Changes in Metabolic Parameters With Switching to Aripiprazole From Another Second-Generation Antipsychotic: A Retrospective Chart Review

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Objective: This is a retrospective chart review of psychiatric outpatients switched to aripiprazole from another second-generation antipsychotic (SGA) examining whether metabolic parameters improved after the switch.

Method: Twenty-four psychiatric outpatients who had been switched to aripiprazole from another SGA were evaluated. Data were collected from October 6, 2004, until February 25, 2005, through review of medical records. Laboratory values and physical data were extracted to assess levels of fasting blood glucose, triglycerides, total cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL), and weight.

Results: After switching to aripiprazole, total cholesterol was significantly decreased, with a mean (SD) difference of –28.8 (32.1) mg/dL ($p = .001$), and LDL was significantly decreased, with a mean (SD) difference of –20.75 (21.7) mg/dL ($p = .0017$). Weight was also significantly decreased, with a mean (SD) difference of –11.7 (16.6) lb ($p = .003$). There were no significant differences in HDL, triglycerides, or fasting blood glucose. When a subgroup of 15 patients switched from olanzapine to aripiprazole was examined separately, these changes were even more robust. In this subgroup, total cholesterol was significantly decreased, with a mean (SD) difference of –32.0 (35.6) mg/dL ($p = .01$). LDL was significantly decreased, with a mean (SD) difference of –21.6 (24.7) mg/dL ($p = .011$), and weight was significantly decreased, with a mean (SD) difference of –16.7 (14.7) lb ($p < .001$). Changes in total cholesterol, LDL, and HDL were not significantly different between subjects taking lipid-lowering medications and those not taking them.

Conclusion: Psychiatric outpatients switched to aripiprazole from another SGA showed a decrease in weight, total cholesterol, and LDL. Switching to aripiprazole, when clinically indicated, may lead to improvement in metabolic parameters associated with cardiovascular disease.

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Second-generation antipsychotics (SGAs) are effective for the treatment of schizophrenia, with a lower risk of the extrapyramidal side effects and tardive dyskinesia seen with first-generation agents.[1] The efficacy and improved neurologic side effect profile of SGAs has led to widespread use of these agents in psychiatric illnesses, including schizophrenia, schizoaffective disorder, and bipolar disorder. However, mounting evidence indicates an association between SGAs and worsening metabolic parameters, including weight gain, diabetes, and an atherogenic lipid profile.[2] This association is especially concerning since cardiovascular disease ranks with suicide as the 2 most common causes of death in schizophrenia.[3] In addition, the prevalence of cardiovascular disease as a cause of death in patients with schizophrenia is 2 to 3 times that of the general population.[4,5]

The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III)[6] recognizes elevated low-density lipoprotein (LDL) cholesterol as the primary target of coronary heart disease risk modification. The ATP III adds as a secondary target of risk-reduction therapy a constellation of metabolic factors usually referred to as the metabolic syndrome. Characteristics of the metabolic syndrome are defined by the ATP III as "abdominal obesity, atherogenic dyslipidemia (elevated triglyceride, small LDL particles, low HDL [high-density lipoprotein] cholesterol), raised blood pressure, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states."[6(p6)]

A growing body of literature is examining whether there are significant differences among the SGAs in regard to

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their effect on metabolic parameters that have been identified as risk factors for coronary heart disease. A meta-analysis by Allison et al.[7] in 1999 compared weight change associated with first- and second-generation antipsychotics and found that clozapine and olanzapine were associated with the most weight gain. Meyer and Koro[8] reviewed the effects of antipsychotics on serum lipids and found evidence of marked increases in triglycerides for clozapine and olanzapine when compared with conventional antipsychotics or risperidone, with smaller effects on total cholesterol and LDL cholesterol. A consensus statement[9] from the American Diabetes Association (ADA) and the American Psychiatric Association (APA), published in 2004, reviewed the evidence of weight gain, hyperglycemia, and dyslipidemia associated with SGAs. They concluded that the risk for weight gain, dyslipidemia, and hyperglycemia varies among SGAs, with clozapine and olanzapine being associated with "the greatest weight gain and the highest occurrence of diabetes and dyslipidemia."[9] Risperidone and quetiapine were found to have intermediate effects. The newest agents, ziprasidone and aripiprazole, were found to have the least risk. More recently, the National Institute of Mental Health–sponsored Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) found olanzapine to be associated with greater weight gain, increased glucose, and higher occurrences of dyslipidemia than risperidone, quetiapine, or ziprasidone.[10]

There is a paucity of literature examining whether metabolic parameters improve with switching from SGAs associated with more weight gain and dyslipidemia to the newer agents. A study by Kingsbury et al.[11] looked at 37 patients with diagnoses of schizophrenia or schizoaffective disorder switched to ziprasidone from other antipsychotics. They found a significant decrease in LDL ($p < .001$) and a less robust decrease in triglycerides ($p = .018$), with no significant difference in weight or fasting glucose level after 6 weeks. Pigott et al.[12] looked at 310 patients with schizophrenia switched to either aripiprazole or placebo from another antipsychotic in a 26-week, double-blind, randomized trial. They found that switching to aripiprazole led to modest weight loss. Casey et al.[13] looked at 309 patients switched from other antipsychotics to aripiprazole in an 8-week, open-label study and also found modest weight loss.

Aripiprazole, the newest SGA, is a novel molecule that functions as a partial agonist at the D_2 dopamine and 5-HT_{1A} serotonin receptors.[14,15] Aripiprazole has been shown to improve positive and negative symptoms in schizophrenia[16] and has also been approved by the U.S. Food and Drug Administration for the treatment of acute bipolar manic or mixed episodes. We present a retrospective review of medical records of psychiatric outpatients with severe mental disorders who have been switched from another SGA to aripiprazole that was conducted to look for improvement in metabolic parameters. To our knowledge, there are no published studies specifically examining whether metabolic parameters beyond weight gain improve with switching to aripiprazole from another SGA in this population.

METHOD

Strong Ties Community Support Program (STCSP) is an outpatient program of the Department of Psychiatry, University of Rochester Medical Center, Rochester, N.Y., treating over 1000 severely mentally ill adults with antipsychotic medications. STCSP provides comprehensive care to mentally ill adults including general medical and pharmacy services. Consistent with this comprehensive approach, there is increasing vigilance of metabolic parameters and attempts to change medications, when possible, to reduce worsening of these parameters. Consistent with ADA/APA guidelines,[9] ongoing quality-improvement efforts at STCSP include routine monitoring of body weight, fasting lipid profile, and fasting serum glucose.

The University of Rochester Human Subjects Review Board reviewed and approved a chart review of existing quality-improvement data comparing metabolic parameters in patients taking SGAs. It was determined from the database maintained by the Strong Ties Pharmacy how many patients had filled a prescription for aripiprazole over the 2-month period from August 2, 2004, to October 6, 2004. Of those patients who had filled a prescription for aripiprazole, it was determined which patients were taking aripiprazole as their only antipsychotic medication. For those patients, charts were reviewed to determine which patients had been switched from a single SGA as their only antipsychotic medication to aripiprazole as their sole antipsychotic medication. The following data were gathered from subject medical records: age, gender, psychiatric diagnosis, medical diagnosis, concurrent medications, length of exposure to previous SGA, length of exposure to any antipsychotic, and length of cross taper. In addition, physical assessment and laboratory data were collected from the medical records, including weight and levels of fasting blood glucose (FBG), serum total cholesterol, triglycerides, HDL, and LDL. Data were recorded from the time of initiation of aripiprazole and again approximately 6 months after completion of the cross taper. These data were collected by chart review by one of the authors (R.D.S.) from October 6, 2004, until February 25, 2005. Pretreatment and posttreatment measurements were then analyzed for each of the metabolic parameters abstracted from the medical records as a means of looking for significant differences associated with changing from another SGA to aripiprazole.

Data analysis was conducted using SAS, version 8.2 (SAS Institute, Inc., Cary, N.C.). The following variables were examined on study subjects before and after the

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initiation of aripiprazole: weight, total cholesterol, triglycerides, HDL, LDL, and FBG. To determine if the mean value of the change scores of each of these continuous variables from pretreatment to posttreatment is different from 0, paired t tests were performed on the pretreatment and posttreatment data. For weight, a t test was also performed on the ratios of posttreatment and pretreatment values to determine whether its mean value is different from 1. Indicator variables were used to examine the effect of prior and current medication. A t test was performed to determine if there is a difference in the change scores between the subjects with olanzapine as a prior medication and those without olanzapine. A t test was performed to see if there is a difference in change scores between the subjects taking cholesterol-lowering medication versus those not taking cholesterol medication. A t test was also performed to look for differences between subjects taking oral hypoglycemic medication versus those not taking oral hypoglycemics. Multiple t tests were used instead of analysis of variance due to overlaps among the medication groups. Also, given the rather small sample size, interaction of the different medications may not be detectable. For this reason, we used simple comparison for marginal effects. All tests performed were 2-sided, with significance level $\alpha = .05$, unless noted otherwise.

RESULTS

There were 133 individuals who filled a prescription for aripiprazole at the Strong Ties Pharmacy during the 2-month study period. At the time of chart review, 29 individuals (22%) were now off aripiprazole, and 4 (3%) were noncompliant with follow-up. Of the remaining 100 individuals, 56 were receiving another antipsychotic in addition to aripiprazole. Of the 44 individuals on aripiprazole monotherapy, only the 28 who were taking a single, known SGA prior to switching to aripiprazole were considered for data analysis. Of those, 24 had laboratory and physical assessment data recorded in the medical record, allowing comparison prior to and after switching to aripiprazole. Data from these 24 patients were used for statistical analysis. Pretreatment and posttreatment weight data were available for 23 of these patients. Nineteen patients had pretreatment and posttreatment data for total cholesterol and triglycerides. Eighteen had data for HDL and FBG, and 16 patients had data for LDL.

Mean (SD) age was 44.6 (9.1) years, and 16 (67%) of 24 patients were male. Nineteen (79%) of 24 were white. Nine patients (38%) had a primary diagnosis of schizophrenia, 6 (25%) had a diagnosis of schizoaffective disorder, 5 (21%) had a diagnosis of bipolar disorder, 3 (13%) had a diagnosis of major depressive disorder with psychosis, and 1 (4%) had a diagnosis of dysthymia. Fifteen (63%) of the patients had been switched from olanzapine, 6 (25%) had been switched from risperidone, and 3 (13%) had been switched from quetiapine. Ten (42%) of the 24 patients were taking a lipid-lowering agent, and with none of these patients was the lipid-lowering agent started, changed, or increased in dose during the period of SGA crossover. Five (21%) of the 24 were taking an oral hypoglycemic agent. Many of the patients were taking other psychotropic medications in addition to an SGA. Eleven (46%) of the 24 were also taking an antidepressant, 6 (25%) of 24 were taking a mood stabilizer, and 7 (29%) of 24 were taking a benzodiazepine.

For the whole sample of 24 subjects, total cholesterol was significantly decreased, with a mean (SD) difference of –28.8 (32.1) mg/dL ($p = .001$) when comparing values before and after switching to aripiprazole. LDL was significantly decreased, with a mean (SD) difference of –20.75 (21.7) mg/dL ($p = .0017$). Weight was significantly decreased, with a mean (SD) difference of –11.7 (16.6) lb ($p = .003$). There were no significant differences in HDL, triglycerides, or FBG. Patients treated with a cholesterol-lowering agent did not differ significantly from those not taking a cholesterol-lowering agent in total cholesterol ($p = .590$), HDL ($p = .502$), or LDL ($p = .801$). Patients treated with glucose-lowering agents did not differ significantly from those not taking a hypoglycemic agent in FBG ($p = .373$). When the 15 patients switched from olanzapine to aripiprazole were examined separately, total cholesterol was significantly decreased, with a mean (SD) difference of –32.0 (35.6) mg/dL ($p = .01$); LDL was significantly decreased, with a mean (SD) difference of –21.6 (24.7) mg/dL ($p = .011$); and weight was significantly decreased, with a mean (SD) difference of –16.7 (14.7) lb ($p < .001$) when comparing values before and after switching to aripiprazole. For the subgroup of 9 patients switched from risperidone or quetiapine to aripiprazole, LDL was significantly decreased, with a mean (SD) difference of –18.25 (10.8) mg/dL ($p = .043$). There were no significant differences in total cholesterol, HDL, triglycerides, FBG, or weight for patients switched from risperidone or quetiapine to aripiprazole.

DISCUSSION

In this naturalistic, retrospective study, the 24 patients switched from a single SGA to aripiprazole did have significant decreases in weight and levels of total cholesterol and LDL. When those patients switched from olanzapine to aripiprazole were looked at separately, these same improvements in weight, total cholesterol, and LDL remained. The small sample size of the quetiapine and risperidone group may explain the lack of significant differences in total cholesterol and weight in patients switched from these agents to aripiprazole. Our findings of improvement in weight, total cholesterol, and LDL when

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switching from olanzapine to aripiprazole are consistent with findings from a 26-week randomized controlled trial by McQuade et al.[17] comparing metabolic changes in patients diagnosed with schizophrenia who were treated with either olanzapine or aripiprazole.

It is unclear why we did not find a difference in triglycerides with switching to aripiprazole since changes in triglycerides have been found to be more marked than changes in total cholesterol or LDL fraction in other studies.[8] It may be that the patients in our population who had an increase in triglycerides with a previous SGA had already been switched to another agent or placed on lipid-lowering therapy. The 10 patients who were taking lipid-lowering medications were analyzed separately to see if this could account for the differences seen in our review. There were no significant differences in changes in total cholesterol, LDL, or HDL between subjects taking lipid-lowering medications and subjects not taking these medications.

In the present study, a large proportion (22%) of outpatients who were identified as having filled a prescription for aripiprazole was no longer taking the medication. This fact may reflect difficulty with tolerating the medication, lack of efficacy, or, more generally, the severity of illness in this particular patient population. A similarly high discontinuation rate was seen in the CATIE study, in which olanzapine was noted to be the most effective medication in phase 1 of the study.[10] The level of acuity of illness and history of illness refractory to medications, which was not examined in this study, may have influenced the success of aripiprazole. A large proportion of the outpatients who had remained taking aripiprazole was also taking another antipsychotic agent (56%). Our review was not designed to look at reasons for concurrent treatment with more than 1 antipsychotic. We speculate that there were multiple causes, including extended cross tapering of medications, failure to tolerate tapering of the previous antipsychotic, and patients who were clinically improved on a combination of antipsychotic medications.

Our study is a retrospective chart review and has a number of limitations that should be noted. The study lacks a control group. While the measurements of lipid profile and blood glucose were intended to be fasting values, they were not collected in a uniform manner and may not reflect true fasting values. Due to the nature of the study, we were unable to evaluate subjects' level of compliance. Research suggests that compliance in standard clinical settings can be low.[18] The length of time of crossover from the previous SGA to aripiprazole monotherapy varied, as well as the length of treatment with the previous SGA, which could increase the variance in our measurements. Our small sample size also reduces the likelihood of finding significant differences in metabolic parameters. Several patients were also taking other psychotropic medications, including antidepressants, mood stabilizers, and benzodiazepines. These concurrent medications may also affect weight and associated metabolic parameters.

Despite the limitations of our study, the improvements in weight, total cholesterol, and LDL cholesterol seen with switching to aripiprazole from another SGA add to a small but growing body of literature suggesting that metabolic parameters associated with coronary heart disease are improved with switching to aripiprazole.

Drug names: aripiprazole (Abilify), clozapine (FazaClo, Clozaril, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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