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A Double Blind, Placebo- controlled Trial of Rosiglitazone for Clozapine induced Glucose Metabolism Impairment in patients with Schizophrenia

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Abstract

Objective—The primary purpose of this eight week double blind, placebo-controlled trial of rosiglitazone 4 mg/day was to examine its effect on insulin sensitivity index (SI) and glucose utilization (SG) in clozapine-treated schizophrenia subjects with insulin resistance.

Methods—Eighteen subjects were randomized and accessed with a Frequently Sampled Intravenous Glucose Tolerance Test (FSIVGTT) at the baseline and week 8 to estimate SG, and SI.

Results—Controlling for the baseline, comparing the rosiglitazone group to placebo group, there was a non-significant improvement of SG (0.016± 0.006 to 0.018± 0.008, effect size= 0.23, p= 0.05) with a trend of improvement in SI in the rosiglitazone group (4.6± 2.8 to 7.8± 6.7, effect size= 0.18, p= 0.08). There was a significant reduction in small low-density-lipoprotein cholesterol (LDL-C)- particle number (987± 443 to 694± 415, effect size= 0.30, p= 0.04).

Conclusion—Rosiglitazone may have a role in addressing the insulin resistance and lipid abnormalities associated with clozapine.

Keywords

Clozapine; Rosiglitazone; metabolic syndrome; Lipids

Introduction

Clozapine-induced increase in cardiometabolic risk factors in patients with schizophrenia is of great concern. Cardiovascular diseases remain the leading cause of medical morbidity and mortality among schizophrenia patients[1], and the rate is much higher compared to the general population[2, 3]. Several meta-analyses suggest that clozapine can cause clinically significant weight gain, mostly during the first 6 to 12 months of its use[4, 5]. Similarly,

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evidence suggests that clozapine is associated with hyperlipidemia [6] and glucose metabolism abnormalities including insulin resistance(IR) [7], hypertension (HTN) [8], type 2 diabetes mellitus (type 2 DM) and diabetic ketoacidosis [9-11].

Obesity, especially visceral, IR and dyslipidemia together with hypertension are key components of metabolic syndrome (MetS), which is a predictor of type 2 DM and is associated with macro vascular complications. A 10 year naturalistic study of patients treated with clozapine showed an increased risk of death from myocardial infarction secondary to clozapine-associated medical disorders such as obesity, hyperlipidemia, HTN, and type 2 DM [12].

Studies have shown that clozapine is associated with IR in even non-obese patients [13]. Some studies have also found IR as the inciting factor for the development of DM and other metabolic abnormalities in the general population [14, 15]. Improvement in IR may therefore address other metabolic components of MetS and reduce the risk of DM and cardiovascular disease. It is also a logical assumption that the overall improvement in metabolic profiles would improve general health and improve adherence to clozapine therapy. Given the association between clozapine and insulin resistance, drugs that improve insulin resistance may be useful. Morrison et al [16] openly treated 19 adolescents, who were receiving either olanzapine, risperidone, quetiapine or valproate, with metformin 500 mg three times a day. The mean weight loss at 12 weeks was 2.93±3.13 kg with 15 of 19 patients losing some weight. Wu et al. randomized 40 first episode schizophrenia patients to treatment with olanzapine 15 mg/day plus metformin 750 mg/day or olanzapine plus placebo for 12 weeks [17]. They found that weight, BMI, waist circumference, insulin and insulin resistance increased less with the combination. Baptista et al reported a 12 week study with metformin (850-1700 mg) plus sibutramine (10-20 mg, n=13) or placebo (n=15) in olanzapine-treated chronic schizophrenia patients. Weight loss was similar in both groups though the combination did prevent a triglyceride increase.

Rosiglitazone, a thiazolidinedione, was approved by Food and Drug Administration (FDA) in 1999 as a monotherapy or as part of combination therapy with sulphonylureas, metformin or insulin in patients with DM [18]. Rosiglitazone activates the peroxisome-proliferator-activated receptors gamma type (PPAR-γ), a transcription factor in the cell nucleus responsible in glucose and fat metabolism. This drug effectively lowers fasting and postprandial blood glucose levels and also reduces glycosylated hemoglobin, but is not associated with hypoglycemia [19-25]. A Diabetes Outcome Progression Trial (ADOPT) found that rosiglitazone is the best monotherapy compared to metformin or sulphonylurea in maintaining long term glycemic control in newly diagnosed type 2 DM [25]. Another study, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM), found that rosiglitazone can prevent the progression of IR to type 2 DM by 62% and revert insulin resistance to normoglycemia by 70% relative to placebo [26].

This study examined the effect of rosiglitazone on IR in clozapine-treated schizophrenia patients with insulin resistance or impaired fasting glucose. The study secondarily examined whether an improvement in IR leads to an overall improvement in other metabolic

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disturbances such as lipid profile, blood pressure, weight and the cardiometabolic biomarkers.

Methods and Materials

Subjects were recruited from the Freedom Trial Clinic at the Erich Lindemann Mental Health Center and were studied at the Mallinckrodt General Clinical Research Center (GCRC) at Massachusetts General Hospital (MGH), Boston. The study was approved by the institutional review boards of MGH General Clinical Research Center, and the Massachusetts Department of Mental Health. 50 male and female outpatients between the ages of 18 and 65 years from diverse social, economic and racial backgrounds with the diagnosis of schizophrenia or schizoaffective disorder were screened for the study. Eligibility was determined by interview and a medical record review for history and recent laboratory values. After providing written informed consent, subjects underwent a diagnostic evaluation by a research psychiatrist using the Structured Clinical Interview for *DSM-IV (SCID)*[27]. Patients who were treated with clozapine for a minimum of one year, showed evidence of insulin resistance or impaired glucose metabolism such as impaired fasting glucose (≥ 110 mg/dl), elevated fasting insulin (≥ 15 ng/dL) or homeostasis model assessment-insulin resistance (HOMA-IR) ≥2 were eligible for the study. Patients were excluded on the basis of current substance abuse; type 1 or 2 DM; thyroid disease; pregnancy; significant medical illness including severe cardiovascular, hepatic, or renal diseases; or unstable psychiatric illness. Patients treated with the following medication known to affect glucose tolerance were also excluded: birth control pills containing norgestrel, steroids, beta-blockers, anti-inflammatory drugs (including aspirin and ibuprofen), thiazide diuretics and valproate sodium. Similarly, patients treated with agents that induce weight loss or, with other oral hypoglycemic agents or insulin or, with other antipsychotic drugs or, having a known hypersensitivity to rosiglitazone or to any of its components, were excluded from the study. A urine pregnancy test was performed prior to the study for female subjects of childbearing potential. They were given an instruction to practice appropriate birth control methods during the study period. Additionally, as the luteal phase is associated with a reduction in insulin sensitivity [28], menstruating women were interviewed on their menstrual history and date of last menses, instructed to keep a log, and underwent the Frequently Sampled Intravenous Glucose Tolerance Test (FSIVGTT) during the early follicular phase of their menstrual cycle (days 1-7).

Subjects were given a diet plan calculated to maintain body weight and to provide a minimum of 250 g of carbohydrate for each of the 3 days prior to the FSIVGTT. Subjects were also instructed to fast for 12 hours preceding the FSIVGTT and to hold their morning medications the day of the test. Family, residential program staff, and outreach workers assisted subjects to maintain a high-carbohydrate intake and to guarantee fasting. Subjects were admitted to the MGH GCRC at 6:45 AM on the morning of the test. A complete nutritional assessment was conducted on admission and immediately prior to the initiation of the FSIVGTT.

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Nutritional Assessment and Frequently Sampled Intravenous Glucose Tolerance Test

Anthropometric measurements, such as height, weight, circumferences, skin fold and body fat were conducted utilizing previously reported methods. [29, 30]. The fasting FSIVGTT was conducted utilizing previously reported methods [31-33]

Following baseline assessment and FSIVGTT, 18 subjects (M: F=13:5) subjects were eligible for randomization to rosiglitazone 4 mg/day (n=8) or placebo (n=10).

Laboratory Assays

Laboratory assays were performed by the chemistry laboratory and the MGH GCRC Core Laboratory. Insulin immunometric assays were performed using an Immulite Analyzer (Diagnostic Product Corp; Los Angeles, CA) with an intra-assay coefficient of variation of 4.2% to 7.6%. The standard fasting lipids were measured utilizing conventional blood analysis Low-density lipoprotein cholesterol (LDL-C) values were estimated indirectly for participants with plasma triglyceride levels less than 400 mg/dL (4.52 mmol/L) and directly if the triglyceride was > 400 mg/dL [34]. Lipoprotein particle measurements were done by nuclear magnetic resonance spectroscopy (Liposcience, Inc., Raleigh, NC). Plasminogen activator inhibitor-1(PAI-1), C-reactive proteins (CRP), soluble intercellular adhesion molecules-1 (sICAM-1), and Von Willebrand Factors (vWF) were measured by the conventional blood analysis.

Minimal Model Calculation

SI, SG, the acute insulin response to glucose (AIRG), and disposition index (DI) were calculated from plasma glucose and serum insulin values using the MINMOD Millennium computer program developed by Richard Bergman, PhD[32, 35]. The SI represents the increase in net fractional glucose clearance rate per unit change in serum insulin concentration after the intravenous glucose load. The SG represents the net fractional glucose clearance rate due to the increase in glucose independent of any increase in circulating insulin concentrations above baseline. The AIRG measures the acute (0-10 minutes) beta-cell response to a glucose load calculated by the areas under the curve higher than basal insulin values. The AIRG was assessed as the incremental area under the curve (calculated by the trapezoid rule) from 0 to 10 minutes of the FSIVGTT. The DI (which equals SI × AIRG), an index of beta-cell function that takes account of prevailing insulin sensitivity and exploits the hyperbolic relationship between the two [31, 36] was calculated by the method described by Kahn et al [36]. The HOMA-IR was calculated by the following formula: fasting serum insulin concentration × fasting plasma glucose concentration/22.5 [37, 38]. The HOMA-IR was calculated by taking the mean of 3 fasting values (times, −10, −5, and 0).

Psychopathology Assessment and the Systematic Assessment for Treatment Emergent Events

Positive and Negative Symptom Subscale (PANSS) [39]and Hamilton rating Scale for Depression (HAM-D)[40] were used to assess psychopathology. The Systematic Assessment for Treatment Emergent Events (SAFTEE)[41] consisting of General inquiry and the Systematic inquiry to assess possible side effects was done at baseline and repeated at week 4 and 8.

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Statistical Analysis

Statistical analysis was performed using SPSS (version 13.0, Chicago, IL). For all analyses, a p value less than 0.05 (2-tailed) were used for statistical significance. Descriptive statistics were used to describe demographic and clinical characteristics of the study sample. Chi square was used to access differences in frequency. Group comparisons were performed using independent t test for continuous variables and Chi-square test for categorical variables. Analysis of covariance (ANCOVA) was used to examine change scores from baseline to week 8 between groups after controlling for baseline scores.

Results

Demographics

34 subjects consented for the study. Data from 18 subjects is presented. Seven subjects withdrew consent prior to baseline assessments; three subjects were screened fails based on abnormal baseline laboratory values (liver function tests (2) or elevated fasting glucose (1)). Two subjects were hospitalized after consenting (one for psychotic decompensation due to poor adherence, one for new onset DM), one subject was unable to comply with fasting prior to the FSIVGTT, intravenous access was not obtained in one subject because of poor veins, and one subject experienced unpleasant hypoglycemia symptoms during the baseline FSIVGTT and the procedure was terminated. One subject was withdrawn from the study following approximately a 10 lb weight gain and pedal edema over 2 weeks (placebo). Data from the remaining 18 patients are presented. There were no differences between the placebo and rosiglitazone groups for the mean age, gender, and ethnicity, percentages of alcohol and tobacco users, clozapine daily dose, and clozapine and norclozapine level. Two (11%) subjects were also treated with quetiapine and one (6%) with risperidone. The rosiglitazone group had a higher family history of diabetes (p=0.05) whereas family history of cardiovascular diseases and hypertension were similar in both groups (Table 1). The placebo group was treated with clozapine for 8±3 years (range 5-12) and the rosiglitazone group for 9±4 years (range 2-14 years).

Glucose metabolism

The ANCOVA, comparing change scores (baseline to week 8) between the rosiglitazone group and the placebo group after controlling for the baseline scores showed an improvement of SG in the rosiglitazone group that just missed significance (0.016± 0.006 min^{-1} to 0.018± 0.008 min^{-1}; effect size= 0.23; p= 0.05); and a trend of improvement in SI in the rosiglitazone group (4.6± 2.8×10-4 min^{-1} per μu/mL to 7.8± 6.7×10-4 min^{-1} per μu/mL; effect size= 0.18, p= 0.08). Similarly, the analysis showed that the rosiglitazone group had non-significant reductions in fasting serum insulin level and HOMA-IR (Table 2). There were no significant differences between groups for fasting glucose and insulin, AIRg, DI, and HgbA1c

Lipids

The analyses of lipoprotein particle measurements showed a significant reduction in small LDL particle number in the rosiglitazone group (987± 443 nmol/L to 694± 415 nmol/L;

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effect size=0.30; p=0.04) and trend of increase in LDL-C particle size in the rosiglitazone group (21± 0.7 nm to 21± 0.8 nm; effect size= 0.227; p= 0.08). The decrease in small LDL particle number and the increase in LDL-C particle size suggest improvements in atherogenic LDL-cholesterol. However, non-significant mixed results were observed in conventional lipid panel (increased LDL-C and total cholesterol with reduced high density lipoprotein cholesterol (HDL-C) and reduction in triglycerides level) in rosiglitazone group compared to placebo (Table 2). Triglycerides decreased in the rosiglitazone group, but it was not significant.

Anthropometric measurements and Cardio metabolic biomarkers measurements

All anthropometric measurements (body weight, body mass index, body fat, waist-hip ratio and waist circumference) at baseline were higher in the rosiglitazone group compared to placebo group, but not statistically significant. Though not significant, mean change in waist circumference in placebo group increased comparing baseline to week 8; however other anthropometric changes were not appreciable in either group at week 8 compared to the baseline measurements (Table 2). There were nonsignificant reductions in CRP and PAI-1 values from baseline to week 8 in the rosiglitazone group compared to placebo group. (Table 2)

Psychopathology and the Systematic Assessment for Treatment Emergent Events

There were no changes in psychopathology in either group from the baseline to week 8 (Table 3). Frequently observed side-effects during the study were heart burn (25% vs. 0%), cough (25% vs. 0%), dyspnea (25% vs. 0%) and problems with memory or concentration (37.5% vs. 10%) (Table 3). There were no significant differences between groups on any side effect.

Discussion

In this study, rosiglitazone 4 mg daily for 8 weeks produced improvements in IR and some lipid abnormalities, though not all findings were statistically significant in this study of clozapine-treated schizophrenia subjects. The maximal effect of rosiglitazone for such changes may take more than 8 weeks or a higher dose of rosiglitazone. The reduction in SI and SG (though not significant) represented an effect size of 0.18 and 0.23 respectively. These results suggest that there were modest improvements in not only insulin sensitivity, but also in glucose effectiveness or utilization. The latter suggests a potential increase in glucose transporters by rosiglitazone. One study observed that clozapine incubated for only few minutes can block glucose transporters in rat pheochromocytoma (PC12) cell in vitro [42]. Rosiglitazone also has been found to increase glucose transporter activity [43].

Our findings of a significant decrease in number of small dense LDL-C particles with rosiglitazone treatment compared to placebo is consistent with earlier findings in type 2 DM patients and a reduction in cardiovascular risks [44]. Oxidized or glycolated LDL-C particle size and number is implicated in the initiation and progression of atherosclerotic vascular diseases in diabetic patients. This component is considered the most important predictor for the risk of cardiovascular disease in metabolic syndrome.[45-49] The European Prospective

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Investigation into Cancer and Nutrition (EPIC)-Norfolk study found that LDL-C particles, and not LDL-C, was strongly associated with coronary artery disease when adjusted for the Framingham risk scores.[50]

A meta-analyses, taking into account several adequately powered randomized controlled trials with rosiglitazone, have demonstrated its direct benefit on macrovascular complications associated with type 2 DM. Studies show that rosiglitazone effectively improves some atherogenic lipid levels[23, 44], decreases blood pressure[51-53], enhances myocardial function[54, 55], promotes fibrinolysis and possibly stabilizes coronary plaques prone to rupture[44], and decrease neointimal proliferation[23] by virtue of its anti-inflammatory and anti-oxidant properties[56-58]. However, recent concern has been raised regarding rosiglitazone and risk of myocardial infarctions and death from cardiovascular disease and has lead to an international debate which is yet unresolved [26, 5960, 616263]. In our study, there were nonsignificant improvements in inflammatory cardiovascular risk markers, consistent with finding in the literature with rosiglitazone treatment [64].

Our findings in this study were limited by the small sample size. It is possible that with a larger sample, significant improvements might be observed not only in glucose metabolism but also in lipid metabolism. As each variable examined in this pilot study is essentially an independent hypothesis, multiple same or similar hypotheses-driven tests of statistical significance on the same data can result in significant findings by chance. It is also possible that 8 mg/day dose of rosiglitazone would be more clinically useful in this population, along with a greater length of time for observation.

In conclusion, the metabolic abnormalities associated with clozapine treatment leads clinicians to a challenging situation to balance the risks and benefits. At present, rosiglitazone, and perhaps, other thiazolidinediones such as pioglitazone, may potentially address the metabolic side effects of clozapine treatment and reduce cardiovascular risks associated with it. Though the sample size was small, rosiglitazone's improvements in SI and SG and especially lipid metabolism are encouraging findings of our study. Further clinical trials with rosiglitazone or other thiazolidinediones in schizophrenia subjects to address the impairment in glucose and lipid metabolism, and to reduce cardiometabolic risks, are warranted. The long-term safety concerns with rosiglitazone must also be addressed.

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Significant Outcomes

- Rosiglitazone treatment showed trends towards improving both insulin sensitivity and glucose utilization in clozapine-treated schizophrenia subjects with insulin resistance
- Rosiglitazone treatment resulted in a decrease in small LDL-C particle number and a trend towards increasing LDL-C particle size, both of which reduces atherogenic risks.
- Treatment with Rosiglitazone was well tolerated without significant adverse events.

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Major Limitations

- The sample size of the study may have been too small to detect statistically significant differences glucose metabolism outcomes and some lipids.
- The dose of rosiglitazone may have been too low in this study.
- The duration of the study may have been too short to detect statistically significant differences.

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Table 1

Demographic and clinical characteristics, comparing rosiglitazone to placebo in an 8-week study of clozapine-treated schizophrenia subjects (N=18)

	Placebo (N=10)		Rosiglitazone (N=8)		*t*	*df*	*p*
	Mean	**SD**	**Mean**	**SD**			
Age, years	39.7	7.4	39.2	9.2	-0.1	16	0.91
Clozapine dose, mg/day	363	133	338	162	-0.4	16	0.72
Clozapine blood level, ng/mL	538	419	635	529	0.4	13	0.69
Norclozapine blood level, ng/mL	343	233	307	278	-0.3	13	0.79
	N	%	N	%	x^2	*df*	*p*
Sex					0.06	1	0.81
Male	7	70	6	75			
Female	3	30	2	25			
Race					1.8	1	0.18
Caucasian	8	80	8	100			
Hispanic	2	20	0	0			
Alcohol use							
Yes	2	20	1	12.5	0.18	1	0.67
No	8	80	7	87.5			
Tobacco use							
Yes	5	50	4	50	0.0	1	1.00
No	5	50	4	50			
Family history of Cardiovascular disease							
Yes	3	30	3	37.5	0.11	1	0.73
No	7	70	5	62.5			
Family history of Hypertension							
Yes	3	30	3	37.5	0.11	1	0.73
No	7	70	5	62.5			
Family history of Diabetes							
Yes	3	30	6	75	3.60	1	0.05

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	Placebo (N=10)		Rosiglitazone (N=8)		*t*	*df*	*p*
	Mean	**SD**	**Mean**	**SD**			
No	7	70	2	25			

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Table 2

Outcome measures comparing rosiglitazone to placebo in an 8-week study of clozapine-treated schizophrenia subjects (N=18)

	Placebo(N=10)				Rosiglitazone (N=8)						
	Baseline		Week 8		Baseline		Week 8		ANCOVA		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*F*	*df*	*p*
Anthropometric measurements											
Body weight, lbs	189	49	190	48	198	36	197	36	0.13	1,15	0.72
Body mass index, kg/m^2	29.3	6.5	29.4	6.4	32.4	5.8	32.3	6	0.23	1,15	0.64
Waist circumference, cm	98	13	103	18	107	10	108	8.8	0.03	1,10	0.86
Waist-hip ratio	0.96	0.1	0.99	0.09	1.02	0.06	1	0.06	0.01	1,10	0.94
Body fat, %	28.1	6.9	28.6	7.2	31.3	7.7	30.8	7.1	0.2	1,15	0.66
Glucose metabolism measurements											
Fasting plasma glucose, mg/dL	95	11	99	15	94	5	96	8	0.1	1,15	0.75
Fasting serum insulin, μIU/mL	5.9	4.8	6	3.8	10.4	5.2	7.4	4.3	0.24	1,15	0.63
HOMA-IR	1.7	1.1	1.8	1.1	2.6	1.8	1.6	1	2.3	1,14	0.15
HbA1c, %	5	0.4	5	0.3	5.6	0.5	5.7	0.3	1.1	1,12	0.31
SI,×10-4 min^{-1} per μu/mL	4.1	2.5	4.5	2.6	4.6	2.8	7.8	6.7	3.3	1,15	0.08
SG,min^{-1}	0.02	0.01	0.01	0	0.02	0.01	0.02	0.01	4.5	1,15	0.05
AIRG (AUC,0-10),U/mL per 10 min	184	254	203	232	328	641	177	184	1.7	1,15	0.21
DI	438	245	678	556	974	1301	891	503	0.03	1,15	0.86
Convention lipid panel											
LDL-C, mg/dL	92	22	90	9	95	24	124	25	0.79	1,12	0.39
HDL-C, mg/dL	38	11	35	7	43	10	38	11	0.03	1,15	0.85
Triglycerides, mg/dL	195	140	266	153	186	68	132	109	0.86	1,15	0.36
Total Cholesterol, mg/dL	164	24	178	15	175	22	188	36	0.59	1,15	0.45
NMR lipoprotein particle measures											
LDL Particle Number, nmol/L	1365	325	1386	461	1370	305	1307	331	2.96	1,12	0.11

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	Placebo(N=10)				Rosiglitazone (N=8)						
	Baseline		Week 8		Baseline		Week 8		ANCOVA		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*F*	*df*	*p*
LDL Particle Size, nm	21	0.9	21	1.1	21	0.7	21	0.8	3.52	1,12	0.08
Small LDL Particle Number, nmol/L	905	488	862	634	987	443	694	415	5.09	1,12	0.04
Small LDL Size, nm	0.6	0.52	0.7	0.5	0.4	0.5	0.8	0.5	2.01	1,12	0.18
Large HDL Particle Number, μmol/L	3.8	3.6	4.7	4.5	3.2	2.9	3.4	3	0.33	1,12	0.57
Cardiometabolic biomarkers measurements											
CRP, mg/L	3.6	2.9	3.3	2	8.8	11	3.5	2.4	1.21	1,15	0.28
PAI-1, ng/mL	107	63	96	50	126	86	108	35	0.09	1,6	0.76
vWF, IU/dL	407	259	569	234	421	331	421	275	0.91	1,13	0.35
sICAM-1, pg/mL	432	138	394	111	364	95	346	103	0.02	1,12	0.9

HOMA-IR: Homeostasis model assessment of insulin resistance; HbA1c: Glycosylated hemoglobin; SI: Insulin sensitivity index; SG: Glucose effectiveness; AIRG: Acute insulin response to glucose; AUC: Area under the curve; DI Disposition index, CRP: C-reactive protein; PAI-1: Plasminogen activator inhibitor-1; vWF: Von Willebrand factor; sICAM-1: Soluble intercellular adhesion molecule-1

ANCOVA: Analysis of covariance. The analysis compared change scores (baseline to week 8) between the two treatment groups after controlling for baseline scores

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Table 3

Psychopathology and Side effects comparing rosiglitazone to placebo in an 8-week study of clozapine-treated schizophrenia subjects (N=18)

	Placebo(N=10)				Rosiglitazone (N=8)						
	Baseline		Week 8		Baseline		Week 8		ANCOVA		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*F*	*df*	*p*
Psychopathology measurements											
PANSS-Total	61.8	17.9	62.7	16.1	58.4	13.4	58	12	0.29	1,14	0.59
PANSS-Positive	13.9	6.9	12.6	5.1	14.9	5	13.9	3.7	2.9	1,14	0.1
PANSS-Negative	17.5	7.8	19.7	4.7	15.2	4.3	15.8	5.9	1.8	1,14	0.2
PANSS-General	30.4	8.2	30.8	8.9	28.2	6.9	28.4	5.7	0.01	1,14	0.91

Reported Side Effects (change from Baseline):

	Placebo (N=10)		Drug (N=8)				
	N	%	N	%	x2	df	p
Heart burn	0	0	2	25	2.81	1	0.09
Cough	0	0	2	25	2.81	1	0.09
Dyspnea	0	0	2	25	2.81	1	0.09
Hypersalivation	2	20	3	37.5	0.68	1	0.41
Headache	1	10	1	12.5	0.03	1	0.86
Backache	0	0	1	12.5	1.32	1	0.25
Arthralgia/Myalgia	0	0	1	12.5	1.32	1	0.25
Confusion/Problems with concentration and memory	1	10	3	37.5	1.95	1	0.16
Drowsiness / Tiredness	2	20	3	37.5	0.68	1	0.41
Increased urinary frequency	0	0	1	12.5	1.32	1	0.25

PANSS: Positive and Negative Syndrome Scale, including Positive Symptoms, Negative Symptoms and General Psychopathology subscales ANCOVA: Analysis of covariance. The analysis compared change scores (baseline to week 8) between the two treatment groups after controlling for baseline scores