Changes in Weight and other Metabolic Indicators in Persons with Schizophrenia Following a Switch to Aripiprazole

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Abstract

For patients who gain a troublesome amount of weight on antipsychotics, switching to a less obesogenic agent is an option. Aripiprazole appears to cause less weight gain than many other antipsychotics. We report on changes in weight, and other risk factors for heart disease, in thirty-three schizophrenia patients who agreed to switch from other antipsychotics to aripiprazole in an open, flexible-dose, eight-week trial. All patients were successfully switched. There were no significant changes in PANSS symptom scores or in CGI. Weight (Wt), waist circumference (WC), and low-density lipoprotein (LDL) decreased significantly in the group as a whole. In patients switched from olanzapine to aripiprazole, Wt, WC, LDL, fasting glucose, and triglycerides were significantly decreased as compared to baseline. Substantial decreases in several risk factors were also seen in patients switched from quetiapine, but these changes did not reach statistical significance.

Key Words: Schizophrenia, Obesity, Metabolic Syndrome, Aripiprazole, Olanzapine, Medication Switching, Cardiovascular Disease, Antipsychotics, Glucose, Weight Loss

Introduction

Aripiprazole is a new antipsychotic medication with a mechanism of action involving partial dopamine antagonism at the D2 receptor and low affinity for histamine H1 receptors (1). Aripiprazole has been shown to have similar efficacy to older antipsychotics and some novel agents in the treatment of schizophrenia (2-4). As compared to agents like olanzapine, aripiprazole also appears to be associated with less weight gain (5). There are case reports of weight loss in patients who were switched to aripiprazole from other antipsychotic medications. A multi-center, randomized clinical trial of patients switched to aripiprazole (6) was not designed to study changes in metabolic parameters, but did find mean decreases in weight (although it is not reported if these were statistically significant). In a recent controlled clinical trial of patients randomly assigned to either olanzapine or aripiprazole (7), there was mean weight loss in the subjects assigned to aripiprazole and mean weight gain in subjects assigned to olanzapine. It is likely that the low affinity of aripiprazole for histamine H1 receptors might account for its relatively low risk of causing weight gain. Recent reviews have suggested that, in patients who have experienced troublesome weight gain on other antipsychotics, a switch to aripiprazole might be considered (8).

However, much of the published data on aripiprazole comes from Phase 3 studies, or other strictly controlled

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Clinical Implications

We believe that many patients experiencing weight gain on other drugs can be safely switched to aripiprazole. Most of these patients, especially if they are currently taking olanzapine or quetiapine, are likely to experience beneficial reductions in weight and related metabolic factors associated with the risk of cardiovascular disease. The limitations of this study are that there was no control group and that the subjects were not randomly selected for switching. Our study was also relatively short, but longer trials have found that, even over one year, aripiprazole had equivalent efficacy to olanzapine, but less weight gain and less adverse metabolic changes (17). Notwithstanding these limitations, we believe that the broad inclusion criteria did allow us to present the results of switching in patients who are common in clinical practice, but who might have been excluded from earlier randomized clinical trials. Hence, these results may provide useful additional data for clinicians.

clinical trials, aimed at establishing efficacy and approval from regulatory bodies. Clinicians are often also looking for data from "real world" studies with broad inclusion criteria to verify the effectiveness of new medications in more representative clinical populations. Given that obesity and comorbid metabolic problems such as dyslipidemias, diabetes, and hypertension are considerably more common in schizophrenia patients than in the general population, we were interested in studying the effects of switching patients who were overweight or obese and who were taking other antipsychotic medications. Such switching is actually common in clinical practice, but there is still a paucity of systematically collected data on the metabolic benefits, if any, of such clinical strategies. One earlier retrospective chart review, of twenty-four subjects, found decreases in weight, cholesterol, and LDL after patients were switched to aripiprazole (Spurling et al. [9]). Surprisingly, Spurling et al. (9) did not find significant decreases in triglycerides after the switch. The authors of this study also noted the limitations of their retrospective and chart review design. We, therefore, conducted this prospective study involving outpatients with schizophrenia, who were overweight or obese, and who were concerned about the health risks associated with obesity. We chose to conduct an open trial in order to minimize the obstacles to participation from both subjects and clinicians.

Methods

Thirty-six individuals who were in outpatient treatment at a large, urban psychiatric hospital were recruited. All subjects were referred by their treating clinicians who had been made aware of the study by presentations by the investigators and IRB-approved flyers posted in the clinic. There was no "cold calling" of potential subjects by the investigators nor their staff. All referred subjects participated in an informed consent discussion with research staff, and signed a consent document, which had been approved by the University of Pittsburgh Biomedical Institutional Review Board. Inclusion criteria were intentionally broad so as to include subjects who were broadly representative of the clinic population from which they were drawn. Since the focus of the study was on the potential for weight loss after switching, a minimum body mass index (BMI) of 26 was required to be eligible for the study, ensuring that, were weight loss to occur, the patient ran little risk of becoming underweight. We included subjects of both genders, between the ages of 18 and 65 years, with a *DSM-IV* diagnosis of schizophrenia or schizoaffective disorder (as determined by the Structured Clinical Interview for DSM Disorders [SCID]). Patients were eligible if their Positive and Negative Syndrome Scale (PANSS) score on screening was between 60 and 90, which we chose so as to include only mild to moderately ill subjects. Female subjects with childbearing potential were required to agree to use medically accepted methods of contraception while in the study. Subjects were eligible if they were on one antipsychotic (novel or conventional), other than aripiprazole or clozapine, and all doses of psychotropic medication were required to have been stable for thirty days prior to screening for research participation. Persons who met criteria for mental retardation, those who could not give informed consent, and those with serious or unstable medical illnesses, were ineligible to participate.

The study lasted for eight weeks for each subject, following a screening visit. Once enrolled, the subjects were cross titrated from their current antipsychotic medication to aripiprazole by one of the study psychiatrists (R. Ganguli, R. Basu, or R. Garbut). The study protocol recommended that the cross titration be completed over the initial two weeks, but the treating psychiatrist was allowed to extend the titration period if he felt it was clinically indicated. The initial daily dose was 15 mg, and this could be increased up to 30 mg per day, or reduced if the patient experienced discomfort with the starting dose. In order to preserve the naturalistic design of the study, the treating psychiatrist who saw the patient weekly for the first four weeks had discretion with regard to the speed of dose increases and of the final dose. Clinical symptoms were assessed using the PANSS (10) at baseline, at week 4 (midpoint), and at week 8 (study termination). Weight, serum lipids, fasting blood sugar, and blood pressure were recorded at baseline and at study termination.

The change in each measure was created by subtracting the value at week 8 from the value at the baseline. In some analyses, weight loss was also treated as a dichotomous variable (1=yes, 0=no) that took a value of 1 if the weight at week 8 was less than that at baseline and took a value of 0 otherwise.

Nonparametric Wilcoxon rank-sum test was used to assess the relationship between weight loss (yes/no) and the metabolic parameters measured at baseline. Spearman's correlation coefficient was used to assess the relationship between change in weight and change in other metabolic parameters. Nonparametric signed-rank test was used to test the difference in changes in metabolic parameters from baseline to week 8.

Results

Thirty-six patients currently taking antipsychotics other than aripiprazole consented to participate. Three subjects changed their minds and withdrew consent prior to any change in medication, and they have been excluded from the analysis. Another three subjects withdrew prior to completion of the full eight-week study; their last weights and other measures have been used in the analysis. Demographics of all consenting subjects are shown in Table 1. All of the patients who started the study were successfully switched to aripiprazole. Of the 33 subjects, 20 (61%) lost weight after they were switched to aripiprazole. The mean change in weight (lb)± standard deviation (SD) for the whole group was -4.8lb±8.1 (p=0.005). The distribution of weight changes in subjects is shown in Figure 1. For the metabolic parameters, the changes are shown in Table 2. While there were decreases in all parameters, only the decreases in weight, waist circumference, and LDL reached statistical significance. Change in weight was significantly correlated with change in waist circumference (Spearman's correlation 0.55, p=0.0018) and with change in LDL (Spearman's correlation 0.64, p=0.001). There were no significant changes in PANSS scores.

Table 1 Sample Demographics

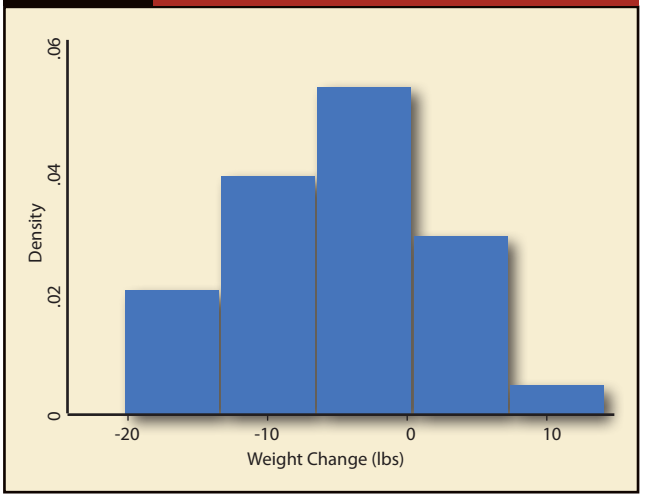
Age (±SD)	47.8 (±8.8)
Gender	**N (%)**
Men	10 (28)
Women	26 (72)
Ethnicity	**N (%)**
African American	24 (66)
Caucasian	11 (31)
Asian	1 (3)

Table 2 Changes in Metabolic Parameters 8 Weeks after Switching to Aripiprazole

Metabolic Parameter	Mean±SD	P-Value*
Weight (lb)	-4.8±8.1	0.005
Waist Circumference (inches)	-1.3±2.8	0.004
Fasting Glucose (mg/dL)	-4.0±29.6	0.19
LDL (mg/dL)	-17.3±19.4	0.001
HDL (mg/dL)	-1.7±18.9	0.46
Triglycerides (mg/dL)	-51.4±161.8	0.19

*Signed-rank test for the significant change from baseline to endpoint

Figure 1 Distribution of Changes in Weight after Switching to Aripiprazole



We examined the weight loss after switching, based on the previous antipsychotic which was prescribed. The results are presented in Table 3. In patients switched from olanzapine, there were statistically significant reductions in weight, waist circumference, LDL, triglycerides, and glucose. There were also quite large mean decreases in triglycerides and weight, following the switch from quetiapine, but these changes failed to reach statistical significance.

Discussion

With respect to weight, our results indicate that there is a high probability that obese or overweight patients taking other antipsychotic medications will lose weight and decrease their waist circumference if switched to aripiprazole. For the group as a whole, there were beneficial changes in several other metabolic parameters, but only the decreases in weight, waist circumference, and LDL reached statistical significance. However, it is possible that most, or all, of the

Table 3 Changes in Metabolic Parameters Based on Prior Antipsychotic

Prior Antipsychotic	Weight (lb)	Fasting Glucose (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	Triglyceride (mg/dL)
Olanzapine (n=11)	-9.6*	-25.5*	-31.9*	-9.1	-99.0*
Quetiapine (n=10)	-6.14	5.5	-8.5	7.6	-86.8
Risperidone (n=6)	-1.17	-2.17	-18.8	3.5	15.7
Haloperidol (n=3)	0.67	11.5	-2.5	-11.7	-29.0
Ziprasidone (n=2)	-1.5	13.5	-10.0	-7.0	33.0
Perphenazine (n=1)	14.0	-11.0	-3.0	7.0	-4.0

*p≤.05 for the signed-rank test of the significant change from baseline to week 9

changes might have been statistically significant if the sample had been larger. The weight loss was most pronounced when the person has been previously taking olanzapine or quetiapine. The changes in lipids were generally consistent with changes in weight for patients switched from olanzapine. In fact, the mean reduction in triglycerides for patients previously on olanzapine was 99, and for those previously on quetiapine it was 86, eight weeks after the switch to aripiprazole. Five of the subjects who started the study with triglycerides above the normal range (150 mg/dL for our laboratory) had normal serum triglycerides by the end of the study.

We had three subjects on haloperidol, two on ziprasidone, and only one subject on perphenazine. It would be unwise to draw any conclusions from the outcome with these subjects due to the small number of subjects and wide range of results between subjects.

There have been recent reports of normalizing of raised prolactin levels (11) and of relief of sexual dysfunction (12) following switch to aripiprazole. Unfortunately we did not measure prolactin in our sample or use any specific scales to elicit sexual dysfunction.

It is important to point out that switching to aripiprazole might not be the best option for all patients. There is no evidence that aripiprazole is especially effective in patients who have not responded to adequate trials of other antipsychotics; hence, clozapine, despite its adverse metabolic profile, might be the best choice for nonresponders. Practitioners might also find that an individual patient might do better on olanzapine than on the alternatives. It is, therefore, important to draw attention to the growing evidence from controlled clinical trials for the efficacy of dietary and behavioral techniques for inducing weight loss in individuals with schizophrenia; these should be recommended to patients and their caregivers to help mitigate the metabolic consequences of treatment when switching medications is not a good option (13-16).

The limitations of this study are that there was no control group and that the subjects were not randomly selected for switching. Our study was also relatively short, but longer trials have found that, even over one year, aripiprazole had equivalent efficacy to olanzapine, but less weight gain and less adverse metabolic changes (17). Notwithstanding these limitations, we believe that the broad inclusion criteria did allow us to present the results of switching in patients who are common in clinical practice, but who might have been excluded from earlier randomized clinical trials. Hence, these results may provide useful additional data for clinicians.

In conclusion, we believe that many patients experiencing weight gain on other drugs can be safely switched to aripiprazole. Most of these patients, especially if they are currently taking olanzapine or quetiapine, are likely to experience beneficial reductions in weight and related metabolic factors associated with the risk of cardiovascular disease.

Disclosures

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