Stable monotherapy with clozapine or olanzapine increases the incidence of diabetes mellitus in people with schizophrenia


Q Does stable antipsychotic monotherapy increase the risk of diabetes mellitus and diabetic ketoacidosis in people with schizophrenia?

**METHODS**

- **Design:** Prospective cohort study.

- **Follow up period:** 25 months.

- **Setting:** Department of Veterans Affairs Connecticut Mental Illness Research, Education and Clinical Center, USA; recruitment June 1999 to September 2000.

- **People:** 56,849 people with schizophrenia who received a stable regimen of antipsychotic monotherapy in any 3 month period during the recruitment phase of the study. Exclusions: ziprasidone and aripiprazole, less than two primary care visits in the previous 6 months; or previous diagnosis of diabetes mellitus.

- **Risk factors:** Participants diagnosed with diabetes mellitus or hospitalised with diabetic ketoacidosis were identified from the Department of Veterans Affairs and were predominantly older and female. Time to diagnosis and hospitalisation was modelled using the Cox proportional hazards models. Attributable risks of each outcome associated with different antipsychotics were calculated. The five antipsychotics groups analysed were: clozapine, olanzapine, quetiapine, risperidone, and control (all conventional antipsychotics).

- **Outcomes:** Diagnosis of diabetes mellitus; hospitalisation for diabetic ketoacidosis.

**MAIN RESULTS**

At 25 months, 4132 (7.3%) people were diagnosed with diabetes mellitus and 88 (0.2%) were hospitalised with ketoacidosis. Clozapine and olanzapine had the highest risk for diabetes compared with conventional antipsychotics. However, there was no statistically significant difference in the risk for diabetes between both olanzapine and conventional antipsychotics, or quetiapine and conventional antipsychotics. Clozapine and olanzapine also increased the risk of diabetic ketoacidosis (clozapine v control: HR 3.8, 95% CI 1.4 to 10.1; olanzapine v control: HR 1.8, 95% CI 1.1 to 3.0). However, when the analysis was restricted to people with diabetes mellitus, the results were no longer statistically significant.

**CONCLUSIONS**

Diabetes mellitus incidence is increased in people with schizophrenia who are prescribed a stable regimen of clozapine or olanzapine. However, it is unclear whether the medication itself or other confounding factors in these people are responsible for this result (see http://www.ebmentalhealth.com supplemental for table).

**Commentary**

A typical antipsychotics (clozapine, risperidone, olanzapine, quetiapine, and others) are often used to manage schizophrenia and other psychotic disorders. Some atypical drugs are also used to manage bipolar disorder and behavioural disturbances in dementia. Atypical drugs are thought to have several advantages over typical antipsychotics such as haloperidol: first, they have superior efficacy in addressing the negative symptoms of schizophrenia; second, they appear to have a lower propensity than typicals to cause extrapyramidal symptoms such as parkinsonism and tardive dyskinesia. Whereas typical antipsychotics have been available for 50 years, atypicals have only been introduced into clinical practice over the past 10 years. In this time, evidence has accumulated to suggest that atypicals are associated with a different spectrum of adverse effects. These newly recognised adverse effects include weight gain, dyslipidaemia, and alterations in glucose metabolism including diabetes. The mechanisms that contribute to the development of diabetes in patients taking atypicals are unknown. To complicate matters, people with schizophrenia appear to have a higher risk of diabetes than the general population, regardless of drug treatment.

The study by Leslie and Rosenheck generally supports findings from other studies. The current study suggests that the risk of diabetes attributable to atypical use is relatively small. Several important points should be kept in mind. First, although some studies (including this one) suggest that the risk for diabetes is highest in patients taking clozapine or olanzapine, there is ongoing debate as to whether use of other atypical agents also confers an increased risk of diabetes. Second, it is not clear whether the risk of diabetes with atypical use is generalisable to patients with conditions other than schizophrenia.

Further evidence on this important potential adverse drug effect is needed. Pending further study, a consensus group has published guidelines to assist in the monitoring of patients who receive atypical antipsychotic medications.

Sudeep S Gill, MD, MSc, FRCPc
Queen’s University, Kingston, Ontario, Canada

For correspondence: Dr D Leslie, Northeast Program Evaluation Center/182, 950 Campbell Ave, West Haven, CT, USA; douglas.leslie@yale.edu
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