Weight, Lipids, Glucose, and Behavioral Measures With Ziprasidone Treatment in a Population With Mental Retardation

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Background: Atypical antipsychotics effectively reduce maladaptive behavior in individuals with mental retardation, yet bring significant weight gain and metabolic anomalies. Ziprasidone, a weight-neutral antipsychotic in patients with schizophrenia or schizoaffective disorder, has not been studied in a population with mental retardation and maladaptive behaviors.

Method: Forty patients with mental retardation and maladaptive behaviors who had gained excessive weight or were inadequately responsive to other agents were switched to ziprasidone. Weight, total cholesterol, HDL, LDL, triglycerides, and frequency of maladaptive behavior were recorded at baseline and after 6 months of ziprasidone treatment.

Results: Ziprasidone treatment was associated with a significant weight loss of 8.1 lb (3.6 kg) as well as a significant reduction in total cholesterol and triglycerides ($p \leq .05$). The monthly frequency of the maladaptive behavior remained unchanged or improved in 72% (18/25) of the patients in whom maladaptive behavior was assessed.

Conclusion: Ziprasidone effectively reduces the frequency of maladaptive behavior in a patient group with mental retardation without causing weight gain or metabolic disturbances.

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The atypical antipsychotics are associated with an improvement in negative symptoms and cognitive functioning, with a reduced liability for causing extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) in comparison to the conventional antipsychotics. However, this new generation of medication is associated with substantial weight gain and a significantly increased risk of a variety of metabolic disturbances, such as type 2 diabetes mellitus, hypercholesterolemia, and hypertriglyceridemia.[1] The available literature notes that ziprasidone is a weight-neutral antipsychotic[2] and that lipid anomalies improve when patients are switched from other atypical antipsychotics to ziprasidone.[3] These data are derived from studies of patients with schizophrenia or schizoaffective disorder. No such data have been published in individuals with mental retardation.

The atypical antipsychotics are commonly used as part of the treatment plan to reduce maladaptive behavior in individuals with mental retardation. Previously, we reported that risperidone is effective in reducing assault, self-injury, and property destruction in a population with severe and profound mental retardation.[4] However, we also found that these patients gained approximately 20 lb (9 kg) over the first 2 years of treatment and then another 20 lb over the subsequent 2 years whether or not they were calorie restricted.[5]

In this setting, it was necessary to switch our patients with mental retardation and behavioral disturbances who had gained excessive weight or not responded adequately with other agents to ziprasidone. We report our experience with the first 40 patients for whom we have made this change who completed 6 months of ziprasidone treatment, noting its effect on weight, lipids, glucose, and behavior.

METHOD

The present study consisted of a chart review of our first 40 patients who completed at least 6 months of treatment with ziprasidone. The majority of these patients (70% [N = 28]) were previously treated with risperidone (Table 1). Thirty of these patients resided at Fircrest, a residential habilitation center for adults with mental retardation in the greater Seattle, Wash., area. The other

Table 1. Baseline Demographics for 40 Patients With Mental Retardation Receiving Ziprasidone

Characteristic	Value
Age, mean (SD), y	48.0 (11.0)
Female, N (%)	16 (40.0)
Preswitch (–6 mo) weight, mean (SD), lb	165.1 (40.8)
Preswitch treatment, N (%)	
Risperidone	28 (70.0)
Quetiapine	5 (12.5)
Olanzapine	2 (5.0)
Haloperidol/clozapine	1 (2.5)
None	4 (10.0)
Maximum dose of ziprasidone, mean (SD), mg	145.0 (39.2)

10 patients resided in a variety of community placement settings.

We specifically assessed age, gender, medication treatment prior to ziprasidone, weight 6 months prior to the switch to ziprasidone, and maximum dose of ziprasidone (Table 1). In addition, we recorded weight and total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, and glucose levels at the time of the switch to ziprasidone and after 6 months of treatment with ziprasidone (Table 2). Blood tests were taken while the patients were fasting. HDL and LDL levels were not measured for the 10 outpatients. Differences between baseline and 6 months of ziprasidone treatment were evaluated with paired-sample t tests. Results were considered to be statistically significant at the level of $p \leq .05$.

In addition, we recorded the mean score on the Maladaptive Behavior Scale (unpublished scale; available on request from the authors), which rates the frequency of assault, self-injury, and property destruction, for the 3 months prior to baseline, the first 3 months of ziprasidone treatment, and months 4 through 6 of ziprasidone treatment. These data were not tracked in the 10 outpatients and were available for 25 of the 30 institutionalized patients (Table 3). We also recorded the mean monthly score on the Maladaptive Behavior Scale for the 6 months of ziprasidone treatment and compared it with the mean for the 3 months before the switch to ziprasidone. In accordance with institutional policy, informed consent for the use of both ziprasidone and behavioral intervention programs was obtained from the patients' legal guardians. The Human Rights Committee at Fircrest also approved the use of ziprasidone and behavior intervention programs in each case. All patients were treated with ziprasidone on an open-label basis, and all staff caregivers were aware of the nature of the treatment.

The caloric consumption of the 10 outpatients was not specifically monitored. 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.

RESULTS

The mean weight gain during the 6 months prior to the switch to ziprasidone was 4.1 lb (1.8 kg). After 6 months of ziprasidone treatment, the mean weight loss from baseline was 8.1 lb (3.6 kg), which was statistically significant. There were also statistically significant decreases in cholesterol and triglyceride levels between baseline and 6 months of ziprasidone treatment. HDL, LDL, and glucose levels remained consistent during ziprasidone treatment (Table 2).

Scores on the Maladaptive Behavior Scale (Table 3) remained consistent for the 25 patients in whom these data were measured during the 6 months of treatment with ziprasidone. In comparing the change in mean monthly score on the Maladaptive Behavior Scale from 3 months before the switch to ziprasidone to 6 months after the switch to ziprasidone treatment, we found the scores of 12 (48%) of 25 patients to improve, 6 (24%) of 25 to remain the same, and 7 (28%) of 25 to worsen. Six patients were outliers in terms of their score on the Maladaptive Behavior Scale. Their Maladaptive Behavior Scale reached a frequency of maladaptive behaviors of at least 50 per month sometime during the 9-month data collection period. When the remaining 19 patients were analyzed separately, 9 (47%) of the patients' scores decreased, 6 (32%) of 19 remained the same, and 4 (21%) of 19 worsened when patients were treated with ziprasidone.

Another 2 patients were started on ziprasidone therapy who did not complete 6 months of treatment during the time frame when the other 40 patients were treated. They both received up to 200 mg of ziprasidone per day, 1 on ziprasidone treatment for 3 months and the other, for $4\frac{1}{2}$ months. Due to deterioration in these patients' behavior, ziprasidone was discontinued and they returned to treatment with risperidone. Post–ziprasidone treatment data were not available, and thus they were not included in the data analysis.

DISCUSSION

The data show a significant reduction in weight and total cholesterol and triglyceride levels without a significant change in maladaptive behavior when a group of patients with mental retardation were treated with ziprasidone for 6 months. To our knowledge, no previous work has demonstrated the health benefits of this agent in a population with mental retardation.

The behavioral benefits of risperidone in this population are significant.[4,6] These benefits make it difficult for the caregivers of these individuals to consider a switch away from such an effective medication. We met with such hesitation in our patient sample when making this recommendation. Historically, one had to weigh the benefits of conventional antipsychotics against their liability

Table 2. Weight, Lipid Levels, and Glucose Levels in Patients With Mental Retardation Receiving Ziprasidone[a]

		Baseline		After 6 Months of Ziprasidone Treatment		Statistical Analysis		
Measure	N	Mean	SD	Mean	SD	t	df	p
Weight, lb	40	169.2	39.4	161.1	38.5	4.7	39	.000
Cholesterol, mg/dL	30	200.5	74.8	176.4	41.5	2.3	29	.032
Triglycerides, mg/dL	29	147.8	82.7	123.4	85.5	2.2	28	.035
Glucose, mg/dL	27	87.0	21.5	83.4	16.8	0.7	26	.498
LDL, mg/dL	19	113.9	27.0	110.7	19.7	0.6	18	.555
HDL, mg/dL	19	41.3	12.2	41.5	10.2	–0.2	18	.885

[a]Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Table 3. Maladaptive Behaviors in Patients With Mental Retardation Receiving Ziprasidone

		No. of Behaviors	
Group	N	Mean	SD
Patients with low-to-moderate frequency of maladaptive behaviors			
Preswitch (–3 mo to baseline)	19	5.1	5.5
Early ziprasidone treatment (baseline to 3 mo)	19	4.7	6.7
Late ziprasidone treatment (4 to 6 mo)[a]	17	2.4	3.6
Patients with high frequency of maladaptive behaviors			
Preswitch (–3 mo to baseline)	6	64.7	67.5
Early ziprasidone treatment (baseline to 3 mo)	6	72.5	73.4
Late ziprasidone treatment (4 to 6 mo)[b]	5	66.0	50.5

[a]Data missing for 2 patients.
[b]Data missing for 1 patient.

for causing EPS and TD. Now, one is faced with weighing the benefits of the atypical agents against their liability for causing weight gain, type 2 diabetes mellitus, hypercholesterolemia, and hypertriglyceridemia. Our data suggest that patients with mental retardation and maladaptive behavior can derive similar behavioral benefit from ziprasidone compared with other agents while improving their overall health and presumed longevity by decreasing their weight, cholesterol, and triglycerides.

It should be pointed out that not only did this sample lose a mean of 8.1 lb (3.6 kg) with 6 months of ziprasidone treatment, but this weight reduction represented a reversal from the 6 months before the switch, during which time there was a mean weight increase of 4.1 lb (1.8 kg). Due to significant weight gain with the prior medication, many of our patients were calorie restricted.[5] With the change to ziprasidone and subsequent weight decrease, many of our patients were no longer calorie restricted. One patient lost 25 lb (11 kg) in the first month after switching to ziprasidone. His dietary intake was then intentionally changed from calorie restriction to double portions. Thus, the weight loss noted in Table 2 probably underrepresents the actual weight loss associated with the switch to ziprasidone.

The data also suggest a trend toward a reduction in the frequency of maladaptive behaviors, with longer duration of treatment in the group with low-to-moderate frequency of such behaviors. This finding suggests that long trials of 6 months' duration may be warranted. Future studies to assess the long-term effects of ziprasidone in a population with mental retardation and behavioral disturbance are indicated.

Criswell et al.[7] demonstrated that clozapine blocked the self-mutilation resulting from dihydroxyphenylalanine administration to neonatal 6-hydroxydopamine–lesioned rats. This work led to the suggestion that clozapine and other serotonin/dopamine antagonists may be effective in treating patients with aggressive behaviors. Indeed, ziprasidone has a ratio of 5-HT_{2A}–to-D_2 blockade of approximately 11:1.[8] Perhaps this contributed to its apparent effectiveness in our patient group. The mechanism of antipsychotic-induced weight gain has not been clearly established, although neurobiological mechanisms involving the hypothalamus and its monoaminergic and histaminergic influences have been a point of focus.[9] Thus, the mechanism responsible for the weight neutrality of ziprasidone and the weight loss seen in our sample remains unknown.

Our work should be regarded as preliminary pending replication. However, the data suggest that the clinician treating an individual with mental retardation and behavioral disturbance should consider the use of ziprasidone, which may be effective in reducing maladaptive behavior without causing significant metabolic disturbance and compromising the patient's overall health status.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

REFERENCES

1. McIntyre RS, McCann SM, Kennedy SH. Antipsychotic metabolic effects: weight gain, diabetes mellitus and lipid abnormalities. Can J Psychiatry 2001;46:273–281
2. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156:1686–1696
3. Kingsbury SJ, Fayek M, Trufasiu D, et al. The apparent effects on ziprasidone on plasma lipids and glucose. J Clin Psychiatry 2001;62:347–349
4. Lott RS, Kerrick JM, Cohen SA. Clinical and economic aspects of risperidone treatment in adults with mental retardation and behavioral disturbance. Psychopharmacol Bull 1996;32:721–729
5. Cohen S, Glazewski R, Khan S, et al. Weight gain with risperidone among patients with mental retardation: effect of calorie restriction. J Clin Psychiatry 2001;62:114–116
6. McDougle CJ, Holmes JP, Carlson DC, et al. A double-blind placebo-controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders. Arch Gen Psychiatry 1998;55:633–641
7. Criswell HE, Mueller RA, Breese GA. Clozapine stops self-mutilatory behavior induced by L-dopa in 6-OHDA lesioned rats. Eur J Pharmacol 1989;159:141–147
8. Meltzer HY. Role of serotonin in the action of atypical antipsychotic drugs. Clin Neurosci 1995;3:64–75
9. McIntyre RS, Mancini DA, Basile VS. Mechanisms of antipsychotic-induced weight gain. J Clin Psychiatry 2001:62(suppl 23):23–29