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Aripiprazole added to Overweight and Obese Olanzapine-treated Schizophrenia Patients

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Abstract

Olanzapine treatment has been associated with clinically meaningful weight increases, hypertriglyceridemia, insulin resistance and diabetes mellitus. There are few options for olanzapine-responders who fail other antipsychotic agents. Aripiprazole is a potent (high-affinity) partial agonist at D2 and 5-HT_{1A} receptors and a potent antagonist at 5-HT_{2A} receptor and is associated with less weight gain than olanzapine. We report the results of a 10-week placebo controlled, double-blind crossover study that examined 15 mg/day aripiprazole's effects upon weight, lipids, glucose metabolism, and psychopathology in overweight and obese schizophrenia and schizoaffective disorder subjects treated with a stable dose of olanzapine. During the 4 weeks of aripiprazole treatment there were significant decreases in weight ($p = .003$) and BMI ($p = .004$) compared to placebo. Total serum cholesterol ($p = .208$), HDL-cholesterol ($p = .99$), HDL-2 ($p = .08$), HDL-3 ($p = .495$) and LDL-cholesterol ($p = .665$) did not change significantly comparing aripiprazole treatment to placebo treatment. However, total serum triglycerides ($p = .001$), total VLDL-cholesterol ($p = .01$), VLDL 1- & 2-cholesterol ($p = .012$) decreased significantly during the aripiprazole treatment phase. VLDL-3-cholesterol tended lower during aripiprazole, but the decrease was not significant ($p = .062$). There was a decrease in c-reactive protein comparing aripiprazole treatment to placebo though it did not reach significance ($p = .087$). The addition of aripiprazole to a stable dose of olanzapine was well tolerated and resulted in significant improvements on several outcome measures that predict risk for medical morbidity.

Keywords

Aripiprazole; Olanzapine; Schizophrenia; Lipid Metabolism; Medical Morbidity

INTRODUCTION

In early clinical trials, olanzapine treatment was associated with clinically meaningful weight increases (greater than 7% of baseline weight) in 31.7% of patients who were underweight, 18% of normal weight patients, and 11% of overweight patients¹. In 4 studies,

the mean incidence of weight gain of 7% or greater was 40.5% in patients treated with olanzapine compared to 12.4% of those receiving haloperidol, and 3.1% of those receiving placebo ¹. A study of 25 olanzapine-treated inpatients demonstrated a mean weight gain of 12 pounds after 12 weeks on a mean olanzapine dose of 13.8 mg ². Another study found that 94% of day-treatment patients treated with olanzapine (mean dose 14.1 mg) experienced weight gain of greater than 7%. The mean weight gain was 22.1 lbs over a 7-months, though the weight gain correlated with clinical response ³.

Hypertriglyceridemia has been linked to olanzapine therapy ^{4,5}. Melkersson and Dahl ⁶ also assessed 34 schizophrenia patients treated with either clozapine or olanzapine and observed hyperinsulinemia and hyperlipidemia (elevated triglyceride and total cholesterol) in both groups with a positive correlation with clozapine serum levels but not its metabolites. Atmaca and Kuloglu ⁷ examined 56 subjects treated with atypical antipsychotic agents and observed a significant increase in weight and triglyceride levels in olanzapine-treated groups. Sheitman and colleagues ⁸ reported an increase in serum triglyceride from baseline to 16-month re-assessment where triglycerides increased more than 40% while cholesterol remained essentially unchanged. Osser and colleagues ⁹ compared 25 subjects at baseline and 12 weeks after olanzapine-initiation, both weight (mean of 12 lb.) and fasting triglycerides (mean change of 60 mg/dL) significantly increased. There was a strong association between weight change and triglyceride change. Clozapine and olanzapine treatment have also been most closely associated with insulin resistance in both obese and nonobese schizophrenia patients ¹⁰⁻¹².

While switching to a more weight-neutral atypical antipsychotic agent offers promise in halting or reversing weight gain, many patients and their clinicians are reluctant to risk a worsening or return of psychotic symptoms and risk relapse ¹³⁻¹⁶. Non-pharmacologic means of weight control have yielded mixed results ^{17,18, 19}. A number of pharmacologic interventions have also been evaluated including reboxetine²⁰, fluoxetine²¹, sibutramine ²², amantadine ²³, and topiramate²⁴, and metformin^{25,26}. Aripiprazole is a potent (high-affinity) partial agonist at D2 ²⁷ and 5-HT1A receptors and a potent antagonist at 5-HT2A ²⁸ receptors. In a study of 24 patients with treatment resistant schizophrenia who had aripiprazole added to decreased doses of clozapine, Karunakaren et al ²⁹ reported an average weight loss of 5.1 kg over 34 weeks. A 6-week open-label trial to examine the effects of adjunctive aripiprazole in ten clozapine-treated subjects observed a significant decrease in weight (from 219.4 ± 40.0 lbs to 213.7 ± 38.3 lbs) and triglycerides (from 274 ± 229 to 176 ± 106 mg/dL) ³⁰.

We now present the results of a 10-week placebo controlled, double-blind crossover study to examine aripiprazole's effects upon weight, lipids, glucose metabolism, and psychopathology in overweight and obese schizophrenia and schizoaffective disorder subjects treated with a stable dose of olanzapine.

METHODS AND MATERIALS

Subjects were recruited from an urban community mental health clinic. The study was approved by the institutional review board of the Massachusetts Department of Mental

Health. Outpatients between the ages of 18 and 65 years with the diagnosis of schizophrenia or schizoaffective disorders were included in the study after providing written informed consent. Patients with active substance abuse, pregnancy, significant medical illness (unstable cardiac disease, malignancy, severe liver or renal impairment), and unstable psychiatric illness (CGI's severity of illness question of 5 or greater) were excluded from the study. Each patient underwent a diagnostic evaluation by a research psychiatrist (X.F.), using the Structured Clinical Interview for DSM-IV (Spitzer et al 1992). Eligibility was determined by interview, chart review for history and baseline vital signs and laboratory values. Subjects were eligible for the study if their body mass index (BMI) was $\geq 30 \text{ Kg/m}^2$; or $\geq 27 \text{ Kg/m}^2$ with other risk factors (treatment for hypertension of blood pressure (BP) $> 140/90 \text{ mm Hg}$; lipid abnormalities: total cholesterol $\geq 200 \text{ mg/dL}$, triglyceride $\geq 150 \text{ mg/dL}$; or fasting glucose $\geq 100 \text{ mg/dL}$). Subjects had to be maintained on a stable dose of olanzapine for at least one month.

Anthropometric, Blood pressure and Metabolic Assessments

A physical examination and medical history was performed at baseline and measurements of vital signs, weight, height, body mass index (BMI), and waist (supra-iliac) and hip circumference were performed at each visit. EKG's were analyzed by the MGH Department of Cardiology at baseline and weeks 4, 6, and 10. Side effects were assessed at baseline and weeks 2, 4, 6, 8, and 10 using the Systematic Assessment for Treatment Emergent Events (SAFTEE)³¹. Energy expenditure and dietary intake were assessed at baseline, weeks 4, 6 and 10. Subjects were instructed to wear an accelerometer for four consecutive days to obtain an objective measure of physical activity. The raw data obtained from a single channel accelerometer (Actigraph model 7164) were processed by custom data processing program to estimate energy expenditure^{32,33}. During the same four days the subjects maintained a four-day food record of all food and beverages consumed. Fasting blood samples were assayed for a complete blood count and chemistries at baseline and weeks 4, 6, and 10 using standard laboratory procedures. Lipoprotein subfractionation profile, Vertical Auto Profile (VAP) (Atherotech Inc., Birmingham, AL) was performed by Laboratory Corporation of America, Labcorp. Fasting total plasma cholesterol and triglycerides levels were measured enzymatically (McNamara and Schaefer 1987)³⁴, with an intra-assay coefficient of variation of 1.7% to 2.7% and 0.9% to 1.2%, respectively. Lipoproteins were measured by vertical density-gradient ultracentrifugation followed by measurement of the cholesterol distribution. The major lipoproteins and their subfractions were separated by density gradient centrifugation, and the cholesterol component of each fraction was measured³⁵. The VAP measured LDL-, HDL-, VLDL-cholesterol, triglycerides, intermediate-density lipoprotein (IDL-c), and lipoprotein(a). VLDL-C was separated into VLDL-C1 and 2, which are more buoyant and the main carriers of triglyceride; VLDL3-C are small, dense atherogenic VLDL remnant particles. HDL2-C confers the greatest degree of protection against coronary heart disease and HDL3-C is less protective. Insulin immunometric assay were performed with an Immulite Analyzer (Diagnostic Product Corporation, Los Angeles, CA) with an intra-assay coefficient of variation of 4.2%–7.6%. HOMA-IR was calculated by the following formula: fasting insulin (uU/mL) $\times$ fasting glucose (mg/dL) /22.5³⁶.

Subjects were assessed with a battery of symptom rating scales at baseline, weeks 4, 6 and 10. The assessment battery was comprised of the Positive and Negative Syndrome Scale (PANSS), Scale for Assessment of Negative Symptoms (SANS), Hamilton Depression Rating Scale (HAM-D), Global Assessment Scale (GAS), Fatigue Scale Inventory (FSI), 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.

Randomization

This double-blind, placebo-controlled, crossover study consisted of two random order 4-week treatment arms (aripiprazole 15 mg or placebo) separated by a 2-week adjuvant treatment washout. Following baseline, subjects were randomized, double-blind, to either aripiprazole or placebo for 4 weeks. After the initial 4 weeks of medication subjects were reassessed, had a 2-week washout period and then another complete assessment before receiving the other treatment for another 4 weeks. All assessments were again repeated at week 10.

Statistical analysis

The data were analyzed using SPSS (version 13.0; SPSS inc., Chicago, IL). Descriptive statistics was conducted to characterize the study sample. For the primary outcome variables of interest, analysis of covariance (ANCOVA) was conducted with change scores over 4 weeks of treatment as dependent variables and baseline scores as covariates. Treatment condition (placebo versus aripiprazole) along with treatment order (placebo first versus aripiprazole first) main effects and their interaction term were tested. Since treatment order main effect and the interaction term (treatment condition X treatment order) were found non-significant for all dependent variables analyzed, ANCOVA models with treatment condition main effect only were reported. This pilot trial included multiple outcome measures intended to provide an indication of effect size for the purpose of designing future studies. Given the exploratory nature of the study, Bonferroni corrections were not used to control for potential Type I error across multiple comparisons.

RESULTS

Sixteen subjects consented to participate. One subject was found ineligible for the study because of recent changes in medications. Available data from the remaining 15 subjects are included in all analyses. The mean age of subjects was 49 ± 8 years and ten (67%) were male. Three subjects were African American (20%) and twelve (80%) were Caucasian. The mean length of treatment with olanzapine was 71 ± 29 months; and the mean olanzapine dose was 22 ± 11 mg daily. Three (20%) were treated for hyperlipidemia with a lipid-lowering statin; three were treated for hypertension (with a beta-blocker); one for hypothyroidism (with thyroid replacement); and one for type 2 DM (with metformin). Six had family histories for obesity, seven for hypertension, seven for DM, and five for cardiovascular disease.

Fourteen subjects completed the 10-week trial; one subject dropped out following the week 4 assessment due to a housing change. During the 4 weeks of aripiprazole treatment there

were significant decreases in weight ($p = .003$) and BMI ($p = .004$) compared to placebo (Table 1). Mean waist circumference tended to decrease during treatment with aripiprazole, compared to placebo, but was not significant ($p = .063$). Fasting plasma glucose and fasting insulin concentrations did not change significantly. Insulin resistance, calculated by HOMA-IR analysis revealed a nonsignificant decrease. Hemoglobin A1c also slightly, but not significantly, decreased during aripiprazole treatment, compared to placebo. There was a decrease in C-reactive protein comparing aripiprazole treatment to placebo though it did not reach significance ($p = .087$).

Lipids

Total serum cholesterol ($p = .208$), HDL-cholesterol ($p = .99$), HDL-2 ($p = .08$), HDL-3 ($p = .495$) and LDL-cholesterol ($p = .665$) did not change significantly comparing aripiprazole treatment to placebo treatment. However, total serum triglycerides ($p = .001$), total VLDL-cholesterol ($p = .01$), VLDL 1- & 2-cholesterol ($p = .012$) decreased significantly during the aripiprazole treatment phase. VLDL-3-cholesterol tended lower during aripiprazole, but the decrease was not significant ($p = .062$). The results suggest that a reduction on both the large buoyant VLDL (fractions 1 & 2) and a trend toward reduction in small remnant VLDL (fraction 3) occurred. Four subjects LDL density pattern improved (from small dense LDL pattern to large buoyant or mixed during aripiprazole treatment compared to 1 during placebo treatment (chi square=1.9, $p = .166$).

Psychopathology and Side Effects

There was no significant change in total PANSS total or subscores, Barnes Akathisia Scale, Simpson-Angus Scale, GAS, HAM-D or QOL scale when comparing each treatment group. There was no significant difference between treatment groups for change in dietary intake or energy expenditure.

Overall, treatment with aripiprazole was well tolerated. Changes in systolic and diastolic blood pressure readings were not statistically significant between the two treatment groups. The most common side effects observed were a change in appetite (decrease 20%; increase 13%), difficulty falling asleep (27%), and tiredness (27%), none of which were statistically significant.

DISCUSSION

The addition of aripiprazole to a stable dose of olanzapine was well tolerated and resulted in significant improvements on several outcome measures that predict risk for medical morbidity. Of note, subjects experienced significant reductions in weight, BMI, triglycerides, total VLDL-cholesterol, and VLDL 1&2-cholesterol. The small sample size and short duration of active treatment and washout period may have prevented detection of other metabolic benefits, including possible reductions in fasting insulin, and insulin resistance (measured by HOMA-IR). In addition aripiprazole treatment did not significantly change PANSS scores or other psychiatric measures.

The significant decrease in lipids, particularly triglycerides and VLDL-cholesterol is consistent with previous findings³⁰. The triglyceride fluctuation for subjects during placebo

treatment is likely related to the food ate the day before and the amount of time they have been fasting. The statistical analysis takes this fluctuation into consideration. The relationship between hyperlipidemia and weight gain remains unclear in antipsychotic agent-treated patients. The dyslipidemia associated with insulin resistance includes hypertriglyceridemia, an increase in very-low-density lipoprotein (VLDL) secretion from the liver, an increase in the atherogenic small dense low density lipoprotein (LDL) and a decrease in high-density lipoprotein (HDL) cholesterol ^{37,38}. Abnormalities of triglyceride and HDL metabolism are an early manifestation of insulin resistance, often detectable even before the development of abnormal postprandial or fasting glucose levels ³⁹.

Weight loss in the current study could be related to aripiprazole's low histaminergic antagonism or its serotonergic 5-HT_{2c} agonist activity. In an analysis of 17 antipsychotic drugs' receptor affinities the most robust predictor of a drug's propensity to induce weight gain was antagonism of the H₁-histamine receptor ⁴⁰. The moderate binding affinity of aripiprazole for this receptor predicts that it would exhibit a minimal propensity to induce weight gain as well as less sedation. However, there was no difference in energy expenditure measured by the Actigraph between placebo and aripiprazole treatment and the changes can not be explained by an increase in activity. While antagonism at the serotonin 5HT_{2C} receptor cannot fully explain antipsychotic-induced weight gain ^{41,42}, 5HT_{2C} receptors have been implicated in the control of appetite ^{43,44}. Thus, it is possible that 5HT_{2C} agonist actions of aripiprazole may be partly responsible for the minimal weight gain associated with this compound and for weight loss in the current study.

In conclusion, the addition of aripiprazole in olanzapine-treated subjects with schizophrenia or schizoaffective was well tolerated and did not result in a change of psychiatric symptoms in this small, placebo-controlled crossover study of psychiatrically stable schizophrenia subjects. Improvements were observed on measurements that predict medical morbidity and mortality, including weight, BMI, and triglycerides. However, the combination of olanzapine and aripiprazole cost may be prohibitive and alternatives approaches such as switching agents may be more suitable. Long-term, placebo-controlled trials are warranted to further assess the efficacy, safety, cost effectiveness, and metabolic benefit of the addition of aripiprazole to olanzapine-treated patients.

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REFERENCES

1. Beasley CM Jr, Tollefson GD, Tran PV. Safety of olanzapine. *J Clin Psychiatry*. 1997; 58(Suppl 10):13–17. [PubMed: 9265911]
2. Osser DN, Najarian DM, Dufresne RL. Olanzapine increases weight and serum triglyceride levels. *J Clin Psychiatry*. 1999; 60:767–770. [PubMed: 10584766]
3. Gupta S, Droney T, Al-Samarrai S, et al. Olanzapine: weight gain and therapeutic efficacy. *J Clin Psychopharmacol*. 1999; 19:273–275. [PubMed: 10350036]

4. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: A five-year naturalistic study. *Am J Psychiatry*. 2000; 157:975–981. [PubMed: 10831479]
5. Koro CE, Fedder DO, L'Italien GJ, et al. An assessment of the independent effects of olanzapine and risperidone exposure on the risk of hyperlipidemia in schizophrenic patients. *Arch Gen Psychiatry*. 2002; 59:1021–1026. [PubMed: 12418935]
6. Melkersson KI, Dahl ML. Relationship between levels of insulin or triglycerides and serum concentrations of the atypical antipsychotics clozapine and olanzapine in patients on treatment with therapeutic doses. *Psychopharmacology (Berl)*. 2003; 170:157–166. [PubMed: 12851739]
7. Atmaca M, Kuloglu M, Tezcan E, et al. Weight gain, serum leptin and triglyceride levels in patients with schizophrenia on antipsychotic treatment with quetiapine, olanzapine and haloperidol. *Schizophr Res*. 2003; 60:99–100. [PubMed: 12505146]
8. Sheitman BB, Bird PM, Binz W, et al. Olanzapine-induced elevation of plasma triglyceride levels. *Am J Psychiatry*. 1999; 156:1471–1472. [PubMed: 10484969]
9. Osser DN, Najarian DM, Dufresne RL. Olanzapine increases weight and serum triglyceride levels. *J Clin Psychiatry*. 1999; 60:767–770. [PubMed: 10584766]
10. Newcomer JW, Haupt DW, Fucetola R, et al. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. *Arch Gen Psychiatry*. 2002; 59:337–345. [PubMed: 11926934]
11. Henderson DC, Cagliero E, Copeland PM, et al. Glucose Metabolism in Patients With Schizophrenia Treated With Atypical Antipsychotic Agents: A Frequently Sampled Intravenous Glucose Tolerance Test and Minimal Model Analysis. *Arch Gen Psychiatry*. 2005; 62:19–28. [PubMed: 15630069]
12. Henderson DC, Copeland PM, Borba CP, et al. Glucose metabolism in patients with schizophrenia treated with olanzapine or quetiapine: a frequently sampled intravenous glucose tolerance test and minimal model analysis. *J Clin Psychiatry*. 2006; 67:789–797. [PubMed: 16841629]
13. Casey DE, Carson WH, Saha AR, et al. Switching patients to aripiprazole from other antipsychotic agents: a multicenter randomized study. *Psychopharmacology (Berl)*. 2003; 166:391–399. [PubMed: 12610718]
14. Luebbe G, Kropp S, Harms E, et al. Extensive weight loss in a patient with schizophrenia after switching from olanzapine to aripiprazole. A case report. *Pharmacopsychiatry*. 2006; 39:76. [PubMed: 16555168]
15. Spurling RD, Lamberti JS, Olsen D, et al. Changes in metabolic parameters with switching to aripiprazole from another second-generation antipsychotic: a retrospective chart review. *J Clin Psychiatry*. 2007; 68:406–409. [PubMed: 17388710]
16. Weiden PJ, Daniel DG, Simpson G, et al. Improvement in indices of health status in outpatients with schizophrenia switched to ziprasidone. *J Clin Psychopharmacol*. 2003; 23:595–600. [PubMed: 14624190]
17. Ball MP, Coons VB, Buchanan RW. A program for treating olanzapine-related weight gain. *Psychiatr Serv*. 2001; 52:967–969. [PubMed: 11433117]
18. Menza M, Vreeland B, Minsky S, et al. Managing atypical antipsychotic-associated weight gain; 12-month data on a multimodal weight control program. *J Clin Psychiatry*. 2004; 65:471–477. [PubMed: 15119908]
19. Archie S, Wilson JH, Osborne S, et al. Pilot study: access to fitness facility and exercise levels in olanzapine-treated patients. *Can J Psychiatry*. 2003; 48:628–632. [PubMed: 14631884]
20. Poyurovsky M, Isaacs I, Fuchs C, et al. Attenuation of olanzapine-induced weight gain with reboxetine in patients with schizophrenia: a double-blind, placebo-controlled study. *Am J Psychiatry*. 2003; 160:297–302. [PubMed: 12562576]
21. Poyurovsky M, Pashinian A, Gil-Ad I, et al. Olanzapine-induced weight gain in patients with first-episode schizophrenia: a double-blind, placebo-controlled study of fluoxetine addition. *Am J Psychiatry*. 2002; 159:1058–1060. [PubMed: 12042201]
22. Henderson DC, Copeland PM, Daley TB, et al. A double-blind, placebo-controlled trial of sibutramine for olanzapine-associated weight gain. *Am J Psychiatry*. 2005; 162:954–962. [PubMed: 15863798]

23. Deberdt W, Winokur A, Cavazzoni PA, et al. Amantadine for weight gain associated with olanzapine treatment. *Eur Neuropsychopharmacol.* 2005; 15:13–21. [PubMed: 15572269]
24. Levy E, Margolese HC, Chouinard G. Topiramate produced weight loss following olanzapine-induced weight gain in schizophrenia. *J Clin Psychiatry.* 2002; 63:1045. [PubMed: 12469686]
25. Wu RR, Zhao JP, Guo XF, et al. Metformin addition attenuates olanzapine-induced weight gain in drug-naïve first-episode schizophrenia patients: a double-blind, placebo-controlled study. *Am J Psychiatry.* 2008; 165:352–358. [PubMed: 18245179]
26. Morrison JA, Cottingham EM, Barton BA. Metformin for weight loss in pediatric patients taking psychotropic drugs. *Am J Psychiatry.* 2002; 159:655–657. [PubMed: 11925306]
27. Burris KD, Molski TF, Xu C, et al. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. *J Pharmacol Exp Ther.* 2002; 302:381–389. [PubMed: 12065741]
28. Jordan S, Koprivica V, Chen R, et al. The antipsychotic aripiprazole is a potent, partial agonist at the human 5-HT_{1A} receptor. *Eur J Pharmacol.* 2002; 441:137–140. [PubMed: 12063084]
29. Karunakaran K, Tungaraza TE, Harborne G. Is clozapine-aripiprazole combination a useful regime in the management of treatment-resistant schizophrenia? *J Psychopharmacol.* 2006
30. Henderson DC, Kunkel L, Nguyen DD, et al. An exploratory open-label trial of aripiprazole as an adjuvant to clozapine therapy in chronic schizophrenia. *Acta Psychiatr Scand.* 2006; 113:142–147. [PubMed: 16423166]
31. Levine J, Schooler N. SAFETEE: a technique for the systematic assessment of side effects in clinical trials. *Psychopharmacology Bulletin.* 1986; 22:343–346. [PubMed: 3774930]
32. Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. accelerometer. *Med Sci Sports Exerc.* 1998; 30:777–781. [PubMed: 9588623]
33. Swartz AM, Strath SJ, Bassett DR, et al. Estimation of energy expenditure using CSA accelerometers at hip and wrist sites. *Med Sci Sports Exerc.* 2000; 32:S450–S456. [PubMed: 10993414]
34. McNamara JR, Schaefer EJ. Automated enzymatic standardized lipid analyses for plasma and lipoprotein fractions. *Clin Chim Acta.* 1987; 166:1–8. [PubMed: 3608193]
35. Kulkarni KR. Cholesterol profile measurement by vertical auto profile method. *Clin Lab Med.* 2006; 26:787–802. [PubMed: 17110240]
36. Kissebah A, Videlund N, Murry R, et al. Relationship of body fat distribution to metabolic complications of obesity. *J Clin Endocrinol Metab.* 1982; 54:254–260. [PubMed: 7033275]
37. Garg A. Insulin resistance in the pathogenesis of dyslipidemia. *Diabetes Care.* 1996; 19:387–389. [PubMed: 8729169]
38. Karhapää P, Malkki M, Laakso M. Isolated low HDL cholesterol. An insulin-resistant state. *Diabetes.* 1994; 43:411–417. [PubMed: 8314013]
39. Lewis GF, Carpentier A, Adeli K, et al. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. *Endocr Rev.* 2002; 23:201–229. [PubMed: 11943743]
40. Kroeze WK, Hufeisen SJ, Popadak BA, et al. H₁-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmacology.* 2003; 28:519–526. [PubMed: 12629531]
41. Casey DE, Zorn SH. The pharmacology of weight gain with antipsychotics. *J Clin Psychiatry.* 2001; 62(Suppl 7):4–10. [PubMed: 11346195]
42. Zimmermann U, Kraus T, Himmerich H, et al. Epidemiology, implications and mechanisms underlying drug-induced weight gain in psychiatric patients. *J Psychiatr Res.* 2003; 37:193–220. [PubMed: 12650740]
43. Vickers SP, Clifton PG, Dourish CT, et al. Reduced satiating effect of d-fenfluramine in serotonin 5-HT_{2C} receptor mutant mice. *Psychopharmacology (Berl).* 1999; 143:309–314. [PubMed: 10353435]
44. Bickerdike MJ. 5-HT_{2C} receptor agonists as potential drugs for the treatment of obesity. *Curr Top Med Chem.* 2003; 3:885–897. [PubMed: 12678838]

Table 1

Assessment of Metabolic parameters over four weeks of treatment in olanzapine-treated subjects with schizophrenia (N=15).

	Placebo			Aripiprazole			ANCOVA ¹		
	Week 0	Week 4	Changes	Week 0	Week 4	Changes	df	F	P
Weight (lbs)	215.5±37.5	217.7±37.3	2.1±3.3	216.5±37.4	213.5±38.5	-2.9±4.7	1,26	10.5	0.003
Waist Circumference (cm)	113.5±11.4	114.7±10.8	1.2±3.2	113.6±11.3	112.8±11.2	-0.76±2.3	1,26	3.7	0.063
Waist Hip ratio	0.9±0.0	0.9±0.1	0.0±0.0	0.9±0.1	0.9±0.01	0.0±0.0	1,26	0.1	0.747
Body fat (%)	37.9±7.7	39.8±4.8	1.7±6.9	38.1±5.9	37.2±6.3	-0.9±3.9	1,25	2.2	0.149
BMI (kg/m ²)	32.9±4.4	33.2±4.5	0.3±0.5	32.9±4.7	32.5±4.7	-0.4±0.7	1,26	10.4	0.003
Fasting glucose (mg/dL)	110±53	104±41	-7±20	100±17	98±10	-2±13	1,25	0.1	0.704
Fasting serum insulin (µIU/L)	10.8±5.9	12.0±5.4	1.2±3.9	12.5±9.4	10.7±6.4	-1.7±8.6	1,25	1.1	0.297
HOMA-IR ²	2.9±2.2	3.4±2.7	0.3±1.0	3.2±2.9	2.5±1.5	-0.6±2.6	1,24	1.9	0.171
HbA1C ³	5.9±1.2	5.9±1.4	0.04±0.2	5.9±0.9	5.8±0.6	-0.9±0.3	1,24	1.3	0.263
CRP ⁴	4.8±3.2	4.0±2.9	-0.5±1.1	8.5±10.2	4.5±4.5	-4.0±7.0	1,26	3.2	0.087
Triglycerides	173.9±97.0	221.2±134.2	47.6±52.7	199.4±125.2	147.7±61.6	-51.7±78.2	1,25	15.8	0.001
LDL-C	114.2±22.3	117.9±23.7	3.1±15.0	112.7±19.6	112.5±33.5	-0.2±22.2	1,25	0.19	0.665
Lipoprotein A	5.8±2.7	6.2±2.5	.38±1.5	5.9±2.6	5.3±2.5	-.60±2.7	1,26	1.39	0.25
VLDL 1+2	14.4±7.3	17.3±10.0	2.7±4.6	15.0±9.6	13.1±6.2	-1.9±4.7	1,25	7.38	0.012
VLDL 3	17.5±5.9	19.2±8.6	1.84±6.1	17.6±8.1	16.0±5.4	-1.6±3.2	1,25	3.82	0.062
Total VLDL-C	31.5±12.3	36.6±18.1	5.1±9.3	32.6±17.4	29.1±11.4	-3.4±7.2	1,25	7.76	0.010
HDL 2	10.0±3.5	10.3±2.9	0.46±2.1	10.1±4.2	9.3±2.7	-0.8±2.3	1,25	3.29	0.081
HDL3	31.3±5.6	31.1±6.6	0.15±2.6	31.4±6.8	32.6±6.0	1.2±5.8	1,25	0.47	0.495
HDL-C	41.3±8.4	41.4±7.9	0.6±3.0	41.5±10.3	41.9±8.4	0.4±7.2	1,25	0.00	0.999
Total Cholesterol	187±32	196±37	9±22	187±29	184±41	-3±24	1,25	1.66	0.208

Data are mean± SD.

¹ ANCOVA, analysis of covariance.² HOMA-IR, Homeostasis Model of Assessment of Insulin Resistance (Fasting serum insulin ×Fasting plasma glucose/22.5).³ Glycosylated hemoglobin. ⁴ C-reactive Protein