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An Open, Randomized, Parallel-Group Study to Compare the Efficacy and Safety Profile of Inhaled Human Insulin (Exubera) With Glibenclamide as Adjunctive Therapy in Patients With Type 2 Diabetes Poorly Controlled on Metformin

Response to Kanna and Abreu-Pacheco

We thank Kanna and Abreu-Pacheco (1) for their comments on our study (2). As Kanna and Abreu-Pacheco point out, overweight and obesity are strongly linked to the development of type 2 diabetes and can complicate its management. While most patients with type 2 diabetes are overweight (3), this study (2) included individuals with a range of BMI values typical of those seen in clinical practice; mean BMI in the inhaled insulin and glibenclamide groups was 31.8 (range 19–51) and 31.1 (22–47), respectively. When analyzed by baseline BMI values, the mean change from baseline A1C in the moderately high A1C arm (≥8 to ≤9.5%) was −1.6, −1.3, and −1.5% in patients with baseline BMI values of <30, 30–35, and ≥35 kg/m^2, respectively, compared with −1.5% for all subjects. In the very high A1C arm (>9.5%), mean change from baseline A1C was −3.1, −2.8, and −2.8% in patients with baseline BMI values of <30, 30–35, and ≥35 kg/m^2, respectively, compared with −2.9% for all subjects. The results show no meaningful differences between the BMI categories, and the authors therefore believe it to be unlikely that the baseline BMI values could have confounded the A1C results.

For the duration of the study, patients were required to follow an American Diabetes Association diet (with 30% fat and calories sufficient to maintain ideal body weight) and to perform 30 min of moderate exercise at least 3 days per week. There was no specific measure of compliance with diet and exercise regimens during the study, but patients were reminded of their importance at each clinic visit.

Finally, we would like to point out that our study was open label and not blinded. As highlighted in the article, a double-blind study, while desirable, was not possible for two principal reasons: *1*) it was not possible to manufacture a suitable placebo for inhaled insulin, and *2*) it is generally inappropriate to blind treatment when individualized flexible dose titration is needed for effective management with exogenous insulin.

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Hyperglycemia and Diabetes in Patients With Schizophrenia or Schizoaffective Disorders

Response to Cohen et al.

We commend Cohen et al. (1) on their report on hyperglycemia and diabetes in patients with schizophrenia and schizoaffective disorders. To our knowledge, this is the first large study of oral glucose tolerance tests in this population.

Cohen et al. found that the prevalence rate of diabetes was significantly higher in patients with schizophrenia and schizoaffective disorders than in the general population. They did not detect a differential effect of antipsychotic monotherapy in diabetogenic effects, and they consequently proposed a modification of the consensus statement on antipsychotic drugs, obesity, and diabetes, i.e., measurement of fasting glucose in all patients with schizophrenia irrespective of the prescribed antipsychotic drug. We argue that the differences in the metabolic effects of different antipsychotic agents are too clear in the literature to justify any notion that the antipsychotic agents are comparable in their metabolic effects.

Comparative studies of antipsychotic agents are limited in their scope by the difficulty in conducting randomized controlled trials of antipsychotic agents. For many patients, specific antipsychotic agents are indicated ahead of the others based on the information available at that time. For example, clozapine is difficult to study in comparative investigations because it is not recommended by most as a first-line treatment. A recent study (2) addressed this issue to some extent by conducting a randomized controlled trial of risperidone and olanzapine in dogs. The dogs who received olanzapine developed hepatic insulin resistance, whereas those who received risperidone did not. Fur-