Incidence of Newly Diagnosed Diabetes Attributable to Atypical Antipsychotic Medications

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Objective: The purpose of the study was to determine the proportion of patients with schizophrenia with a stable regimen of antipsychotic monotherapy who developed diabetes or were hospitalized for ketoacidosis.

Method: Patients with schizophrenia for whom a stable regimen of antipsychotic monotherapy was consistently prescribed during any 3-month period between June 1999 and September 2000 and who had no diabetes were followed through September 2001 by using administrative data from the Department of Veterans Affairs. Cox proportional hazards models were developed to identify the characteristics associated with newly diagnosed diabetes and ketoacidosis.

Results: Of the 56,849 patients identified, 4,132 (7.3%) developed diabetes and 88 (0.2%) were hospitalized for ketoacidosis. Diabetes risk was highest for clozapine (hazard ratio=1.57) and olanzapine (hazard ratio=1.15); the diabetes risks for quetiapine (hazard ratio=1.20) and risperidone (hazard ratio=1.01) were not significantly different from that for conventional antipsychotics. The attributable risks of diabetes mellitus associated with atypical antipsychotics were small, ranging from 0.05% (risperidone) to 2.03% (clozapine).

Conclusions: Although clozapine and olanzapine have greater diabetes risk, the attributable risk of diabetes mellitus with atypical antipsychotics is small.

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Dosing were statistically significant when the analysis was limited to diabetes mellitus patients.

**Discussion**

The incidence of diabetes mellitus in this population was relatively high, even among patients for whom a stable regimen of a conventional antipsychotic was prescribed. The overall annual diabetes mellitus incidence rate of 4.4% in this study is considerably higher than the estimated rate of 6.3 cases per 1,000 in the general U.S. population (11). It is unclear how much of the increased diabetes mellitus incidence in the sample was due to the use of antipsychotic medications (conventional or atypical antipsychotics), the underlying disease of schizophrenia, or other factors such as poorer overall physical health, less healthy lifestyles, or poorer access to health care services.

Differences in diabetes mellitus risk across antipsychotic medications did not become apparent until 14 months after the end of the stable period (Figure 1). Hence, the additional diabetes mellitus risk associated with clozapine and olanzapine took more than a year to develop. This interval should offer ample time for clinicians to identify weight gain and/or elevated diabetes mellitus risk and perhaps to change the antipsychotic regimen accordingly.

Our results do not support the claim that weight gain and elevated risk of diabetes mellitus are a “class effect” of all atypical antipsychotic medications. In addition, the attributable risks of diabetes mellitus and diabetic ketoacidosis associated with atypical antipsychotics were small. However, diabetes mellitus and diabetic ketoacidosis are severe, life-threatening disorders, and while these attributable risks are small, they may still be of concern.

Several limitations of the study deserve comment. First, we examined the incidence of diabetes mellitus diagnosed in the VA system among patients with schizophrenia for whom a stable regimen of an antipsychotic medication was prescribed. Hence, our results may not be generalizable to other populations or health care systems. In addition, there may have been cases of diabetes mellitus that were undiagnosed or diagnosed outside of the VA. Although we were unable to identify undiagnosed diabetes mellitus cases, we have no reason to believe that the likelihood of failure to diagnose diabetes mellitus would be different across groups of patients for whom different antipsychotic medications were prescribed. Finally, our analysis attributed all of the diabetes mellitus risk to the atypical antipsychotic that was consistently prescribed for the patient during a 3-month window. Different medications may have been prescribed either before or after the medication identified in our study, and the increased risk of diabetes mellitus might be partially attributable to these other medications. Data were not available to identify medications taken earlier, and the proportions of patients whose drugs were switched during the follow-up.

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**FIGURE 1. Fitted Survival Functions From the Cox Proportional Hazards Model Predicting Time to Diabetes Mellitus Onset Among Outpatients With Schizophrenia For Whom a Stable Regimen of Antipsychotic Monotherapy Was Prescribed**

- Hazard ratio = 1.57, 95% confidence interval (CI) = 1.31–1.89
- Hazard ratio = 1.15, 95% CI = 1.07–1.24
- Hazard ratio = 1.20, 95% CI = 0.99–1.44
- Hazard ratio = 1.01, 95% CI = 0.93–1.10

**Proportion of Subjects Without Diabetes Diagnosis**

- Subjects receiving clozapine
- Subjects receiving olanzapine
- Subjects receiving quetiapine
- Subjects receiving risperidone
- Comparison group receiving conventional antipsychotic medication
period were small (17% overall) and were similar across medication groups.

Despite these limitations, the results offer insight into the risk of diabetes mellitus and diabetic ketoacidosis in an older, predominantly male population with schizophrenia for whom antipsychotic medications are prescribed.

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References