

Antipsychotics & Metabolic Effects: 2002 –2003 Update

VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

Background and Intent: The association of the atypical antipsychotics (AAP) with hyperglycemia, elevated lipids, and weight gain was recognized soon after the introduction of clozapine and has become of increased concern as the use and uses of AAPs have expanded. The extent and risk for these adverse effects with each AAP has been primarily based on case reports and limited epidemiologic data. Several hypotheses have been generated that may explain the mechanism for these effects. Schizophrenics, independent of treatment, are believed to have up to a two-fold increased risk of diabetes mellitus compared to the general population. It is the intent of this report to review the evidence of association and hypothesis testing that has been published in 2002 and 2003.

Methods: A MEDLINE review was conducted using each of the atypical antipsychotics individually as keywords as well as antipsychotics as a general search term. These were combined with outcomes of interest such as diabetes mellitus, hyperglycemia, obesity, hyperlipidemia, leptin and hypertriglyceridemia. Preference was for original research papers including those prospective in design or that applied pharmacoepidemiologic methods to large databases. The bibliographies of original research papers and selected others were reviewed for additional references. Data on aripiprazole and ziprasidone are limited due to their more recent availability.

Effect on Glucose and Incident Diabetes: Clinical practice and expert opinion suggest the risk for hyperglycemia or incident diabetes to be more frequent with the AAPs than the conventional antipsychotics (CAP); with the risk greatest for clozapine and olanzapine. These observations are supported by a nested case-control study using the United Kingdom General Practice Database that found current users of AAPs and CAPs to be 4.7 and 1.7 times greater to develop incident diabetes compared to nonusers, respectively (1). A second nested case-control study from the same database found olanzapine to have more than 4 times the associative risk of incident diabetes compared to all other antipsychotics or not taking an antipsychotic (2). Risperidone was not associated with a significantly elevated risk in either comparison. A retrospective study using the Canadian Healthcare Database reported that risk of incident diabetes was 20% greater with olanzapine compared to risperidone, with women having a 30% increased risk (3). The risk was present only if the duration of exposure had been less than 3 months, exposure for 3 months or longer was not associated with an increased risk. Age was not identified as a risk factor. A retrospective review of VISN 10 also found that the risk for markers of diabetes to be significantly greater for olanzapine than risperidone, while the risk for risperidone did not differ from haloperidol or fluphenazine (4). A retrospective review of the WHO International Drug Monitoring Database found that clozapine, olanzapine, and risperidone were all disproportionately associated with reports of glucose intolerance or diabetes; such a relationship was not found for haloperidol or chlorpromazine (5).

A prospective trial measured fasting glucose concentration at baseline, and at 8 and 14 weeks in patients with schizophrenia or schizoaffective disorder started on clozapine, risperidone, olanzapine or haloperidol. Only olanzapine was found to significantly increase blood glucose at 14 weeks (6).

Effect on Lipids: Serum cholesterol concentrations were also measured in the 14-week prospective trial (see above). Clozapine and olanzapine were found to significantly increase serum cholesterol at week 8, but only remained marginally significant at week 14. The mean cholesterol concentrations for each of the four groups was <200 mg% at each study point.

In a 6-week prospective, naturalistic study in 45 hospitalized schizophrenics prescribed olanzapine, quetiapine, or haloperidol measured change in serum triglycerides after 6-weeks (7). Triglycerides were found to increase with the changes being significantly greater for olanzapine compared to quetiapine and haloperidol. The change was also significant for quetiapine compared to haloperidol.

Six months after being switched from another antipsychotic to ziprasidone, 40 individuals with mental retardation were found to have significantly lower total cholesterol and triglyceride concentrations (8).

Effect on Weight and Leptin: Mean change in weight was reported to be 4.8 kg for clozapine, 7.3 kg for olanzapine, 2.4 kg for risperidone, and 0.9 kg for haloperidol after 14-weeks in one of the prospective studies. Mean weight change was also reported in the 6-week study of quetiapine, olanzapine, and haloperidol as 3.9 kg, 8.4 kg and 0.5 kg, respectively. This study also reported significant differences in mean changes in leptin concentrations between olanzapine and quetiapine, as well as between olanzapine

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and haloperidol. A significant positive correlation was found between change in leptin concentration and duration of illness in patients taking quetiapine or olanzapine, but not haloperidol.

A retrospective chart review of 40 individuals with mental retardation found ziprasidone to be associated with a significant weight loss of 3.6 kg six months after being switched from another antipsychotic (70% risperidone) (8).

Results of a 4-week, double blind, placebo-controlled study comparing aripiprazole to haloperidol found mean changes in body weight to be 0.2 kg placebo, 0.4 kg aripiprazole (15 mg/d), 0.9 kg aripiprazole (30 mg/d), and 0.5 kg haloperidol (10 mg/d). One percent of patient on placebo experienced a $\geq 7\%$ increase in weight compared to 7%, 4%, and 10% in the aripiprazole and haloperidol groups, respectively (9).

Mechanisms of Glucose Dysregulation: Oral glucose tolerance testing and glucose clamp assessment have been used to determine if the mechanism of antipsychotic-induced hyperglycemia is related to insulin resistance and/or damage to pancreatic islet cells (10). Forty-eight schizophrenics (risperidone n= 10, olanzapine n=12, clozapine n=17, and conventional antipsychotics n=31) and 31 healthy controls under went oral glucose tolerance testing. Blood glucose was sampled at fasting and 15, 45 and 75 minutes after the glucose load. Controls were matched on age, BMI, and balanced on ethnicity. Individuals with abnormal glycemic parameters at baseline were excluded. Subjects in the olanzapine group were found to have significantly higher blood glucose concentrations (bglc) at all sample times compared to the control and CAP groups. In the clozapine group, bglc were significantly greater at fasting and 75 minutes compared to the control and CAP groups. Risperidone patients bglc were significantly greater at fasting, 45 and 75 minutes compared to controls, but not CAP users. There were no differences in bglc between CAP and controls at any time point. Results were not affected by gender, BMI, ethnicity, or concurrent use of antidepressants or mood stabilizers. Insulin concentrations at 75 minutes post glucose load were significantly higher for AAPs users than CAPs users or controls. Using the homeostasis model assessment (HOMA) index, beta cell function remained stable for all groups. The HOMA index for insulin resistance increased significantly in the olanzapine group ($p<0.05$) and modestly in the clozapine group ($p=0.06$) compared to the CAP group. The authors concluded that antipsychotic effects on glucose dysregulation could vary in severity independent of adiposity and age.

A second study administered two glucose tolerance tests to 10 schizophrenics treated with olanzapine and 10 healthy controls in an 8-week interval (11). Weight and fat mass were measured. The HOMA index for beta cell function did not change significantly, whereas the HOMA index for insulin resistance did increase in the olanzapine group ($p=.006$). Body weight ($p=.001$) and body fat ($p=.004$) increased in olanzapine treated patients, but not in controls. The authors concluded that glucose dysregulation associated with olanzapine was primarily due to insulin resistance.

A hyperglycemic clamp was used to assess the effect of olanzapine (n=17), risperidone (n=13) and placebo (n=18) on beta-cell function in healthy volunteers. Insulin secretion was quantitated at baseline and after 15-17 days of exposure. Both olanzapine and risperidone increased insulin response by approximately 25% and decreased insulin sensitivity by approximately 18%; no changes were seen with the placebo control. Mean weight increased in all three groups; olanzapine 2.8 ± 1.7 kg, risperidone 3.1 ± 2.1 kg, and placebo 0.5 ± 1.2 kg. These increases were significant only for olanzapine and risperidone for both within group ($p<0.01$) and placebo ($p<.001$) comparisons. When the hyperglycemic clamp results were adjusted for weight change, there was no significant change in insulin response or sensitivity after exposure to olanzapine or risperidone. The authors concluded that neither olanzapine nor risperidone directly impair pancreatic beta-cell function (12).

Summary: Both conventional and atypical antipsychotics are associated with weight gain and metabolic changes, particularly hyperglycemia. Data from epidemiologic studies support the clinical observation that the risk for weight gain and metabolic abnormalities is greater for the AAPs than the CAPs. Among the AAPs, the risk is greater with clozapine and olanzapine compared to risperidone and quetiapine. There is insufficient published data on ziprasidone and aripiprazole to make conclusions regarding their risk for affecting weight, lipids and glucose control. Available data suggest that their risk is lower than that of clozapine or olanzapine. Antipsychotic-induced changes in glucose regulation appear to be secondary to increased insulin resistance rather than impaired beta-cell function.

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Addendum 1: A Department of Veterans Affairs advisory on second-generation antipsychotics (AAPs) and diabetes mellitus, circulated via a memorandum date January 8, 2004 from Dr. Laurent Lehman, Chief Consultant, Mental Health Strategic Health Care Group, reached similar conclusions. The advisory asked that clinicians consider the potential for these adverse effects when treating patients with existing cardiovascular disease or diabetes mellitus, or with risk factors for these conditions. The advisory recommended baseline and periodic monitoring of weight, body mass index (BMI), fasting blood glucose, lipids and blood pressure in patients prescribed AAPs. Patients should be educated about the signs and symptoms of these potential adverse effects.

Addendum 2: The findings of a consensus development conference on antipsychotic drugs, obesity and diabetes conducted by the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity were published in *Diabetes Care* 2004; 27(2): 596-601. Their conclusions were similar to those above and the Department of Veterans Affairs advisory. Specific monitoring recommendations as well as education of health professionals, patients, family members, and caregivers were made.

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