” (5).

Zinman and colleagues report on a relatively small study of patients with type 2 diabetes (n = 233) from 49 centers where exenatide, 10 μg twice daily (n = 121), or placebo (n = 122) was added to rosiglitazone (≥4 mg/d) or pioglitazone (≥30 mg/d) alone or in combination with metformin (79%) for 16 weeks to assess both efficacy and safety. The study results were the basis for the U.S. Food and Drug Administration (FDA) approval of the combination with a TZD as a new indication for exenatide (3). The FDA had previously approved exenatide in combination with metformin or sulfonylureas. The regulatory barriers for approving a new indication for a drug that is already in the market are usually less severe than for a first-time approval of a new molecular entity, perhaps because the safety information for a drug that is already in the market provides regulators with a sense of security. A recent editorial has contested this rationale and the less stringent requirements for study size and duration, singling out type 2 diabetes as a case in point (1).

Zinman and colleagues’ presentation, which is very objective and balanced, shows that adding exenatide to a TZD reduced the mean hemoglobin A1c level by almost 1.0 percentage point. Patients receiving exenatide lost a mean of 1.5 kg of body weight, while those in the placebo group maintained their baseline weight. Lipid profile and blood pressure did not change. Hence, the addition of exenatide for up to 16 weeks improved glucose control and moderately reduced weight in patients inadequately managed with submaximal dosages of TZDs alone or with metformin, with no additional metabolic benefit observed.

Several aspects of the study design raise concerns about whether these results apply to most patients with type 2 diabetes whose physicians are considering starting an injectable drug because of poor control with TZDs and metformin. While the study patients were inadequately controlled, many were not receiving maximal therapy when the study began.

In contrast to standards of recommended care for patients with type 2 diabetes, Zinman and colleagues did not use lifestyle interventions to maximize diabetes control at baseline, and they do not comment about diabetes education or dietary control (6–9). Without these interventions, metabolic control would be suboptimal, which could enhance the effect of any medication.

Inadequate conventional drug therapy is another reason for concern that the study patients weren’t typical, poorly controlled diabetics. Twenty-one percent of patients were not receiving metformin, which is first-line therapy for type 2 diabetes because of its proven efficacy, safety record, and cost-effectiveness (6–9). Moreover, the patients taking metformin were not always taking maximal dosages, which is customary before adding a drug like exenatide. The authors do not describe their rationale for not using the maximal tolerated therapeutic dosage of metformin in all suboptimally controlled patients. In addition, some patients were receiving submaximal dosages of TZDs. The authors do not state how many patients received maximal dosages of metformin or TZDs.

The authors’ failure to provide lifestyle and diet advice and their use of submaximal dosages of the oral medications detracts from their study because, in clinical practice, a physician would optimize current therapy before adding a new medication. We simply don’t know whether patients optimally treated with diabetes education, diet, TZDs, and metformin will receive as much benefit from exenatide as the paper reports.

Adverse effects, as noted in previous studies, were common. Of the 121 patients who were initially randomly assigned to receive exenatide, only 86 (71%) completed the 16 weeks of the trial, compared with 96 of 122 (79%) of patients receiving placebo. Nausea and vomiting were statistically significantly higher in patients receiving exenatide and were the most common reasons for leaving the study (17 of 31 patients). A 26% dropout rate is rarely observed in
short-term clinical studies of antidiabetic drugs. The authors state that many patients dropped out during the initial dose escalation of exenatide and, with time, fewer patients left the study. The reduction of these adverse drug reactions with time could be due to better tolerance. Alternatively, it could be due to a form of survivor bias, wherein patients who were less prone to nausea and vomiting stayed in the study. Because dose increments are necessary to produce the reported results, high rates of desertion are likely when exenatide is used in the general diabetic population. The authors did not provide information about subgroups that were more prone to develop adverse drug reactions. Adverse effects are clearly a substantial problem with exenatide, and physicians considering prescribing exenatide will need help in managing them. The authors collected this information. They should publish it.

Drug administration will be a barrier to using exenatide. Like past formulations of regular insulin, exenatide must be given 15 minutes before meals, which contrasts with newer rapidly active insulins that may be injected during and even after meals, which is far more convenient and reduces the burden of meal planning and timing, as well as the risk for hypoglycemia. Moreover, the manufacturer has formulated exenatide for fixed-dose administration. Fixed dosing vitiates a potential advantage of an injectable drug: the ability to fine-tune the dosage to enhance glucose control or to manage adverse drug reactions by using an injector pen that allows administration of doses in multiples of only 5 µg or 10 µg.

The study was much too small and much too short. The estimated number of patients with type 2 diabetes worldwide in 2007 is 246 million (10). Zinman and colleagues’ study exposed only 121 patients from 49 different centers to exenatide and TZDs. Because of its short duration, small size, and lack of power, the study fails to clarify many questions. Among the most important questions are: Will glucose control last more than 16 weeks? Who is at greatest risk for adverse drug reactions? Will dose adjustment improve glucose control and decrease adverse drug reactions? Subgroup analyses would answer some of these important questions. A small study precludes meaningful subgroup analyses. More important, small and short studies provide a false sense of safety, because common severe adverse drug reactions may not occur in the condensed timeline and in the limited number of patients.

The design and reporting of Zinman and colleagues’ study reminds us that the manufacturer controls the flow of information about its product. By virtue of FDA approval for the combination of exenatide and TZDs, the data obtained in the study can lead to enormous financial benefits to the sponsor. Millions of patients receive TZDs and metformin—now physicians may consider adding exenatide. Great power requires greater responsibility. Physicians and patients need answers to the many questions raised by this small study.

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Disclaimer: The views expressed in this editorial are those of the author and do not constitute an official position of the U.S. Department of Health and Human Services.

Potential Financial Conflicts of Interest: Before his employment at the National Institutes of Health, Dr. Malozowski was a medical officer at the U.S. Food and Drug Administration, during which he supervised the initial review of exenatide. He is currently a National Institute of Diabetes and Digestive and Kidney Diseases representative to a National Institutes of Health-sponsored clinical study, where exenatide has been provided free of charge by the manufacturer.

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