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Ziprasidone as an adjuvant for clozapine- or olanzapine-associated medical morbidity in chronic schizophrenia

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Objective This study sought to examine the effect of ziprasidone on olanzapine or clozapine-associated medical morbidity such as insulin resistance, diabetes mellitus (DM) and impaired fasting glucose, obesity, and hyperlipidemia in patients with schizophrenia or schizoaffective disorder.
Method This was a 6-week, open label trial of ziprasidone 160 mg/day added to a stable dose of olanzapine or clozapine in 21 schizophrenia or schizoaffective patients with DM, impaired fasting glucose, or insulin resistance.
Results Ten olanzapine-treated subjects and 11 clozapine-treated subjects were enrolled in the study. There were no significant differences between the two groups at baseline for age, gender, education, ethnicity, BMI, cholesterol levels, or fasting glucose. At week 6, there were no significant changes in weight, BMI, cholesterol levels, or fasting glucose. There was no significant difference in psychotic, negative, or depressive symptoms. QTc significantly increased at week 2 but not at week 6.
Conclusions The addition of 160 mg/day of ziprasidone was well tolerated but did not produce significant improvement in fasting glucose, insulin resistance, hyperlipidemia or lead to weight loss in olanzapine- or clozapine-treated subjects with schizophrenia or schizoaffective disorder.

KEY WORDS — clozapine; olanzapine; ziprasidone; weight; lipids; insulin resistance; schizophrenia

INTRODUCTION

Clozapine, an atypical antipsychotic agent, remains the most effective psychopharmaceutical agent for treatment-resistant schizophrenia. Unfortunately, the side effects of clozapine are often difficult for patients to tolerate, particularly sedation and weight gain. Although some clozapine patients are able to remain out of the hospital, they continue to have significant psychiatric symptoms despite adequate doses of clozapine. In other symptomatic patients, the clozapine dose is limited by significant side effects. Treatment options for patients who do not fully respond to clozapine have not been fully elucidated. Several years ago, Henderson and Goff (1996) reported that chronic schizophrenia patients demonstrated an improved response to clozapine when risperidone was utilized as an adjunctive agent. In this open trial, significant improvements in ratings of positive, negative, and depressive symptoms were found. Furthermore, a more recent study found significant improvement in the disorganized thought subscale of the Positive and Negative Syndrome Scale (PANSS) (Freudenreich *et al*., 2007). However, the metabolic sequelae of combination therapy have not been fully investigated, though elevations of the combination lead to significant elevations in prolactin compared to treatment with clozapine alone (Henderson *et al*., 2001).

Numerous reports of clozapine- and olanzapine-associated insulin resistance, hyperglycemia diabetic ketoacidosis associated with clozapine and olanzapine have emerged (Ananth *et al*., 2002; Baptista *et al*., 2002; Caro *et al*., 2002; Colli *et al*., 1999; Gianfrancesco *et al*., 2002; Hagg *et al*., 1998; Henderson *et al*., 2000b, 2005, 2006a; Kato and Goodnick, 2001; Koller and Doraiswamy, 2002; Koller *et al*., 2001; Newcomer *et al*., 2002). By increasing a patient's risk of obesity, antipsychotic agents may be placing

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patients at risk for associated morbidity and mortality (Pi-Sunyer, 1993). Patients who gain greater than 10% of their total body weight are at risk for developing weight associated conditions such as hypertension and type 2 diabetes mellitus (DM). Henderson *et al.* (2000a) found a high rate of diabetes in this cohort as 30 of 82 patients (36.6%) treated with clozapine developed DM over a 60-month period. Olanzapine has also been associated with significant weight gain (>7% total body weight), insulin resistance, hyperlipidemia, and new onset DM (Cohen *et al*., 2003; Melkersson *et al*., 2000; Opp and Hildebrandt, 2002; Seaburg *et al*., 2001; Wilson *et al*., 2003). While switching to an agent associated with less weight gain (such as ziprasidone or aripiprazole) offers the greatest opportunity for resolution of clozapine- or olanzapine-associated DM, many clinicians and patients are reluctant to do so. Because clozapine is reserved for treatment-resistant schizophrenia patients, switching to another antipsychotic agent may not be feasible. The best intervention for clozapine patients may be to add an agent associated with less weight gain and eventually lower the dose of clozapine. In this setting, weight loss and improvements in glucose metabolism may occur.

Additionally, when switching patients treated with antipsychotic agents, many times clinicians make the switch rapidly and provide little time for overlap. Patients treated in this manner may have a higher risk of relapse that is often considered a drug trial failure, but in fact it may be that the second agent did not have time to take hold. Determining whether combination antipsychotic agents therapy results in an improvement in metabolic parameters and psychopathology would be helpful to clinicians in their decision-making regarding pharmacotherapy. The results of this study may provide clinicians and patients with a potentially effective intervention to counteract the weight and metabolic effects of clozapine and olanzapine, while also showing the benefits of continued or improved efficacy. It may also allow clinicians and patients to be more comfortable with a much slower and safer switch to ziprasidone as the medical morbidity benefits may begin as soon as the drug is started. If a patient experiences early medical benefits from ziprasidone, the speed of switching can be much slower while also significantly reducing the risk of relapse.

Ziprasidone is an atypical antipsychotic agent with high affinity for dopamine D2 and 5-HT_{2A} receptors where it acts as an antagonist. Clinical trials indicate that ziprasidone is effective against positive, negative, and affective symptoms in schizophrenia and schizoaffective disorder with minimal motor, cognitive, weight, prolactin related, or anticholinergic side effects (Daniel and Copeland, 2000). Ziprasidone also acts as an agonist of the 5-HT_{1A} receptor and moderately inhibits the re-uptake of serotonin and norepinephrine. The low liability of ziprasidone with respect to weight gain may have significance for patients even beyond the cardiovascular and other health effects (Alao *et al*., 2002; Allison *et al*., 1999; Cohen *et al*., 2003; Spivak *et al*., 2002; Wetterling, 2001). The distressing side effect of weight gain frequently leads to patient-driven decisions to switch or discontinue medications.

Ziprasidone was chosen as its side effect profile greatly differs from both clozapine and olanzapine and there was already pilot data examining aripiprazole (Henderson *et al*., 2006b). Different receptor affinities may play a role in weight gain and the development of DM in patients on antipsychotic medication. Aripiprazole may have partial agonist properties at 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} serotonin receptors (Shapiro *et al*., 2003), whereas ziprasidone is a D_2 and 5-HT_{2A} antagonist, and an agonist at 5-HT_{1A} receptors. Clozapine and olanzapine, which offer the greatest risk of weight gain, are structurally similar and both have binding capacities for serotonin 5-HT_{2C}, histamine H1, and muscarinic M1 receptors (Bymaster *et al*., 1996; Millan *et al*., 1998). A study by Kroeze *et al*. (2003) found that affinities for histamine H1, alpha(1A) adrenergic, 5-HT_{2C}, and 5-HT_6 receptors were most strongly correlated with weight gain when screening 17 typical antipsychotics. While neither aripiprazole nor ziprasidone has high affinities for the histamine H1 receptors, the affinity of ziprasidone is lower than that of aripiprazole (Kroeze *et al*., 2003). This discrepancy may be a factor in each drug's ability to counteract clozapine and olanzapine-associated weight gain.

Additionally, 5-HT_{2C} receptors have been implicated in the control of appetite (Vickers *et al*., 1999) and a variant of the 5-HT_{2C} receptor gene (-759C/T) was associated with less weight gain in a study of first episode schizophrenia patients (Reynolds *et al*., 2003). Therefore, it is conceivable that the minimal weight gain associated with aripiprazole may be due to its moderate binding affinity at 5-HT_{2C} receptors. Ziprasidone does not share this capacity for 5-HT_{2C} receptors. Accordingly, effects on clozapine and olanzapine-associated weight gain were not demonstrated with the addition of ziprasidone comparable to aripiprazole.

In the present pilot study, we investigated the benefits for metabolic response, weight loss, and efficacy for positive and negative symptoms of ziprasidone 160 mg/day added to a stable dose of clozapine- or olanzapine-treated subjects with schizophrenia or schizoaffective disorder over a 6-week period.

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Aims of the study

We investigated the efficacy of ziprasidone for weight loss in clozapine- or olanzapine-treated schizophrenia subjects during a 6-week open label trial. Based on our previous study with aripiprazole, 6 weeks was determined to be adequate to see significant weight loss and reduction in lipids (Henderson *et al*., 2006b). The hypotheses were that the addition of ziprasidone 160 mg/day to stable clozapine- and olanzapine-treated schizophrenia or schizoaffective disorder subjects with DM, impaired fasting glucose, or insulin resistance would result in significant weight loss and improvements in glucose and lipid metabolism over a 6-week period.

METHODS

This 6-week open label trial was conducted in the adult outpatient clinic of an urban community mental health center. The Institutional Review Board of the Massachusetts Department of Mental Health approved the study. After providing written informed consent, all participants underwent a diagnostic evaluation by a research psychiatrist using the Structured Clinical Interview for DSM-IV (SCID) (Spitzer *et al*., 1992).

Subjects on clozapine or olanzapine were recruited for the study if they met the following criteria: diagnosis of schizophrenia or schizoaffective disorder, age 18–65 years, capable of providing informed consent, treatment with clozapine or olanzapine for at least 1 year and with a stable dose being administered for at least 1 month. Subjects were required to have a history of DM, impaired fasting glucose, or insulin resistance to participate in the study. Impaired fasting glucose was defined as a fasting glucose of greater than or equal to 100 mg/dl and less than 126 mg/dl. Insulin resistance was defined as fasting insulin greater or equal to 15 mU/L or a Homeostasis Model Assessment- Insulin Resistance (HOMA-IR) units, greater or equal to 2. Subjects were excluded from the study if they were unable to provide informed consent, had a significant unstable medical illness such as unstable cardiac disease, a current substance abuse problem, treatment with medications that significantly prolonged QTc or history of prolongation of QTc interval (>450 ms) on electrocardiogram (EKG), clinically significant EKG abnormalities, hepatic or renal impairment, cancer, poorly controlled seizure disorder, previous treatment with ziprasidone, or treatment with more than one antipsychotic agent. Thirty patients were screened and 24 consented for the study. Of the six subjects that did not give consent, three did not meet the BMI criteria and three decided not to participate. Two subjects consented but were lost to follow-up, and one subject withdrew consent after receiving one dose of ziprasidone. The target for this pilot study was to have 20 subjects complete 6 weeks of the study (10 clozapine and 10 olanzapine).

Subjects were treated with open label ziprasidone 40 mg twice daily for the first 2 weeks. After 2 weeks, ziprasidone was increased to 80 mg twice daily as tolerated. Clozapine or olanzapine doses remained unchanged throughout the study. Patients that chose to remain on ziprasidone after the completion of the 6-week trial were assessed at week 10.

Assays

Fasting blood samples were assayed for a complete blood count and concentrations of plasma glucose, cholesterol (total, HDL and LDL), and triglycerides at baseline, week 4 and week 6 using standard laboratory procedures. Insulin immunometric assays were performed using an Immulite Analyzer (Diagnostic Product Corporation, Los Angeles, CA, USA) with an intra-assay coefficient of variation of 4.2–7.6%. HOMA-IR was calculated from fasting glucose and insulin values at baseline and week 6 (Kissebah *et al*., 1982). The same assays were completed at week 10 for all subjects who chose to remain on Ziprasidone.

Subjects were assessed with a battery of symptom rating scales at baseline, weeks 2, 4, and 6. The assessment battery included the Positive and Negative Syndrome Scale (PANSS) (Kay *et al*., 1987), Scale for Assessment of Negative Symptoms (SANS), Hamilton Depression Rating Scale (HAM-D), Fatigue Scale Inventory (FSI) (Hann *et al*., 2000), the Quality of Life Scale (QOL), the Simpson–Angus Scale, Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale (AIMS). A single rater performed all assessments throughout the trial. A physical examination and medical history was performed at baseline and measurement of vital signs, weight, and waist/hip circumference at each visit. Diet and exercise interventions were not performed during the trial.

Statistical analysis

Two-tailed paired samples *t*-tests were conducted to compare baseline and week 6 values for body weight, BMI, fasting lipids, fasting glucose, fasting insulin, HOMA-IR, fasting lipids, and clinical symptoms. Scores from week 4 (last observation carried forward (LOCF) method) were used for two subjects with missing end point measurements. Separate analyses were performed for the clozapine group and the olanzapine group.

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Additionally, analysis of subjects with DM and subjects without DM was performed. For all analysis, *p*-values of less than 0.05 were considered significant.

RESULTS

Twenty-four subjects consented to participate in the study. Two subjects were lost to follow-up prior to starting the study medication; and one subject discontinued the medication after one dose. The remaining 21 subjects completed the 6-week trial and are included in all analyses. Eleven patients (52%) were receiving clozapine and 10 patients (48%) were receiving olanzapine.

The demographic data are summarized in Table 1. The mean age of the subjects was 49 ± 8 years and 17 (81%) were male. Fifteen subjects (71%) were Caucasian, four (19%) were Black, and one (5%) was Hispanic. There were no significant differences among the clozapine and olanzapine-treated groups for race, marital status, employment status, or family history of hypertension or diabetes. Weight, BMI, cholesterol, and waist and hip measurements did not differ significantly between the clozapine-treated group and the olanzapine-treated group at baseline. Within the clozapine-treated group, nine subjects (82%) were smokers, compared to four subjects (40%) in the olanzapine-treated group ($p = 0.049$). Eight subjects (38%) were treated for type 2 DM at the time of consent for the study.

Table 2 shows anthropometric changes from baseline to week 6 for each group and the entire sample. Comparing baseline to week 6, there was no significant difference in weight, BMI, waist circumference, or waist/hip ratio. The mean weight for the entire sample was 230 ± 35 lbs at baseline, and 229 ± 35 lbs at week 6 ($p = 0.73$). There were no significant changes in total cholesterol, triglycerides, HDL-cholesterol, or LDL-cholesterol. For the entire sample, the mean total cholesterol was 186 ± 40 mg/dl at baseline and 185 ± 34 mg/dl at week 6 ($p = 0.929$). Triglyceride levels decreased from 256 ± 159 mg/dl and 231 ± 34 mg/dl but was not statistically significant ($p = 0.24$). There was no significant difference in any of the above outcome measures comparing baseline to week 6 when analyzing subgroups for clozapine or olanzapine alone.

Table 1. Demographic and clinical characteristics of 21 schizophrenia patients treated with clozapine or olanzapine

Characteristic	Entire sample ($N = 21$)	Clozapine ($N = 11$)	Olanzapine ($N = 10$)	Group comparison	p value
Age	49 ± 8	48 ± 7	52 ± 8	$t(19) = 1.15$	0.263
Education	12 ± 2	12 ± 2	11 ± 2	$t(19) = -0.53$	0.603
Gender, *N* (%)				$\chi^2(1) = 1.01$	0.314
Male	17 (81)	8 (73)	9 (90)		
Female	4 (19)	3 (27)	1 (10)		
Race, *N* (%)				$\chi^2(3) = 2.02$	0.568
Caucasian	15 (71)	7 (64)	8 (80)		
Black	4 (19)	2 (18)	2 (20)		
Hispanic	1 (5)	1 (9)	0 (0)		
Other	1 (5)	1 (9)	0 (0)		
Marital Status, *N* (%)				$\chi^2(4) = 2.29$	0.682
Single	14 (67)	7 (64)	7 (70)		
Married	2 (10)	1 (9)	1 (10)		
Separated	1 (5)	0 (0)	1 (10)		
Divorced	3 (14)	2 (18)	1 (10)		
Widowed	1 (5)	1 (9)	0 (0)		
Employment status, *N* (%)				$\chi^2(8) = 8.05$	0.429
Employed	8 (38)	5 (46)	3 (30)		
Unemployed	13 (62)	6 (55)	7 (70)		
History of hypertension, *N* (%)				$\chi^2(1) = 0.29$	0.593
Yes	3 (14)	2 (18)	1 (10)		
No	18 (86)	9 (82)	9 (90)		
Smoking status, *N* (%)				$\chi^2(1) = 3.88$	0.049
Non-smoker	8 (38)	2 (18)	6 (60)		
Smoker	13 (62)	9 (82)	4 (40)		
Family history of diabetes				$\chi^2(1) = 0.40$	0.528
Yes	12 (57)	7 (64)	5 (50)		
No	9 (43)	4 (36)	5 (50)		
Presence of diabetes				$\chi^2(1) = 2.65$	0.104
Yes	8 (38)	6 (55)	2 (20)		
No	13 (62)	5 (46)	8 (80)		

Values are expressed as means ± SD unless otherwise indicated.

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Table 2. Anthropometric and metabolic measures over 6-week treatment of ziprasidone as an adjuvant for clozapine- or olanzapine-treated patients with schizophrenia ($N = 21$)

Measurement	Baseline	Week 6	Within-group comparison	p value
Entire sample ($N = 21$)				
Fasting plasma glucose (mg/dl)	123 ± 51	123 ± 48	$t(20) = -0.06$	0.956
Fasting serum insulin (μIU/L)	15.0 ± 7.7	15.0 ± 9.5	$t(20) = -0.02$	0.988
HOMA-IR (log transformed)	4.5 ± 3.0	4.7 ± 4.0	$t(20) = -0.22$	0.826
HBA1C	6.5 ± 1.2	6.6 ± 1.1	$t(19) = -0.26$	0.795
Leptin (ng/mL)	70.0 ± 64.6	66.5 ± 57.0	$t(19) = 0.51$	0.615
Total cholesterol (mg/dl)	186 ± 40	185 ± 34	$t(19) = 0.09$	0.929
Triglyceride (mg/dl)	256 ± 159	231 ± 124	$t(18) = 1.21$	0.241
HDL (mg/dl)	43 ± 11	44 ± 9	$t(18) = -0.99$	0.334
LDL (mg/dl)	104 ± 27	102 ± 27	$t(15) = 0.59$	0.561
Weight (lb)	229.7 ± 34.9	229.3 ± 35.1	$t(20) = 0.35$	0.730
BMI (kg/m^2)	34.8 ± 4.0	34.8 ± 4.1	$t(20) = 0.32$	0.754
Waist circumference (cm)	108.4 ± 17.2	112.1 ± 7.2	$t(20) = -1.09$	0.289
Widest hip circumference (cm)	114.7 ± 19.3	118.6 ± 9.8	$t(20) = -1.14$	0.267
Clozapine group ($N = 11$)				
Fasting plasma glucose (mg/dl)	125 ± 43	130 ± 46	$t(10) = -0.37$	0.719
Fasting serum insulin (μIU/L)	14.8 ± 6.9	15.8 ± 11.4	$t(10) = -0.36$	0.728
HOMA-IR (log transformed)	4.9 ± 3.6	4.9 ± 3.6	$t(10) = -0.03$	0.980
HBA1C	6.9 ± 1.2	7.0 ± 1.1	$t(9) = -0.50$	0.629
Leptin (ng/mL)	73.6 ± 63.8	72.4 ± 59.1	$t(10) = 0.31$	0.766
Total cholesterol (mg/dl)	183 ± 29	178 ± 33	$t(10) = 0.58$	0.574
Triglyceride (mg/dl)	293 ± 183	273 ± 129	$t(10) = 0.57$	0.580
HDL (mg/dl)	42 ± 13	42 ± 9	$t(10) = -0.47$	0.647
LDL (mg/dl)	95 ± 23	89 ± 23	$t(7) = 0.88$	0.406
Weight (lb)	230.1 ± 40.8	231.4 ± 40.8	$t(10) = -1.15$	0.278
BMI (kg/m^2)	36.1 ± 3.7	36.3 ± 3.7	$t(10) = -1.22$	0.251
Waist circumference (cm)	112.6 ± 9.5	113.1 ± 6.3	$t(10) = -0.29$	0.779
Widest hip circumference (cm)	119.8 ± 11.8	119.6 ± 9.4	$t(10) = 0.07$	0.942
Olanzapine group ($N = 10$)				
Fasting plasma glucose (mg/dl)	121 ± 61	116.5 ± 51.9	$t(9) = 0.68$	0.517
Fasting serum insulin (μIU/L)	15.1 ± 8.9	14.2 ± 7.5	$t(9) = 0.33$	0.747
HOMA-IR (log transformed)	4.1 ± 2.1	4.5 ± 4.6	$t(9) = -0.27$	0.792
HBA1C	6.2 ± 1.2	6.2 ± 0.9	$t(9) = 0.15$	0.885
Leptin (ng/mL)	64.6 ± 69.2	59.2 ± 56.9	$t(8) = 0.42$	0.686
Total cholesterol (mg/dl)	189 ± 51	193 ± 36	$t(8) = -0.32$	0.754
Triglyceride (mg/dl)	207 ± 110	173 ± 96	$t(7) = 1.69$	0.135
HDL (mg/dl)	45 ± 8	47 ± 9	$t(7) = -1.02$	0.341
LDL (mg/dl)	114 ± 28	114 ± 26	$t(7) = -0.04$	0.973
Weight (lb)	229.2 ± 29.3	227.0 ± 29.6	$t(9) = 1.16$	0.276
BMI (kg/m^2)	33.4 ± 4.0	33.1 ± 3.9	$t(9) = 1.18$	0.267
Waist circumference (cm)	103.9 ± 22.6	111.0 ± 8.2	$t(9) = -1.05$	0.322
Widest hip circumference (cm)	109.2 ± 24.6	117.5 ± 10.7	$t(9) = -1.23$	0.250

Values are expressed as means ± SD unless otherwise indicated, and waist circumference is taken from iliac waist measures.
BMI, body mass index; HOMA-IR, homeostasis model of assessment of insulin resistance.

In the clozapine-treated group, fasting plasma glucose and fasting serum insulin did not change significantly (Table 2). The mean fasting plasma glucose changed from 125 ± 43 mg/dl at baseline to 130 ± 46 mg/dl at week 6 ($p = 0.719$) in the clozapine-treated group. For non-diabetic subjects receiving either olanzapine or clozapine, there were similarly no significant changes in fasting plasma glucose from 104 ± 13 mg/dl at baseline to 102 ± 18 mg/dl at week 6 ($p = 0.577$), or fasting insulin 16.3 ± 8.4 vs. 15.2 ± 11.06 ($p = 0.654$). Furthermore, in non-diabetic subjects, HOMA-IR decreased from 4.2 ± 2.2 at baseline to 3.9 ± 3.4 at week 6 but was not significant ($p = 0.695$).

In addition, ziprasidone produced no significant differences between baseline and week 6 on the PANSS total scores and subscale scores, the SANS, or the HAM-D (Ps > 0.129) (Table 3). There were no serious adverse events as a result of treatment with ziprasidone. Four subjects (18%) experienced constipation, two subjects (9%) experienced diarrhea, and two subjects (9%) experienced tremors while on ziprasidone. From baseline to week 2, the mean QTc

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Table 3. Psychopathology measures over a 6-week treatment of ziprasidone supplemented to clozapine- or olanzapine-treated subjects with schizophrenia ($N = 21$)

Measurement	Baseline	Week 6	Within-group comparison	p value
Entire sample ($N = 21$)				
HAM-D	11.9 ± 8.0	10.5 ± 8.2	$t(20) = 1.40$	0.177
PANSS—total	73.8 ± 15.3	72.1 ± 15.6	$t(20) = 1.35$	0.191
PANSS—positive	17.6 ± 6.6	16.7 ± 5.9	$t(20) = 1.36$	0.188
PANSS—negative	20.9 ± 4.9	21.4 ± 6.0	$t(20) = -0.64$	0.532
PANSS—general	35.2 ± 8.9	34.0 ± 7.8	$t(20) = 1.28$	0.214
SANS—total	59.0 ± 17.6	59.0 ± 16.4	$t(20) = -0.03$	0.981
Clozapine ($N = 11$)				
HAM-D	8.6 ± 6.5	7.4 ± 5.2	$t(10) = 0.96$	0.358
PANSS—total	68.0 ± 16.2	64.9 ± 14.3	$t(10) = 1.66$	0.129
PANSS—positive	17.2 ± 6.7	15.5 ± 6.0	$t(10) = 1.91$	0.086
PANSS—negative	18.8 ± 4.1	18.6 ± 5.9	$t(10) = 0.15$	0.888
PANSS—general	32.0 ± 8.0	30.8 ± 5.7	$t(10) = 1.04$	0.322
SANS—total	53.1 ± 17.3	51.0 ± 14.0	$t(10) = 0.72$	0.488
Olanzapine ($N = 10$)				
HAM-D	15.5 ± 8.1	13.9 ± 10.0	$t(9) = 0.98$	0.355
PANSS—total	80.1 ± 12.1	79.9 ± 13.4	$t(9) = 0.12$	0.907
PANSS—positive	18.1 ± 7.0	18.0 ± 5.9	$t(9) = 0.09$	0.927
PANSS—negative	23.2 ± 4.9	24.5 ± 5.0	$t(9) = -1.23$	0.249
PANSS—general	38.8 ± 8.7	37.4 ± 8.6	$t(9) = 0.79$	0.448
SANS—total	65.4 ± 16.3	67.8 ± 14.7	$t(9) = -0.99$	0.348

Values are expressed as means $\pm$ SD.
HAM-D: Hamilton Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale, including positive, negative, and general subscales; SANS: Scale for the Assessment of Negative Symptoms.

increased from 417 ± 15 to 430 ± 16 ms ($p = 0.002$); however, the change in mean QTc from 417 ± 15 at baseline to 420 ± 21 ms at week 6 was not statistically significant ($p = 0.507$).

DISCUSSION

In this open label trial, the addition of ziprasidone to a steady dose of olanzapine or clozapine resulted in no significant benefit in weight loss or other metabolic parameters in patients with schizophrenia or schizoaffective disorder. Previous research has demonstrated the efficacy of ziprasidone to significantly improve weight and plasma lipids when switching treatment from another atypical antipsychotic medication. A study by Weiden *et al*. (2007) estimated weight loss of 10.3% of mean initial weight and total cholesterol decrease of 9.2% over 58 weeks for patients when switched from olanzapine to ziprasidone. However, the lack of similar effects when used in combination with clozapine and olanzapine suggests that ziprasidone is ineffectual as an adjuvant therapy for weight and metabolism.

These results differ from a previous study, where the addition of aripiprazole to clozapine treatment resulted in significant decreases in weight ($p = 0.003$), BMI ($p = 0.004$), total cholesterol ($p = 0.002$), total triglycerides ($p = 0.040$), and HDL-cholesterol ($p = 0.020$) (Henderson *et al*., 2006b).

The sample size in this study may not have been adequate to demonstrate the effectiveness of ziprasidone as an adjuvant to clozapine or olanzapine and resulted in a type II error. It is also plausible that the receptor-binding profile of ziprasidone does not significantly counteract the mechanisms of weight gain and other metabolic disturbances associated with clozapine and olanzapine.

In the present study, ziprasidone did not worsen extrapyramidal side effects or psychotic symptoms. It also did not result in any significant adverse events or increases in resting heart rate or blood pressure. There was a non-clinically relevant increase in QTc from baseline to week 2 which was not evident at week 6.

CONCLUSIONS

The addition of 160 mg/day of ziprasidone was well tolerated but did not produce significant improvement in fasting glucose, insulin resistance, hyperlipidemia or lead to weight loss in olanzapine- or clozapine-treated subjects with schizophrenia or schizoaffective disorder. This combination may not be of benefit to combat the

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medical morbidity associated with antipsychotic drugs. Investigation into new intervention strategies to control antipsychotic-associated weight gain and metabolic disturbances is needed.

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