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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References

1. Cohen D, Stolk RP, Grobbee DE, Gispen-de Wied CC: Hyperglycemia and diabetes in patients with schizophrenia or schizoaffective disorders. *Diabetes Care* 29:786–791, 2006
2. Ader M, Kim SP, Catalano KJ, Ionut V, Hucking K, Richey JM, Kabir M, Bergman RN: Metabolic dysregulation with atypical antipsychotics occurs in the absence of underlying disease: a placebo-controlled study of olanzapine and risperidone in dogs. *Diabetes* 54:862–871, 2005
3. Silvestre JS, Prous J: Research on adverse drug events. I. Muscarinic M3 receptor binding affinity could predict the risk of antipsychotics to induce type 2 diabetes. *Methods Find Exp Clin Pharmacol* 27:289–304, 2005
4. Schwarz L, Munoz R: Blood sugar levels in patients treated with chlorpromazine. *Am J Psychiatry* 125:253–255, 1968
5. Lieberman JA, Phillips M, Gu H, Stroup S, Zhang P, Kong L, Ji Z, Koch G, Hamer RM: Atypical and conventional antipsychotic drugs in treatment-naive first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. *Neuropsychopharmacology* 28:995–1003, 2003

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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References

1. Jindal RD, Keshavan MS: Hyperglycemia and diabetes in patients with schizophrenia or schizoaffective disorders (Letter). *Diabetes Care* 30:446–447, 2007
2. Cohen D, Stolk RP, Grobbee DE, Gispen-de Wied CC: Hyperglycemia and diabetes in patients with schizophrenia or schizoaffective disorders. *Diabetes Care* 29:786–791, 2006
3. Wirshing DA, Wirshing WC, Kysar L, Berisford MA, Goldstein D, Pashdag J, Mintz J, Marder SR: Novel antipsychot-

ics: comparison of weight gain liabilities. *J Clin Psychiatry* 60:358–363, 1999
4. Kroeze WK, Hufeisen SJ, Popadak BA, Renock SM, Steinberg S, Ernsberger P, Jayathilake K, Meltzer HY, Roth BL: H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmacology* 28:519–526, 2003
5. Cohen D: Diabetes mellitus during olanzapine and quetiapine treatment in Japan (Letter). *J Clin Psychiatry* 66:265–266, 2005
6. Cohen D: *Diabetes Mellitus in Schizophrenia or Schizoaffective Disorder: An Iatrogenic or Endogenic Problem?* Haarlem, Netherlands. PhD thesis. University of Utrecht, Netherlands, 2006
7. Koller EA, Cross JT, Doraiswamy PM, Schneider BS: Risperidone-associated diabetes mellitus: a pharmacovigilance study. *Pharmacotherapy* 23:735–744, 2003
8. Dwyer DS, Pinkofsky HB, Liu Y, Bradley RJ: Antipsychotic drugs affect glucose uptake and the expression of glucose transporters in PC12 cells. *Prog Neuro-Psychopharmacol Biol Psychiatry* 23:69–80, 1999

Modeling Chronic Glycemic Exposure Variables as Correlates and Predictors of Microvascular Complications of Diabetes

Response to Dyck et al.

We read with interest the article by Dyck et al. (1), in which the authors described a chronic glycemic exposure variable (GE_i) in the Rochester Study. They examined GE_i and its individual components (A1C, duration, and age at onset) in terms of prediction/correlation with complications and concluded that GE_i is generally predicted better than its individual components (see Table 3 of ref. 1).

Dyck et al. compared their results with our previously published analyses (2) using a different chronic glycemic exposure variable, A_1 months, noting that (as also reported by the Diabetes Control and Complications Trial [3]) this combination variable did not predict better than its components (A_1 and duration). Our analytic approach, however, was different; we compared the fit of models, including the components to a model, with the composite alone. The differences in fit were small but favored the separate components. It would thus be interesting to compare the total R^2 of alternate models, one with GE_i and another with its components, in the current study. We suspect that, as in our case, differences would be small.

Another interesting issue is the use of "age at onset " and "duration" (1) together effectively defining age itself. Could any enhanced prediction be related to age itself? Inclusion of the partial R^2 for age in Table 3 (see ref. 1) would be useful.

Dyck et al. further suggested that differences between these studies may be explained by the "choice of patients" and differences in outcome assessment. As the Epidemiology of Diabetes Complications study (4) is comprised of community-treated type 1 diabetic individuals from a childhood-onset cohort shown to be epidemiologically representative of type 1 diabetes, selection bias was unlikely. However, the inclusion of type 2 diabetic subjects in the Rochester Study may have influenced results. Nevertheless, we agree that a continuous neuropathy outcome measure may be preferable and that this difference also may have contributed to the differences reported. Consequently, a comparison of A_1 months and GE_i would be more informative if performed for the outcome common to both studies (Diabetes Control and Complications Trial protocol neuropathy).

Finally, one motivation behind developing the A_1 month measure was to address whether a glycemic threshold exists above which complications develop. Were the authors able to examine this issue using GE_i? While unable to determine a clear threshold, we found that ~1,000 A_1 months were experienced before the advent of advanced complications. This translates to 42 years of A1C 2% above normal or 18 years at 5% above normal, which reflects another motivation for our chronic glycemic exposure variable—a clinically useful concept of risk.

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References

1. Dyck PJ, Davies JL, Clark VM, Litchy WJ, Dyck PJB, Klein CJ, Rizza RA, Pach JM, Klein R, Larson TS, Melton LJ III, O'Brien PC: Modeling chronic glycemic exposure variables as correlates and predictors of microvascular complications of diabetes. *Diabetes Care* 29:2282–2288, 2006
2. Orchard TJ, Forrest KY, Ellis D, Becker DJ: Cumulative glycemic exposure and microvascular complications in insulin-dependent diabetes mellitus: the glycemic threshold revisited. *Arch Intern Med* 157: 1851–1856, 1997
3. The Diabetes Control and Complications Trial Research Group: The relationship of glycemic exposure (HbA_{1c}) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes* 44:968–983, 1995
4. Wagener DK, Sacks JM, LaPorte RE, MacGregor JM: The Pittsburgh Study of insulin-dependent diabetes mellitus: risk for diabetes among relatives of IDDM. *Diabetes* 31:136–144, 1982

Modeling Chronic Glycemic Exposure Variables as Correlates and Predictors of Microvascular Complications of Diabetes

Response to Orchard et al.

We are pleased to respond to the letter by Orchard et al. (1), especially since they first raised the following question: Do composite measures of chronic glycemia correlate or predict complications better than individual components? Orchard et al. reported evidence against the hypothesis, while we (2) reported evidence for the hypothesis. Having considered their suggestions, we offer an explanation for why their conclusions differed from ours.

Orchard et al. (3) compared the fit