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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-

thermore, the usual compensatory increase in insulin secretion in response to insulin resistance was lacking in the olanzapine-fed dogs. Apart from the evidence of differential effects of the two agents, the results suggest that olanzapine may induce insulin resistance even in the absence of psychopathology. The lack of compensatory increase in insulin secretion suggests that olanzapine may also impair insulin secretion.

A recent correlational analysis (3) of receptor affinities of individual antipsychotic agents and their diabetogenic effects suggests that muscarinic M3 receptor affinity is the best predictor of risk for development of type 2 diabetes. The study was limited by its use of data from different laboratories, collected under different conditions. Nevertheless, the results are not surprising given the clinical knowledge that two of the antipsychotic agents with the most anticholinergic activity, clozapine and olanzapine, seem to present the greatest risk for development of type 2 diabetes. Among the first generation agents, there are reports (4) of diabetes in patients taking chlorpromazine, an agent with considerable anticholinergic activity. To our knowledge, however, there are no reports of diabetes in those taking haloperidol, an agent without significant anticholinergic activity. Muscarinic receptor affinity may also be the reason why a comparative study (5) of clozapine and chlorpromazine did not find a significant difference between treatments and their effects on weight or glucose metabolism. The study was cited by Cohen et al. (1) in support of their contention that all antipsychotic agents present risks of diabetes.

Taken together, these studies suggest that antipsychotic agents differ from one another in their effects on glucose metabolism. Until this issue is completely resolved, it would be prudent to monitor measurement of fasting glucose in all patients with schizophrenia, irrespective of the prescribed antipsychotic drug, with special attention provided to those taking olanzapine, clozapine, and chlorpromazine.

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Hyperglycemia and Diabetes in Patients With Schizophrenia or Schizoaffective Disorders

Response to Jindal and Keshavan

We thank Jindal and Keshavan (1) for their contribution explaining the results of our study (2), which stated that in a cross-sectional design ($n = 200$), no differences in the prevalence of diabetes or hyperglycemia between typical- or atypical-treated patients were found. We would like to make two comments on this statement. First, although the muscarinic M3 receptor affinity fits well with the diabetogenic properties of antipsychotic drugs, so does H_1-histaminergic (but not muscarinic M3) receptor affinity with short-term weight gain, a factor that is often, but not always, present in antipsychotic-related diabetes (3,4). Second, it has been suggested (5) that risk factors of diabetes exert less predictive power in schizophrenia than in the general population. This hypothesis was tested (6) by examining the effect of the two major risk factors for diabetes: age and weight. In 200 patients with schizophrenia, typical (but not atypical) antipsychotic drugs modified the effect of these risk factors, confirming a less straightforward relationship between diabetes risk factors in schizophrenia than in the general population.

The statement by Jindal and Keshavan (1), that no cases of diabetes have been reported with haloperidol, may be interpreted as stressing the same point. Taken literally, it is simply untrue, as the following cases (7) have been reported: 10 of new-onset diabetes, 2 of worsening of existing diabetes, and 1 with an unknown preexisting status (on haloperidol monotherapy) with 4, 2, and 1 cases on haloperidol-risperidone combination therapy, respectively. More broadly speaking, Jindal and Keshavan (1) justly criticize the typical-atypical classification of antipsychotics as a scientifically unproductive dichotomy. This was shown (8) in cell culture, for instance, where haloperidol's inhibiting effect on cell proliferation was comparable with the atypical clozapine but not to the typicals chlorpromazine and fluphenazine. In this very complex matter, the ability to take any stance on explanatory pathways is currently precluded by the fact that research into the diabetogenic properties of antipsychotic medication and its pathways is just beginning.

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