Original Contributions

Ziprasidone's Effect on Metabolic Markers in Patients with Diabetes and Chronic Schizophrenia

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Abstract

Background: Despite numerous studies of diabetes mellitus type II (DM-II) in schizophrenia and schizoaffective disorder, there have been no studies on the glycemic effects of switching patients with long-standing symptomatic DM-II from their current antipsychotic regimen to ziprasidone. **Methods:** An open-label, prospective inpatient study was conducted with 26 suboptimally responding inpatients with *DSM-IV* diagnoses of schizophrenia or schizoaffective disorder and comorbid DM-II who were switched to ziprasidone monotherapy and followed for 8 weeks. Outcome measures were fasting glucose, triglycerides, cholesterol, insulin levels, capillary blood glucose levels and weight. After a 3-week cross-titration period, patients were treated with ziprasidone up to a dose of 320 mg daily. **Results:** Of the 26 study participants, 16 completed the entire study period of 63 days and 10 (38.46%) discontinued participation, primarily due to psychotic relapse. There was a statistically significant reduction in fasting glucose (F=4.43, p=0.05; 14.68 mg/dL mean reduction), capillary blood glucose levels (F=8.90, p=0.01; 25.36 mg/dL mean reduction), weight (F=4.46, p=0.05; 4.68 lb mean weight loss) and Body Mass Index (F=4.40, p=0.05; 3.62 kg/m² mean reduction). There was also a reduction in the use of antidiabetic medications after the switch to ziprasidone. Nine (34.62%) patients met criteria for metabolic syndrome (MetS) at baseline, as compared to 4 (15.38%) at endpoint. No change was observed in positive symptoms (F=0.62, p=0.44), negative symptoms (F=1.47, p=0.24) and in total PANSS score (F=0.12, p=0.74). **Conclusions:** This study suggests significant improvement in metabolic side effects and MetS in the subset of the patients who were able to tolerate switching from a polypharmacy regimen to ziprasidone. There was a large discontinuation rate, which limited the sustained beneficial effects of ziprasidone. The decision to switch to ziprasidone in patients with prior suboptimal response has to balance the potential metabolic benefits and the potential relapse risks of the individual patient first and foremost.

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Background

The association between schizophrenia and increased risk of diabetes mellitus type II (DM-II) has long been recognized, even before the introduction of second-generation antipsychotics (SGAs) (1-4). In addition to an increased risk of DM-II, schizophrenia is also associated with increased prevalence of metabolic syndrome (MetS) (5, 6), with estimates ranging from 25.1 to 66.7% of females and 19.4 to 47.3% of males (7-10). Elevated rates of DM-II and MetS have also been reported in our own population of inpatients with chronic schizophrenia (7): 43.7% had a Body Mass Index (BMI) ≥30 (indicating obesity) and 26.2% presented with DM-II, impaired fasting glucose, and/or impaired glucose tolerance, while 25.5% met World Health Organization (WHO) criteria for MetS. Among factors implicated in the

Clinical Implications

This is the first study to examine the metabolic effects of switching from a polypharmacy regimen to monotherapy with ziprasidone in a group of suboptimally responding schizophrenic or schizoaffective inpatients with comorbid pre-existing symptomatic diabetes mellitus type II (DM-II). The data from this study of chronic psychiatric inpatients with long-standing symptomatic DM-II suggest significant improvements in metabolic effects and MetS in the subset of the population who were able to tolerate switching to ziprasidone. While switching to ziprasidone may be an important treatment strategy in patients with established comorbid metabolic disorders presenting with tolerability problems under their current antipsychotic treatment (41, 42), there was a large discontinuation rate, which may have limited the sustained beneficial effects of ziprasidone. As with all clinical decisions, the decision to switch to ziprasidone has to balance the potential metabolic benefits and the potential relapse risks of the individual patient first and foremost.

development of DM-II and MetS in this population are the adverse effects of SGAs, reduced access to medical care, high rates of smoking, poor nutrition, and sedentary lifestyle (11, 12).

The contribution of psychotropic medications, particularly SGAs, to the development of MetS and DM-II has been extensively studied (8, 13, 14). Of all the SGAs, ziprasidone and aripiprazole have been shown to have a more favorable side effect profile with respect to DM-II and MetS, and may be appropriate switching agents if one is seeking to ameliorate the metabolic side effects of a previous antipsychotic medication (15-27). Introduced in 2001, ziprasidone is unique among the SGAs in exhibiting antagonist activity at the D2, 5-HT1D, and 5-HT2C receptors, antagonist activity at 5-HT2A receptors, and agonist activity at 5-HT1A receptors. In addition, it has been shown to be an inhibitor of serotonin and norepinephrine reuptake (28, 29).

Numerous studies have demonstrated ziprasidone's efficacy not only in treating psychosis, but in reducing MetS and DM-II relative to other SGAs when patients were switched from both first-generation antipsychotics (FGAs) and SGAs (18, 19, 23, 24, 30-33). However, there have been no studies on the effects of switching suboptimally responding patients with long-standing symptomatic diabetes mellitus from a polypharmacy regimen to ziprasidone. The primary objective was to examine the effects of a switch to ziprasidone on weight, metabolic measures of glucose and lipid metabolism, and on the use of antidiabetic medications. A secondary objective was to evaluate changes in symptomatology in these inpatients using the Positive and Negative Symptoms Scale (PANSS), the Clinical Global Impression Scale (CGI), and two extrapyramidal symptoms (EPS) assessment scales: the Simpson-Angus Scale (SAS) and the Abnormal Involuntary Movement Scale (AIMS).

Methods

Design

This is an open-label, prospective, inpatient study which was implemented on a psychiatric ward designated for patients with Diabetes and Schizophrenia from 2002 to 2008. The Diabetes/Schizophrenia ward is part of a large tertiary care psychiatric hospital. The study was approved by our Institutional Review Board (IRB) at Nathan S. Kline Institute for Psychiatric Research (NKI), Orangeburg, NY, and every enrolled patient signed an informed consent form. There was a screening phase (two weeks) on the patients' prior antipsychotic regimen, a cross-titration phase (three weeks), and a ziprasidone-treatment phase (eight weeks; four time points). Measures were systematically administered and data collected by trained research staff. All patients admitted to the study site (Manhattan Psychiatric Center) were required to participate during the entire hospital stay in regular psycho-educational group activities, which included teaching healthy dietary habits and a daily thirty-minute exercise period. All inpatients at the study site were required to be followed by a dietician and receive a daily caloric intake. Patients with DM-II receive a similar daily calorie requirement. Therefore, all patients enrolled in this study were enrolled in the psycho-educational and exercise program since admission to the site, during the study and after completion of the study.

Patients were included if they were 18–65 years of age, had a *DSM-IV* diagnosis of schizophrenia (all subtypes) or schizoaffective disorder, had DM-II treated with oral antidiabetic drugs or insulin, had a stable dose of antipsychotic medications and, where applicable, had stable doses of adjunctive antidepressant, mood stabilizer and/or anticholinergic medications maintained during the previous month. Exclusion criteria included significant cardiovascular pathology as demonstrated by EKG (QTc >450 msec), severe medical conditions (except for DM-II) requiring frequent changes in medication, a history of unstable epilepsy, suicidality or physically violent behavior in the previous month, a *DSM-IV* diagnosis of substance or alcohol abuse with positive urine toxicology in the past two weeks, liver enzyme values greater than three times upper normal limit for aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and alkaline phosphatase, and greater than two times upper normal limit for lactate dehydrogenase (LDH).

Assessments

The screening period lasted two weeks, during which time patients remained on their former antipsychotic regimen. Antipsychotic treatment data and medication data for treatment of DM-II with oral hypoglycemics and/or insulin were recorded. The following values were collected or calculated for all patients at baseline and days 21, 35, 49 and 63: 1) venous fasting blood glucose levels and capillary blood glucose levels; 2) fasting insulin levels and dosages of supplemental insulin administered as needed; 3) hemoglobin A1C levels; 4) weight; 5) BMI; 6) lipid profile (cholesterol, HDL, LDL, triglycerides); 7) leptin levels; 8) C-peptide levels; 9) complete blood count; 10) chemistry lab values; 11) PANSS; 12) CGI; 13) SAS; 14) AIMS; 15) a physical examination; and, 16) vital signs. For the assessment battery of the PANSS, CGI, SAS and AIMS, a trained single rater performed all assessments for a particular patient throughout the trial. All raters had to demonstrate inter-rater reliability on the PANSS of at least 0.80.

EKG was obtained at the following time points: baseline, Day 5, every week thereafter until ziprasidone dosage reached 160 mg/day (which occurred at Week 4, as per protocol), and at the end of the study. If the patient's dose was increased beyond 160 mg/day (which occurred in 2 patients), EKGs were done weekly until the final dose was reached. EKGs were obtained as close as possible to the estimated 6 hour Tmax after drug administration and in the fed state.

Antipsychotic Medication Treatment

After the 2-week screening phase, patients entered the 3-week cross-titration phase. On Days 1 and 2, patients received 80 mg/day of ziprasidone and 100% of their previous antipsychotic dose. The prior antipsychotic was reduced to 75% of the original dose for the following 12 days, while ziprasidone was increased to 120 mg/day on Day 3 and 160 mg/day on Day 4. All but two of the patients were kept on this dose for the duration of the study, while the prior antipsychotic dose was further reduced to 50% over the next 7 days (Day 15–21), and discontinued thereafter. By Day 21, all patients were on the study medication, ziprasidone, at a dose of at least 160 mg/day. All ziprasidone doses were given with food and doses were divided in half and taken twice daily. In view of the high number of patients who relapsed at 160 mg/day, the last two patients enrolled in the study were further increased beyond this dose to 320 mg by Day 21. The following additional PRN medications for agitation were permitted: lorazepam 1–2 mg PO or IM per dose and/or chlorpromazine 50 mg PO or IM per dose of administration. For insomnia, zolpidem 10 mg PO was permitted.

Analyses

Descriptive statistics were conducted to characterize the study sample. For the primary outcome variables of interest (metabolic variables), ANOVA for repeated measures was conducted with change scores over 10 weeks of treatment as dependent variables for the patients who completed the entire study. For 2 group analysis, i.e., completers versus discontinued patients, ANOVA was conducted; if significant p values were noted, Tukey Post Hoc tests were computed to ascertain the direction of the significant results. In order to examine the relationship of weight gain and change in glucose levels, Pearson correlation of change in BMI with change in glucose was conducted. The data were analyzed using the Statistical Package for the Social Sciences for Windows (SPSS, version 15.0, Chicago, IL).

Results

Demographics

Of the 63 consecutively admitted inpatients with *DSM-IV* diagnosis of schizophrenia or schizoaffective disorder and comorbid diabetes mellitus type II who met inclusion criteria, 30 were enrolled. Four patients withdrew prior to receiving study medication (two withdrew consent, one patient had significant cardiovascular pathology as demonstrated by EKG [QTc >450 msec], and one became agitated), thus resulting in 26 patients included in further analysis. Sixteen (61.54%) patients completed the entire study period (15 completed up to 63 days and one completed up to 61 days) and 10 (38.46%) discontinued participation. The primary reason for discontinuation was psychotic relapse seen at 21 days (1 patient), 36 days (3 patients), 49 days (6 patients), with a mean length of time in the study of 54.88 days (SEM=3.82). No patients experienced cardiac side effects or showed significant EKG changes over the course of the study.

The mean age of all enrolled patients was 45.96 years (SEM=1.68). The average length of hospitalization at the study site prior to the start of the study was 2.33 years (SEM=0.93). Twenty-three of the patients were male and 3 were female. Sixteen (61.54%) patients were African American; 6 (23.08%) were Hispanic; 3 (11.54%) were Caucasian; and, 1 (3.84%) was Asian. Prior to receiving treatment in this study, 10 patients (28.46%) were on haloperidol; 8 each on risperidone (30.77%) and quetiapine (30.77%). There were 26.92% of patients (n=7) on concomitant FGAs and SGAs prior to the switch. 73.08% of patients (n=19) were taking a mood stabilizer in addition to their antipsychotics. 38.46% (n=10) patients reported a family history significant for obesity, 26.92% (n=7) for DM-II, and 3.85% (n=1) for cardiovascular disease. 5.26% (n=2) of patients were treated for hyperlipidemia with a lipid-lowering statin (atorvas-

Table 1	Characteristics of Sample (N=26)	
	Mean	**SD**
Age	45.96	8.58
Length of Stay (in years)*	2.33	4.72
	N	**%**
Gender		
Male	23	88.46%
Female	3	11.54%
Ethnicity		
African American	16	61.54%
Caucasian	3	11.54%
Hispanic	6	23.08%
Asian	1	3.85%
Prior Antipsychotic Medication		
Haloperidol	10	38.46%
Quetiapine	8	30.77%
Risperidone Intramuscular	1	3.85%
Chlorpromazine	1	3.85%
Loxitane	1	3.85%
Aripiprazole	1	3.85%
Olanzapine	2	7.69%
Risperidone	8	30.77%
Concomitant Mood Stabilizers		
Valproic Acid	8	30.77%
Carbamazepine	3	11.54%
Lithium Carbonate	6	23.08%
Lamotrigine	2	7.69%

*Length of Stay refers to the time the patient was admitted to the current inpatient facility up to the time of study entry.

tatin) or for hypertension with a beta-blocker (metoprolol); and, 3.85% (n=1) was treated for hypothyroidism with levothyroxine sodium. All patients were treated for DM-II with metformin, glipizide and/or insulin (see Table 1).

Change in Metabolic Parameters

Comparison of Completers and Patients who Discontinued Early

No significant differences were observed for patients who completed the study (n=16) compared to patients who discontinued early (n=10) for change in glucose (F(1,24)=.014,

p=.91), change in cholesterol levels (F(1,24)=1.09, p=.06), change in triglycerides (F(1,24)=.01, p=.95), change in HDL (F(1,24)=.46, p=.51), or change in weight (F(1,24)=1.55, p=.23) when controlling for baseline differences (see Table 2). Additionally, no significant differences were noted between completers and patients who discontinued early on age (completers: mean=47.80 [SEM=1.57], discontinued: mean=44.54 [SEM=3.17]; p=.38), average length of hospitalization (completers: mean=2.03 years [SEM=0.50], discontinued: mean=2.49 years [SEM=0.62]; p=.39), gender (completers: n=14, discontinued: n=9; p=.16), or ethnicity (African-American: completers, n=9, discontinued, n=7; Caucasian: completers, n=2, discontinued, n=1; Hispanic: completers, n=4, discontinued, n=2; Asian: completers, n=1, discontinued, n=0); Chi square (4)=1.65, p=.80).

Completer Analysis

Log transformation was applied to insulin data for normality. There was a statistically significant reduction in fasting glucose (F(1,15)=4.43, p=0.05), CBG levels (F(1,15)=8.90, p=0.01), BMI (F(1,15)=4.40, p=0.05) and weight (F(1,15)=4.46, p=0.05). Although statistically nonsignificant, a numeric reduction was seen in triglyceride levels (F(1,15)=3.35, p=0.08) from baseline to endpoint (see Table 3 and Figures 1 and 2 for results of additional metabolic markers). Using the World Health Organization definition for MetS, 9 (34.62%) patients met the criteria for MetS at baseline, as compared to 4 (15.38%) patients at endpoint. No patients developed MetS over the course of the study.

After having been switched to ziprasidone, the following changes of the patients' antidiabetic medication regimen were seen: nine patients (34.64%) showed overall reduction in their antidiabetic medication regimen over the course of the study. Two patients taking metformin had their dose reduced by 500 mg/d by Week 10: one from 1,500 mg/d to 1,000 mg/d, and the other from 2,000 mg/d to 1,500 mg/d. Two patients taking both glyburide and metformin had their metformin discontinued by Week 5. Two patients taking

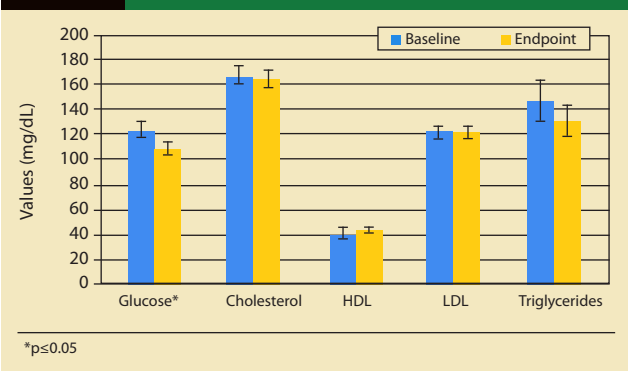| Table 2	ANOVA Comparison of Completers (N=16) and Early Discontinuations (N=10)				
	Early Study Discontinuation (N=10)		**Completers (N=16)**		
Metabolic Markers	**Baseline Mean (SEM)**	**End of Study (SEM)**	**Baseline Mean (SEM)**	**End of Study (SEM)**	**ANOVA F(1,24)**
Glucose	163.17 (17.56)	148.83 (21.35)	124.00 (6.97)	109.32 (5.72)	F=0.04, p=0.91
Insulin	26.45 (9.91)	24.80 (4.23)	25.81 (7.14)	20.49 (3.34)	F=0.51, p=0.49
HgbA1c	8.27 (0.66)	8.34 (0.64)	7.04 (0.27)	6.90 (0.38)	F=0.37, p=0.56
Weight	208.58 (12.22)	200.17 (11.35)	201.763 (7.70)	197.18 (7.18)	F=1.55, p=.23
BMI kg/m^2	30.44 (2.25)	31.14 (2.14)	31.09 (1.45)	30.41 (1.44)	F=1.78, p=0.20
Cholesterol	174.83 (11.72)	178.17 (13.58)	167.42 (7.64)	164.58 (7.11)	F=1.09, p=0.31
HDL	42.17 (3.88)	45.00 (3.93)	41.32 (4.62)	43.58 (2.57)	F=0.46, p=0.51
LDL	101.28 (6.34)	102.23 (6.36)	121.27 (5.28)	129.13 (5.31)	F=1.00, p=0.36
Triglycerides	176.12 (30.91)	149.33 (23.34)	144.42 (15.98)	126.37 (11.27)	F=0.01, p=.95
Leptin	13.87 (1.89)	12.50 (1.28)	19.36 (1.18)	18.08 (3.91)	F=0.12, p=0.74
C-Peptide	3.39 (0.96)	3.24 (0.80)	3.56 (0.72)	3.51 (0.82)	F=0.06, p=0.81

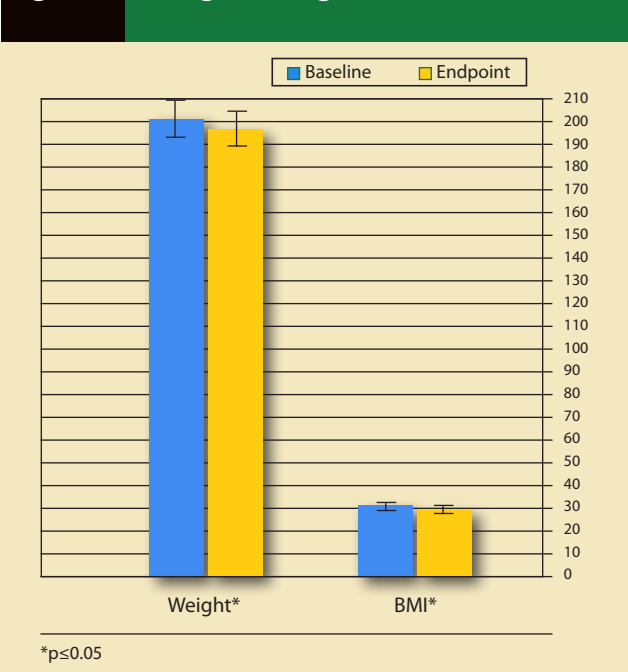| Table 3	Mean Metabolic Changes in Patients who Switched to Ziprasidone and Completed the Entire Study (Day 63; N=16)				
Markers	**Baseline**	**SEM**	**Endpoint**	**SEM**	**ANOVA F(1,15)**
Glucose	124.00	6.67	109.32	5.72	F=4.43, p=0.05*
CBG (mg/dL)	191.93†	12.11	166.57	11.24	F=8.90, p=0.01*
Insulin	25.81	7.14	20.49	3.34	F=0.37, p=0.55
HgbA1c	7.04	0.27	6.90	0.38	F=0.21, p=0.65
Weight	201.76	7.70	197.18	7.18	F=4.46, p=0.05*
BMI kg/m²	32.56	1.45	28.94	1.44	F=4.40, p=0.05*
Cholesterol	167.42	7.64	164.58	7.11	F=0.180, p=0.68
HDL	41.32	4.62	43.58	2.57	F=2.61, p=0.12
LDL	121.27	5.28	129.13	5.31	F=0.07, p=0.90
Triglycerides	146.92	15.98	130.52	11.27	F=3.35, p=0.08
Leptin	19.36	1.18	18.08	3.91	F=0.77, p=0.40
C-Peptide	3.56	0.72	3.51	0.82	F=0.01, p=0.95
White Blood Count	9.91 (5.94, 13.87)	1.79	8.53 (7.48, 9.58)	0.40	F=0.62, p=0.44
Red Blood Count	4.92 (4.35, 5.49)	0.21	5.27 (4.04, 6.50)	0.55	F=0.09, p=0.76

*p≤0.05 † This value represents the mean of the twice daily CBG reading for Day 1.
Tukey Post Hoc comparisons show a significant difference for all significant variables, except Weight, BMI.

Figure 1	Change in Metabolic Parameters (N=16)

*p≤0.05

Figure 2	Change in Weight and BMI (N=16)

*p≤0.05

glyburide had their dose reduced, one from 20 mg/d to 16.5 mg/d at Week 5 and the other from 20 mg/d to 14 mg/d at Week 7. One patient taking glipizide and metformin discontinued his glipizide by Week 10. One patient had his insulin dose reduced from 22 U BID to 20 U BID at Week 3, while another patient switched from insulin to glyburide up to 20 mg/d by Week 10. In summary, 26.92% of patients (n=7) either reduced or discontinued their oral hypoglycemics, 3.85% (n=1) reduced his insulin regimen, and 3.85% (n=1) switched from insulin to an oral hypoglycemic. Additionally, there was a significant correlation between change in BMI and change in glucose levels at endpoint (r=.81, p=.001).

Psychopathology and Side Effect Measures

There was no significant change in positive symptoms (F(1,15)=0.62, p=0.44), negative symptoms (F(1,15)=1.47, p=0.24), or total PANSS (F(1,15)=0.12, p=0.74). PANSS was computed for only the 16 patients who completed the entire study. Patients who dropped out were not included in the analysis of the side effect measures. No significant differences were observed in the Abnormal Involuntary Movement Scale (F(1,15)=1.11, p=0.31) nor the Simpson-Angus Scale (F=4.19, p=0.06) (see Table 4). No significant side effects, nor restlessness, were observed, and treatment with ziprasidone was well tolerated and changes in systolic and diastolic BP readings were not statistically significant from baseline to endpoint (Day 63).
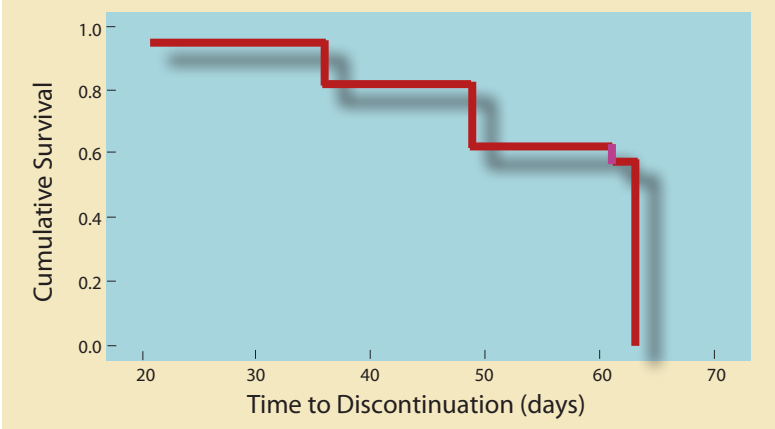
Time to Discontinuation

Figure 3 shows a Kaplan-Meier survival plot for patient discontinuation for all patients who were enrolled in the study (n=26) over the study period (63 days) with the cumulative proportion of patients surviving at each time point.

Table 4	Psychopathology and Extrapyramidal Symptom Outcomes of Completers (N=16)				
Markers	**Baseline**	**SEM**	**Endpoint**	**SEM**	**ANOVA F(1,15)**
PANSS Positive Symptom Subscale	17.90	1.64	18.95	1.83	F=0.62, p=0.44
PANSS Negative Symptom Subscale	19.47	1.24	18.21	0.91	F=1.47, p=0.24
PANSS Total Score	71.00	3.93	72.158	3.77	F=0.12, p=0.74
Simpson-Angus Scale	12.16	0.56	11.11	0.42	F=4.19, p=0.06
Abnormal Involuntary Movement Scale	1.26	0.35	2.00	0.72	F=1.11, p=0.31

Figure 3	Study Survival Time of Patients During Treatment with Ziprasidone (N=26)

At Day 21, an estimate of .96 (SEM=.04) patients continued ziprasidone; at Day 36, an estimate of .88 (SEM=.08) patients continued treatment with ziprasidone, and, at Day 49 an estimate of .63 (SEM=.10) patients continued treatment with ziprasidone. By Day 63, an estimate of .58 (SEM=.10) patients continued treatment with ziprasidone. The estimated time to discontinuation for patients enrolled in treatment with ziprasidone was 54.88 days (SEM=2.46; 95% CI=50.05 to 59.70; -2 Log Likelihood=134.44). Patients who discontinued from ziprasidone early were placed on atypical antipsychotics as follows: 4 patients were placed on olanzapine, 1 patient was placed on risperidone: and haloperidol, 2 patients were placed on risperidone and 3 patients received clozapine immediately after discontinuation from ziprasidone.

Discussion

We believe this is the first study to examine the metabolic effects of switching from a polypharmacy regimen to monotherapy with ziprasidone in a group of suboptimally responding schizophrenic or schizoaffective inpatients with comorbid pre-existing symptomatic DM-II. The switch to ziprasidone resulted in significant improvements in several metabolic measures: fasting serum glucose (14.68 mg/dL decrease), CBG (25.36 mg/dL decrease), triglycerides (16.40 mg/dL decrease), weight (4.68 lb decrease) and BMI (3.62 kg/m² decrease). Our data also show a reduction of the number of patients with MetS, as defined by WHO criteria. Additionally, we saw a reduction or discontinuation in oral hypoglycemic and/or insulin medication regimens during ziprasidone treatment.

Compared to studies with nondiabetic patients, the magnitude of improvement of metabolic measures in our study was on the low to middle end of the reported ranges: fasting serum glucose (range: 1.8–14 mg/dL mean decrease), triglycerides (range: 12.6–46.2 mg/dL mean decrease) and weight (range: 2.64–11.22 lbs mean decrease) (18, 19, 23, 30-33). The difference in the magnitude of the reported improvements between ours and other studies may be due to differences in duration of illness, duration of treatment with pre-existing antipsychotics, as well as the presence of concomitant DM-II. For example, in the Alptekin study, a significant mean weight loss of 4.4 lbs (SD=8.8 lbs; p<0.001) was observed in the olanzapine pre-switch group at week 12, as compared to a nonsignificant mean reduction in body weight of 1.32 lbs (SD=7.04 lbs) in the risperidone pre-switch group (30). Some authors have suggested that the metabolic improvements may be explained by a reversal of metabolic worsening induced by the prior drug, particularly in cases of olanzapine and, to a lesser extent, of risperidone (31). Additionally, most other studies were conducted with nondiabetic outpatients whereas this study was conducted with diabetic chronic inpatients with numerous prior lengthy treatments with a greater number and higher doses of concomitant antipsychotic (and other psychotropic) medications.

The mechanism for ziprasidone's relatively favorable metabolic profile has not yet been fully elucidated. Kroeze et al. (2003) found the most robust predictor of a drug's propensity to induce weight gain to be its affinity for the H1 histamine receptor (32). While clozapine (pKi=1.8nM), olanzapine (pKi=2.8nM) and quetiapine (pKi=8.7nM) have the highest affinities for the H1 receptor, ziprasidone (pKi=47nM) and aripiprazole (pKi=61nM) have moderate affinity (32). One of the mechanism(s) by which H1 receptor antagonism may induce weight gain is through both H1 receptor antagonism and depletion of neuronal histamine, which in turn increases feeding behavior in rodents (33). The H1 receptor also exerts an effect on leptin, an adipocyte-produced humoral factor believed to play a central role in developing insulin resistance (34), suggesting that H1 receptors modulate feeding behavior via a leptin-dependent mechanism.

In this study, our patients did not respond to treatment with ziprasidone particularly well, with a relatively high rate of study discontinuation due to psychotic relapse of approximately 42.3%. Average time to discontinuation for patients enrolled in treatment with ziprasidone was about 8 weeks and reflected a gradual attrition without a clear pattern. Previous studies of switching to ziprasidone have shown a wide range of discontinuation rates ranging from 10 to 60% (18, 19, 23, 24, 30-33, 35). Our higher rates of discontinuation are probably due to a number of reasons. Prior suboptimal response, as in the patients enrolled in our study, is one reason for later discontinuation due to nonresponse (36). Poor tolerability was the principal reason for discontinuation in the Bartkó et al. (2006) study, which showed a discontinuation rate of 18% (31). In the Lublin et al. (2008) study, where the treating psychiatrists could indicate multiple reasons for the switch, the combined suboptimal efficacy and poor tolerability were reasons for switching from the earlier antipsychotic medication in ≥50% of patients and resulted in 32% discontinuation rate (37). The fact that many of our patients were on an antipsychotic polypharmacy regimen and had a prolonged inpatient hospital stay prior to the entry into the study, points to their suboptimal treatment responsiveness.

Another reported reason for higher discontinuation rates may be possibly initial and overall under dosing of ziprasidone. For all but two patients in this study, the mean dosage was equivalent to that used in previous trials (38), which showed that doses of 120–160 mg/day were associated with maximized clinical improvements and no increase in adverse effects (39, 40). In addition, the reduction of the prior antipsychotic in the present study was implemented in a slow and gradual fashion over the course of three weeks in order to prevent withdrawal reactions (36), supporting an appropriate dosing and cross-taper technique.

The switch to ziprasidone has been shown to decrease EPS (19), a trend that was observed in our study as well. Short-term clinical trials of ziprasidone have suggested that ziprasidone has a low liability for movement disorders and, in particular, possesses an EPS profile superior to haloperidol (41). In the present study, baseline EPS were already rather low, allowing little room for further improvement.

There were several limitations to this study. First, it was an open-label, nonrandomized study, in which both patients and treating psychiatrists were aware of the treatment assignment, thereby increasing the possibility of biased positive findings toward ziprasidone. However, our main outcome measures were laboratory analyses, which were all assessed by staff that was unaware of the study's rationale. Second, the reduction in BMI and glucose could be explained by diet and physical exercise; however, it should be noted that all patients received the same psycho-educational and exercise program for the duration of their entire hospitalization, which covered the period before, during and after the study. A possible confounding factor accounting for our results could have been the concomitant use of drugs, which have a known effect on glucose levels and metabolic parameters, such as atrovastatin, metoprolol, levothyroxine, metformin, glipizide and insulin. However, the use of these drugs had been well-established before the onset of the study and were maintained stably during the study. Another limitation is the possibility of a Type I error due to the small sample size. A contributing factor was the high discontinuation rate. We showed, however, comparable changes in metabolic markers in patients who discontinued early as compared to those who completed the study. It is possible that ziprasidone's effect on metabolic markers would have been more pronounced if these patients had benefited from the full exposure time of ziprasidone. Currently, it is not known conclusively whether treatment duration beyond eight weeks could have resulted in more beneficial outcomes, whether the metabolic improvements would be sustained, and what would be the net effect of discontinuation rates with prolonged treatment.

In conclusion, the data from this study, carried out in chronic psychiatric inpatients with long-standing symptomatic DM-II, suggest significant improvements in metabolic effects and MetS in the subset of the population who were able to tolerate switching to this antipsychotic. While switching to ziprasidone may be an important treatment strategy in patients with established comorbid metabolic disorders presenting with tolerability problems under their current antipsychotic treatment (41, 42), there was a large discontinuation rate, which may have limited the sustained beneficial effects of ziprasidone. As with all clinical decisions, the decision to switch to ziprasidone has to balance the potential metabolic benefits and the potential relapse risks of the individual patient first and foremost.

Disclosures

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