

Ziprasidone is Equally Effective, Has Less Adverse Metabolic Effects than Olanzapine

The following is an extract of:

Simpson, GM, Glick ID, Weiden PJ, Romano SJ, Siu CO. Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. *Am J Psychiatry* 2004; 161:1837-1847

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Bottom Line:

- Ziprasidone and olanzapine had similar efficacy.
- Ziprasidone did not significantly increase body weight, total cholesterol, triglycerides, LDL, or fasting insulin levels.
- Olanzapine significantly worsened metabolic parameters:
 - Mean weight: 3.57 kg increase
 - Lipids: total cholesterol, LDL, and triglycerides increased 10%, 13%, and 25%, respectively.
 - Glucose Regulation: insulin levels and median HOMA-IR scores increased 33.7% and 7.4%, respectively.

Study Background

Compared to first generation conventional antipsychotics, second generation atypicals may offer better control of negative and cognitive symptoms of schizophrenia, with lower risk of extrapyramidal symptoms (EPS). Ziprasidone and olanzapine have shown short- and long-term clinical efficacy when compared to placebo and non-inferiority when compared to haloperidol. However, multiple studies of olanzapine have shown associated risk for weight gain, increased triglyceride levels and impaired glucose regulation. Clinical trials of ziprasidone show a low incidence of weight gain and negligible impact on lipid profiles. This study is a head to head comparison of the efficacy and side effect profiles of these two atypical antipsychotics.

Study Details

This trial was a 6 week randomized, controlled, double-blind, multicenter comparison which enrolled recently admitted inpatients who had a primary diagnosis of schizophrenia or schizoaffective disorder. After 1-2 days' screening period when psychotropics were discontinued and one day assessment period when baseline tests were done, participants were randomly assigned to either olanzapine or ziprasidone. Consumers were required to have normal lab results and a normal ECG at baseline. Consumers receiving depot antipsychotics were admitted after one dosing period had elapsed. Exclusion criteria included consumers who: had nonresponse to two past trials of antipsychotics; met criteria for substance abuse or dependence in the past three months; were considered high risk for suicide or violence; or had past use of olanzapine for >14 days or at doses >10 mg. Prescription of lorazepam for agitation or insomnia and benztropine for EPS was permitted. Both agents were used at similar doses and frequencies by consumers in both arms of the trial. During week one, participants received a fixed dose. During weeks 2-6, dosing was flexible. Maximum dose for olanzapine was 15 mg/day and for ziprasidone 160 mg/day. Consumers were eligible for discharge during weeks 3-6 if they met protocol criteria for outpatient treatment. Efficacy was measured with baseline and regularly scheduled assessments using the Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANS), CGI severity scale, CGI improvement scale, and the Calgary

June 21, 2011

Depression Scale for Schizophrenia. All adverse events, including severity, duration, and relationship to the study drugs, were recorded. Regularly scheduled evaluations for movement disorders were done using the Extrapyramidal Symptom Rating Scale, the Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale (AIMS). Measures of cardiometabolic risk, done at baseline, at periodic intervals and at endpoint included: body weight, body mass index (BMI), standard clinical laboratory tests, fasting serum lipids, measures of insulin resistance (fasting blood glucose, fasting insulin levels, HOMA-IR), vital signs and ECGs.

Results and Limitations

Of the total participants randomly assigned to ziprasidone (n=136), 51.5% (n=70) completed the study and 48.5% (n=66) discontinued. All-cause discontinuation rates were lower for olanzapine (36.8%, n=49, $p<.05$). However, there were no significant between-group differences regarding rates of discontinuation due to lack of efficacy. Both agents were equally effective at improving BPRS and CGI severity scores, with no significant between-group differences on these two parameters. The EPS Rating Scale, Barnes Akathisia scale and AIMS scores were similar at baseline and did not show significant between-group differences at endpoint. The mean score on these scales either decreased or remained constant, but did not increase.

Compared to baseline measurements and to the ziprasidone group, consumers treated with olanzapine showed statistically significant changes in weight and metabolic parameters. Weight gain in the olanzapine group was 3.57 kg over the 6 week period, compared to 1.0 kg in the ziprasidone group ($p<0.001$). Compared to baseline, the following increased significantly in the olanzapine group: total cholesterol (median increase 19.5 mg, $p<.0001$), low-density lipoprotein (median increase 13 mg/dl, $p<0.0001$), and triglycerides (median increase 26 mg/dl, $p<0.0003$). There were also significant between group differences regarding changes in homocysteine and apolipoprotein B levels ($p<0.005$ and $p<0.0001$, respectively). While serum glucose levels were not significantly affected by either medication, the olanzapine group had significantly increased levels of fasting insulin ($p<0.0001$), C-peptide ($p<0.0001$), and HOMA-IR ($p<0.0001$). These levels also increased, but were nonsignificant, for the ziprasidone group. The mean change in the QTc interval was 6.08 msec for ziprasidone and 0.52 msec for olanzapine ($p<0.05$). There were no increased adverse cardiac events associated with these QTc prolongations.

Clinical Implications

As expected, both ziprasidone and olanzapine showed similar benefit for controlling symptoms of schizophrenia. Ziprasidone had very little effect on weight, lipids, and measures of glucose control. In comparison, olanzapine showed a mean increase in weight of 3.57 kg (a significant finding). The olanzapine group also showed total cholesterol, LDL, and triglycerides that were 10%, 13%, and 25% higher than baseline, respectively. Moreover, the olanzapine group showed a 33.7% increase over median baseline insulin levels, and a 7.4% increase in median HOMA-IR scores compared to the ziprasidone group, in which insulin levels increased by 2.9% and median HOMA-IR scores increased by 1.8%. Given the high risk for cardiometabolic problems among people with schizophrenia, long-term studies evaluating the relationship of these results to overall health would help clinical practice move toward the goal of improving care for those with serious mental illness.

Limitations of this study include the short follow-up time, and financial sponsorship by Pfizer, the pharmaceutical company holding the patent for ziprasidone.