# The Effect of a Switch to Ziprasidone in an Adult Population With Autistic Disorder: Chart Review of Naturalistic, Open-Label Treatment

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***Background:*** The present investigation retrospectively assessed the effect of an open-label switch to ziprasidone from other atypical antipsychotics on behavior, weight, and lipid levels in an adult population with autistic disorder.

***Method:*** We conducted a chart review of 10 adults (mean ± SD age = 43.8 ± 6.0 years) with DSM-IV autistic disorder who were switched from other atypical antipsychotics to ziprasidone, primarily due to weight gain, but other reasons included hypercholesterolemia, maladaptive behaviors, drowsiness, and depression. They had been treated with ziprasidone for at least 6 months. Our review focused on frequency of maladaptive behaviors, weight, and lipid levels.

***Results:*** The mean ± SD daily dose of ziprasidone was 128 ± 41 mg, and all 10 patients continued with this same treatment after completion of the 6-month trial. Seven patients were found to have an improvement or no change in their maladaptive behavior. Eight patients (80%) lost weight (mean change = –13.1 ± 7.0 lb [–5.9 ± 3.2 kg]), 4 (80%) of 5 patients had a decrease in total cholesterol level, and 3 (60%) of 5 had a decrease in triglyceride levels. Data on lipid levels were available for 5 of the 10 patients. Behavioral activation was not noted in this population. There were no significant adverse effects associated with ziprasidone.

***Conclusion:*** In adults with autism, a switch to ziprasidone from other atypical antipsychotics appears to have the potential for maintaining beneficial effect on behavior while improving major health indices including weight and lipid levels.

*(J Clin Psychiatry 2004;65:110–113)*

*Received April 28, 2003; accepted June 23, 2003. From Fircrest, Seattle (Dr. Fitzgerald), and the Northwest Clinical Research Center, Bellevue (Ms. Khan and Dr. Khan), Wash.; and the Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, N.C. (Dr. Khan). Dr. Cohen is in private practice in Seattle, Wash.*

*Dr. Cohen previously received an Independent Medical Grant from Pfizer Inc, New York, N.Y., to investigate the effect of a switch to ziprasidone in an adult population with mental retardation; has received other grant/research support from Pfizer; and has served on the speakers or advisory boards for Bristol-Myers, Pfizer, and Janssen. Drs. Fitzgerald and Khan and Ms. Khan report no financial affiliation or other relationship relevant to the subject matter of this article.*

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Autism has been associated with abnormalities in serotonergic functioning.[1] Historically, psychopharmacologic treatment focused on reducing assault and self injury with haloperidol, a dopamine-2 ($D_2$) blocking agent. It was found to be effective yet commonly led to dyskinesias.[2] More recently, the atypical antipsychotics, which have both serotonin-2A ($5\text{-}HT_{2A}$) and $D_2$ receptor-blocking properties, have been used in this population. The ratio of $5\text{-}HT_{2A}$ to $D_2$ blockade for ziprasidone is 11:1—larger than that of the other atypical antipsychotics.

Risperidone is the only agent of this class that has been studied in double-blind placebo-controlled fashion.[3,4] It was found to be effective in reducing repetitive behavior, aggression, anxiety or nervousness, depression, irritability, and the overall behavioral symptoms of autism in adults with autism or other pervasive developmental disorders.[3] It was also found to be effective in reducing irritability, hyperactivity, and stereotypy in children and adolescents with autism.[4]

We previously found risperidone to be effective in reducing maladaptive behavior in an adult population with mental retardation[5] yet found significant weight gain that was unresponsive to caloric restriction.[6] Various hypotheses have been offered to explain the weight gain seen with some of the atypical antipsychotics, such as $5\text{-}HT_{2C}$ blockade or changes in leptin levels, yet the etiology for this side effect and other metabolic disturbances remains unknown. Recently, we published our results noting that switching these adults to ziprasidone led to ongoing behavioral stability while there was a significant reduction in weight, cholesterol levels, and triglyceride levels.[7] These individuals did not specifically have autism, yet they all had mental retardation. Only 2 of the 40 patients (who are 2 of the 10 described in this paper) were also diagnosed with autism.

Only 1 report in the literature has specifically looked at ziprasidone in an autistic population.[8] This was a case series of children and adolescents (mean ± SD age = 11.62 ± 4.38 years), 50% of whom were deemed to be responders. These children were switched to ziprasidone from typical and/or other atypical antipsychotics because of inadequate response to prior medications or intolerable side effects, primarily weight gain. The mean

**Table 1. Demographics and Clinical Characteristics of Patients With Autistic Disorder Switched to Ziprasidone (N = 10)**

| Variable | N | % |
|---|---|---|
| Female | 4 | 40 |
| White | 10 | 100 |
| Pre-switch treatment | | |
| Risperidone | 8 | 80 |
| Quetiapine | 1 | 10 |
| Clozapine | 1 | 10 |
| Reasons for switch to ziprasidone | | |
| Overweight | 8 | 80 |
| Hypercholesterolemia | 2 | 20 |
| Maladaptive behavior | 2 | 20 |
| Drowsiness | 2 | 20 |
| Depression | 1 | 10 |
| | Mean ± SD | |
| Age, y | 43.8 ± 6.0 | |
| Dose of ziprasidone, mg/day | 128 ± 41 | |

duration of treatment was 14.15 ± 8.29 weeks and the mean change in body weight was –5.83 ± 12.52 lb (–2.64 ± 5.68 kg).

Age is a factor that may be associated with greater likelihood of specific side effects as well as effectiveness of medications. For example, children treated with lamotrigine are at greater risk of developing Stevens-Johnson syndrome than are adults treated with this agent.[9] Autistic adults treated with fluvoxamine were noted to have a reduction in maladaptive behavior, yet autistic children were found to have significant behavioral activation in the form of agitation, aggression, and insomnia when treated with fluvoxamine.[10]

Thus, we sought to address the effect of a switch to ziprasidone from other atypical antipsychotics in an adult population with autistic disorder. We questioned whether it might appear more effective in reducing maladaptive behaviors in an autistic population than in our general group of patients with mental retardation. Another area of interest was to ascertain whether the behavioral benefit along with weight loss and overall tolerability seen with ziprasidone in children with autism[8] would be any different in an adult population with autistic disorder.

## METHOD

The present study consisted of a chart review of 10 adult patients with DSM-IV autistic disorder who completed at least 6 months of treatment with ziprasidone. Nine (90%) had a diagnosis of profound mental retardation and 1 (10%) had borderline intellectual functioning. Other concurrent diagnoses in this population included epilepsy (N = 4), hypercholesterolemia (N = 2), osteoporosis (N = 2), gastroesophageal reflux disease (N = 1), blindness (N = 1), hypertension (N = 1), tardive dyskinesia (N = 1), and asthma (N = 1).

The majority of these patients (80%) were previously treated with risperidone prior to their switch to ziprasidone (Table 1). The patients resided at Fircrest, a residential habilitation center for adults with mental retardation located in the greater Seattle, Washington area.

We specifically reviewed patients' chart for age, gender, race, medication treatment prior to ziprasidone, reasons for switching to ziprasidone, and daily dose of ziprasidone (Table 1). In addition, we extracted data on weight 6 months prior to the switch to ziprasidone, at the time of the switch to ziprasidone (baseline), and after 6 months of treatment with ziprasidone (Table 2). Differences in weight between 6 months prior to switch and baseline and between baseline and after 6 months of ziprasidone treatment were evaluated with paired sample t tests. Results were considered significant at the $p < .05$ level.

Additionally, we ascertained the average monthly score for each patient on the Maladaptive Behavior Scale for the 6 months prior to baseline and the 6 months of ziprasidone treatment. This score represents the sum of the maladaptive behavior for each individual (i.e., assault, agitation, self-injury, aggression) and is the objective target also utilized in our previous publications, which helps guide decisions with medication changes.[5,7] We also reviewed patients' total cholesterol and triglyceride levels at baseline and after 6 months of ziprasidone treatment (Table 2). High-density lipoprotein and low density lipoprotein cholesterol levels were not available. Differences in behavior between 6 months prior to switch and after 6 months of ziprasidone treatment were evaluated with paired sample t tests.

Many of the Fircrest residents were calorie restricted, and, for some, their caloric consumption was liberalized as they were switched to ziprasidone. None of the patients were noted to have any significant change in their activity level during the 6-month period of treatment with ziprasidone. Concomitant medication, target behavior, and adverse events will be summarized in the results section.

## RESULTS

The mean daily dose of ziprasidone was 128 ± 4 mg, and all 10 patients continued with treatment after the 6-month trial.

The mean weight gain for the 6 months prior to the switch to ziprasidone was 2.6 ± 8.6 lb (1.2 ± 3.9 kg). This weight gain was not statistically significant. After 6 months of ziprasidone treatment, the mean weight loss was 9.5 ± 10.1 lb (4.3 ± 4.6 kg) from baseline, which was statistically significant ($p < .05$, Table 2). Eight of the 10 patients lost weight (mean change = –13.1 ± 7.0 lb [–5.9 ± 3.2 kg]), 1 had no weight change, and another gained 10 pounds.

Data for the Maladaptive Behavior Scale were available for all 10 patients, and data for total cholesterol level or triglyceride levels were available for only 5 of the 10

**Table 2. Changes in Behavior, Cholesterol and Triglyceride Levels, and Weight for Patients With Autistic Disorder Switched to Ziprasidone**

| Variable | N | 6-Mo Pre-Switch, (Mean ± SD) | Baseline, (Mean ± SD) | 6-Mo Post-Switch, (Mean ± SD) | Statistic t | df | p Value |
|---|---|---|---|---|---|---|---|
| Maladaptive behaviors[a] | 10 | NA | 2.0 ± 2.2 | 3.2 ± 7.8 | –0.563 | 9 | .587 |
| Cholesterol level, mg/dL | 5 | NA | 159.2 ± 26.0 | 156.6 ± 17.6 | 0.510 | 4 | .637 |
| Triglyceride level, mg/dL | 5 | NA | 105.8 ± 58.1 | 84.0 ± 45.1 | 1.569 | 4 | .192 |
| Weight, lb | 10 | 200.7 ± 41.5 | 203.3 ± 43.5 | 193.8 ± 43.7 | 0.953 | 9 | .366[b] |
| | | | | | 2.977 | 9 | .016[c] |

[a]Data are expressed as monthly mean on the Maladaptive Behavior Scale in which a higher score indicated higher frequency of actions such as assault, self-injury, or property destruction.
[b]Pre-switch to baseline comparison.
[c]Baseline to post-switch comparison.
Abbreviation: NA = data not available.

patients. Scores on the Maladaptive Behavior Scale, total cholesterol levels, or triglyceride levels (Table 2) did not vary statistically significantly during the 6 months of treatment with ziprasidone.

In comparing the change in average monthly frequency scores of the Maladaptive Behavior Scale for the 6 months before the switch to ziprasidone with that after the 6 months of ziprasidone treatment, we found that the scores of 6 (60%) of 10 patients improved, 1 (10%) of 10 remained the same, and 3 (30%) of 10 worsened.

Four (80%) of 5 patients had a decrease in total cholesterol level, and 3 (60%) of 5 had a decrease in triglyceride levels.

Concomitant medication used by these patients included fluvoxamine (N = 1), atorvastatin (N = 2), propranolol (N = 1), omeprazole (N = 1), gabapentin (N = 1), atenolol (N = 1), enalapril (N = 1), valproate (N = 1), topiramate (N = 1), benztropine (N = 1), alendronate (N = 1), montelukast (N = 1), and albuterol (N = 1).

The target behaviors for ziprasidone treatment were as follows: assault (N = 5), agitation (N = 3), self injury (N = 5), and aggression (N = 1). Two patients became more alert after the 6 months of ziprasidone treatment. None of the 10 patients were found to become behaviorally activated. There were no significant adverse effects seen with the switch to ziprasidone.

## DISCUSSION

We found that 6 of our 10 autistic adults switched to ziprasidone for 6 months had an improvement in their maladaptive behavior, while 1 had no change, and 3 decompensated. This response rate is quite similar to that found in our larger sample of adults with mental retardation, not specifically autistic, in which 72% were improved or unchanged behaviorally.[7] The results were rather comparable if not even favorable to those found in the only published case series of children with autism switched to ziprasidone, 50% of whom were deemed to be responders.[8]

Overall, these 10 autistic adults had a mean weight loss of 9.5 lb (4.3 kg), quite comparable to the 8.1-lb (3.7-kg) weight loss seen in our larger sample of adults with mental retardation[7] and 5.83-lb (2.64-kg) weight loss in the children with autism.[8] We also found a mean decrease in cholesterol levels of 2.6 ± 11.4 mg/dL and a mean decrease in triglyceride levels of 21.8 ± 31.1 mg/dL in these autistic adults, which was not statistically significant. The change in lipid levels seen in the larger group of patients with mental retardation (cholesterol levels decreased by 24.1 mg/dL, and triglyceride levels decreased by 24.4 mg/dL) was statistically significant.[7] This metabolic parameter was not reported in the case series of autistic children.[8]

Clinically, there has been some suggestion that behavioral activation may occur more frequently with ziprasidone than with other atypical antipsychotics in an adult population with psychotic illness.[11] If indeed this is the case, possible explanations might include underdosing of ziprasidone, switching to ziprasidone from larger equivalent doses of a more sedating antipsychotic, or akathisia. In addition, the receptor affinity profile of ziprasidone, which includes serotonin and norepinephrine reuptake inhibition, could lead to behavioral activation.[12] However, behavioral activation was not seen in this group of 10 autistic adults. Two were deemed to be "more alert," yet none became agitated, hyperactive, or developed insomnia, in contrast to the 12 autistic children, 2 of whom were found to develop agitation and insomnia.[8] Both of these patients were also diagnosed with bipolar I disorder. The serotonergic abnormality noted in association with autism may lead to the large 5-$HT_{2A}$ to $D_2$ ratio seen with ziprasidone to be of particular benefit in this population.

Thus, we found improvement in behavior, weight, and lipid levels in autistic adults switched to ziprasidone that was similar to that seen in a group of autistic children[8] as well as a larger sample of adults with mental retardation.[7] Ziprasidone was well tolerated and was not associated with problematic behavioral activation or other troubling side effects.

The limitations of our study are the small sample size and retrospective design. Hence, our results should be regarded as preliminary in nature pending replication in a larger double-blind study.

*Drug names:* albuterol (Ventolin, Proventil, and others), alendronate (Fosamax), atenolol (Tenormin and others), atorvastatin (Lipitor), benztropine (Cogentin and others), enalapril (Vasotec and others), gabapentin (Neurontin and others), lamotrigine (Lamictal), montelukast (Singulair), omeprazole (Prilosec and others), propranolol (Inderal and others), risperidone (Risperdal), topiramate (Topamax), ziprasidone (Geodon).

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