

Effects of switching from olanzapine to aripiprazole on the metabolic profiles of patients with schizophrenia and metabolic syndrome: a double-blind, randomized, open-label study

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Background: Patients with schizophrenia suffer high rates of metabolic derangements on some antipsychotic medications that predispose them to cardiovascular diseases. Keeping this fact in mind, we planned this open-label study to see the effect on various metabolic parameters after switching stable schizophrenia subjects, who had developed metabolic syndrome on olanzapine, to aripiprazole.

Methods: Sixty-two patients with schizophrenia who were stable on olanzapine and were fulfilling modified National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III) criteria for the presence of metabolic syndrome were enrolled on the study. Patients were randomly assigned either to switch to aripiprazole or to stay on olanzapine, on a 1:1 basis. Cross-tapering over a period of 1 month was done while switching patients to aripiprazole. Laboratory assessment for metabolic parameters was done at baseline, 8 weeks, and 24 weeks after enrollment; efficacy assessment was done using the Positive and Negative Syndrome Scale (PANSS) at baseline and 24 weeks, the Clinical Global Impressions severity subscale (CGI-S) at baseline, and the Clinical Global Impressions improvement subscale (CGI-I) at 24 weeks.

Results: All parameters of metabolic syndrome (waist circumference, blood pressure, triglyceride level, fasting blood glucose, and high-density lipoprotein cholesterol) kept deteriorating in the stay group, compared with a continuous improvement in the switch group over time. At the end of the study, 26 patients (100%) from the stay group and 15 patients (42.8%) from switch group met the modified NCEP ATP-III criteria for presence of metabolic syndrome ($P < 0.001$). There were no statistically significant differences between groups in psychopathology changes as measured by the PANSS total score and CGI-I scores.

Conclusion: Clinically stable patients with schizophrenia who are taking olanzapine and who have evidence of metabolic syndrome can be successfully switched to aripiprazole, with improvement in various parameters of metabolic syndrome and without any significant change in efficacy measures.

Keywords: metabolic syndrome, olanzapine, aripiprazole, schizophrenia, switching

Introduction

Metabolic syndrome is a complex disorder comprising a set of cardiovascular risk factors, including obesity, dyslipidemia, deranged glucose metabolism, insulin insensitivity, and hypertension.¹ The clinical significance of metabolic syndrome comes from the fact that it is associated with development of coronary heart disease, cerebrovascular disease, and type 2 diabetes mellitus. Studies show that metabolic syndrome is associated with twofold to threefold increased risk of cardiovascular morbidity.²



Metabolic syndrome is seen more frequently in persons with schizophrenia than in the general population.^{3–5} While it is possible that genetic factors play a role in the increased risk seen in such patients, it is likely that lifestyle issues such as poor nutrition and reduced exercise habits also play a key role. These metabolic abnormalities are further aggravated by antipsychotic medications. The first-generation antipsychotic medications are effective in treating positive symptoms but are not similarly effective for negative and cognitive symptoms; they are also less protective against relapses in the long-term.⁶ In addition, extrapyramidal symptoms are more commonly seen in patients treated with first-generation antipsychotic medications.⁷ In recent years, atypical antipsychotics, or second-generation antipsychotic medications, have been replacing first-generation antipsychotic medications as firstline treatment for schizophrenia with equal efficacy and fewer extrapyramidal side effects, and have thus ensured a better quality of life for the patient.^{8–11} However, other adverse effects, including weight gain, metabolic syndrome, and cardiovascular side effects, have been found after long-term use of some second-generation antipsychotic medications.¹²

Second-generation antipsychotic medications can cause clinically significant weight gain, leading to insulin resistance and type 2 diabetes mellitus, and are thus a major risk factor for the development of metabolic syndrome.¹³ A review of absolute weight gain in various placebo-controlled trials and head-to-head comparisons found that the magnitude of weight gain was not equal among antipsychotic medications.¹² Maximum weight gain was seen with olanzapine treatment, while it was least with aripiprazole and ziprasidone. Olanzapine was associated with a mean weight gain of >6 kg over 1 year,^{14,15} whereas aripiprazole^{16–19} and ziprasidone^{20–22} were associated with a mean weight gain of about 1 kg over 1 year. Aripiprazole has a unique mechanism of action among second-generation antipsychotic medications: it is a partial agonist at D2 dopamine and 5-HT_{1A} serotonin receptors and an antagonist at 5-HT_{2A} serotonin receptors.²³ It has the least chance of inducing weight gain and other metabolic side effects²⁴ and is safe and effective during both the acute and maintenance phases of schizophrenia.^{19,25,26}

Switching antipsychotic medications in the treatment of schizophrenia is a common practice in clinical psychiatry.²⁷ Weight gain and metabolic syndrome are the two main reasons for switching antipsychotics.²⁸ It has been suggested that the ideal drugs for switching are aripiprazole or ziprasidone, with their low risk for metabolic syndrome.²⁹ We in our study chose aripiprazole because it was the newer option available

and we expected it would be of most clinical interest when the study was completed. We hypothesized that switching to aripiprazole would result in an improvement in metabolic measures, compared with staying on olanzapine. We were also interested in determining if switching to aripiprazole would be accompanied by any clinical destabilization. Earlier, Fleischhacker et al³⁰ in their study comparing the efficacy and tolerability of aripiprazole with olanzapine in patients with schizophrenia found that olanzapine had a statistically significant efficacy advantage over aripiprazole, with more reduction in Positive and Negative Syndrome Scale (PANSS) total score. Pae et al³¹ found that patients switched to aripiprazole, with sudden discontinuation of the previous antipsychotic medication, showed an increase in symptom severity during first week of switching. Moreover, few studies have been done in this field,^{32,33} and none has been from our Kashmir region.

Methods

Settings and subjects

The study was carried out at the outpatient unit of a tertiary care psychiatry hospital in North India (Kashmir) from June 2011 to May 2014, after seeking permission from the IEC of the government medical college, Srinagar. Participants were individuals with schizophrenia who had achieved clinical stability with olanzapine and who were assessed as having metabolic syndrome using modified National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III) criteria.^{34,35} Schizophrenia diagnoses were made using the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Text Revision.³⁶ The patients were required to be on olanzapine for a minimum of 3 months without any other antipsychotic medication for 1 month prior to enrollment. The patients entered the study in order to improve their metabolic risk profile. Informed consent was obtained from each patient after fully explaining the study procedures.

Patients were randomly assigned either to switch to aripiprazole or to stay on olanzapine, on a 1:1 basis. Individuals assigned to stay on olanzapine remained on their prestudy dosage, with adjustments only as clinically indicated. Olanzapine was used in a dose range of 10–20 mg/day. Patients assigned to switch to aripiprazole began taking aripiprazole 5 mg/day while continuing olanzapine without dose reduction for 1 week. After 1 week, the aripiprazole dosage was increased to 10 mg/day and the dose of olanzapine was reduced 25%–50%. After 2 weeks, the aripiprazole dosage could be increased to 15 mg/day while the dose of olanzapine was reduced 50%–75% from the original dosage.

After 3 weeks, the available range for aripiprazole was 10–20 mg/day, and olanzapine was stopped. After 4 weeks, aripiprazole was used in a dose range of 10–30 mg/day.

Patients were followed on a weekly basis during the first month of the treatment period and every 4 weeks thereafter; laboratory assessment was carried out at baseline, 8 weeks, and 24 weeks after enrollment. PANSS was used at baseline and 24 weeks, while the Clinical Global Impressions severity subscale (CGI-S) was used at baseline and the Clinical Global Impressions improvement subscale (CGI-I) was used at 24 weeks.

The addition of lithium, valproate, statins, or drugs prescribed for weight loss was not allowed during the study. Those who were taking these medications during the prestudy phase were allowed to continue without dose adjustments. All other medications except for nonstudy antipsychotic drugs were allowed.

Assessment

The waist circumference was measured in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest. The measurements were taken thrice and the mean was computed in all cases. Systolic and diastolic blood pressure were measured twice at an interval of 3 minutes in the sitting position after a 15-minute rest, and the mean was computed. Blood samples (3 mL) were drawn after 8–12 hours of overnight fasting for the measurement of high-density lipoprotein (HDL) cholesterol, triglycerides, and fasting plasma glucose levels. Plasma glucose was measured using the glucose oxidase–peroxidase method, triglycerides by standard enzymatic procedures, and HDL cholesterol by direct assay method.

Metabolic syndrome was diagnosed using modified NCEP ATP-III criteria for the Asian population.³⁵ Diagnosis was made when three or more of the following conditions were met:

- 1) Waist circumference >90 cm for males and >80 cm for females;
- 2) Triglycerides >150 mg/dL;
- 3) HDL levels <40 mg/dL for males and <50 mg/dL for females;
- 4) Systolic blood pressure \geq 130 mmHg and/or diastolic blood pressure \geq 85 mmHg;
- 5) Fasting glucose \geq 110 mg/dL.

A previous diagnosis of high blood pressure was considered sufficient to fulfill criterion 4 and a previous diagnosis of diabetes mellitus was considered as sufficient to fulfill criterion 5.

Assessment for any clinical destabilization was done using the PANSS and CGI scales. Efficacy failure was defined by psychiatric hospitalization, a 25% increase in the total PANSS score,³⁷ or ratings of much worse or very much worse on the CGI improvement subscale.³⁸

Statistical analysis

Data were entered into a Microsoft Excel spreadsheet. Continuous variables were summarized as mean and standard deviation. Categorical variables were summarized as percentages. CGI-I and CGI-S were summarized as median and interquartile range. Repeated-measures analysis of variance was used to analyze the difference in the values of a continuous variable over time. Comparisons between stay and switch groups were analyzed using independent samples Student's *t*-test for continuous variables, Chi-square test for categorical variables, Fisher's exact test for categorical variables when the Chi-square test did not meet Cochran criterion,³⁹ and Mann–Whitney test for ordinal variables (CGI-I and CGI-S). The proportion of metabolic syndrome across time was tested using the Cochran *Q*-test. A *P*-value of <0.05 was taken as significant.

Results

Our sample consisted of 62 patients who were randomly assigned to one of two groups, either the stay group (*n*=31) or the switch group (*n*=31). The distribution of other (nonstudy) allowed medications among the two groups was statistically insignificant and included lithium (*P*>0.999), sodium valproate (*P*>0.999), carbamazepine (*P*>0.999), lamotrigine (*P*>0.999), selective serotonin reuptake inhibitors (*P*>0.999), benzodiazepines (*P*=0.554), and beta blockers (*P*=0.011). The progression of the two groups through the study is shown in Figure 1. Ten patients (32.2%) from the switch group and five (16.1%) from the stay group discontinued the treatment before the final assessment at 24 weeks (*P*=0.138). Table 1 summarizes the sociodemographic characteristics of the participants. Table 2 shows both intergroup and within-group trends in various metabolic and clinical variables. Last observation carried forward was employed for data imputation. Among the various parameters of metabolic syndrome, waist circumference, blood pressure, triglyceride level, and fasting blood glucose kept increasing in the stay group, while HDL level showed a decreasing trend. In the switch group, waist circumference, blood pressure, triglyceride level, and fasting blood glucose kept decreasing, while HDL level increased with time.

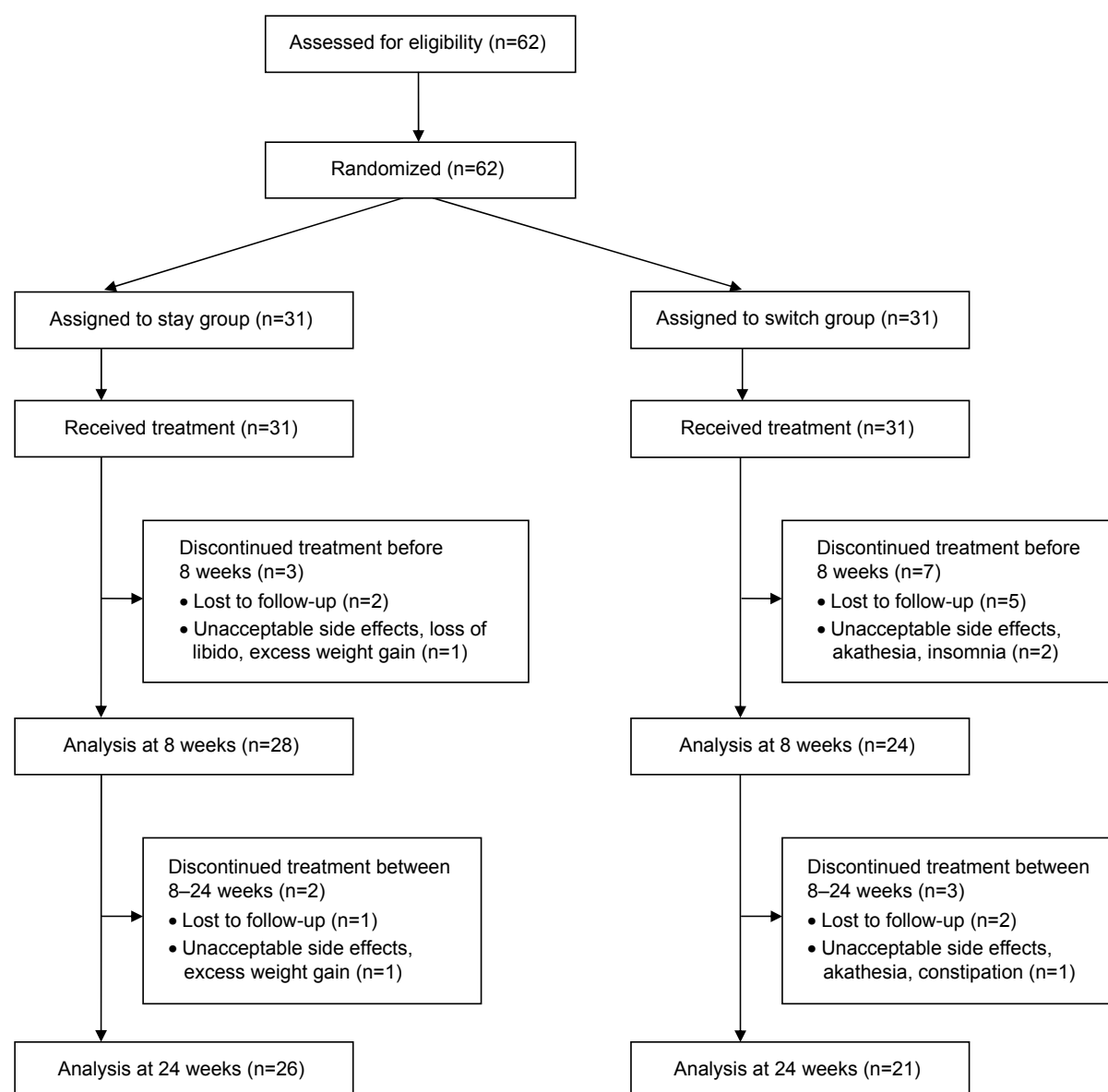


Figure 1 Patient enrollment and follow up in the study.

Table 1 Sociodemographic profiles of two groups

Characteristics	Stay group (n=31)	Switch group (n=31)	P-value
Age in years, mean (SD)	29.84 (5.241)	29.71 (5.001)	0.921 *
Duration of illness in years, mean (SD)	4.8 (3.2)	4.7 (3.4)	>0.999*
Sex, n (%)			
Male	20 (64.5)	19 (61.3)	0.793**
Female	11 (35.5)	12 (38.7)	
Marital status, n (%)			
Married	4 (12.9)	5 (16.1)	>0.999***
Divorced	3 (9.7)	3 (9.7)	
Unmarried	24 (77.4)	23 (74.2)	
Education, n (%)			
Matriculation and above	12 (38.7)	16 (51.6)	0.307**
Under matriculation	19 (61.3)	15 (48.4)	

Notes: *Student's *t*-test. **Pearson Chi-square. ***Fisher's exact test.

Abbreviations: n, number; SD, standard deviation.

Table 2 Metabolic and clinical characteristics of stay group versus switch group

Variables	Week 0		Week 8		Week 24		P-value (within group)**	
	Stay group	Switch group	Stay group	Switch group	Stay group	Switch group	Stay group	Switch group
Waist circumference								
Mean	92.71	90.26	93.71	89.32	96.58	88.23	<0.001	0.001
SD	8.443	10.076	8.017	9.325	7.544	9.215		
P-value	0.303		0.052		<0.001		–	–
(between groups)*								
Systolic blood pressure								
Mean	126.39	127.71	127.06	127.23	129.32	126.71	0.003	0.288
SD	10.544	11.533	11.072	11.236	10.694	10.848		
P-value	0.639		0.955		0.343		–	–
(between groups)*								
Diastolic blood pressure								
Mean	84.32	87.81	85.23	86.77	86.77	86.77	0.003	0.470
SD	9.239	12.462	8.819	11.555	7.911	10.592		
P-value	0.216		0.556		1.000		–	–
(between groups)*								
Fasting blood sugar								
Mean	110.81	118.32	114.23	114.52	118.32	112.26	<0.001	0.001
SD	12.677	16.388	11.724	15.423	11.828	15.044		
P-value	0.048		0.934		0.083		–	–
(between groups)*								
Triglycerides								
Mean	192.19	194.32	207.26	202.74	223.61	196.35	<0.001	0.176
SD	47.002	24.597	75.198	43.353	72.894	44.459		
P-value	0.824		0.773		0.082		–	–
(between groups)*								
HDL								
Mean	41.23	39.68	39.58	41.87	38.03	43.90	<0.001	<0.001
SD	9.124	7.704	8.835	6.937	8.175	7.730		
P-value	0.473		0.261		0.005		–	–
(between groups)*								
PANSS								
Mean	68.58	69.13	–	–	67.61	67.74	0.001	0.002
SD	4.485	5.214	–	–	4.318	4.719		
P-value	0.659		–		0.911		–	–
(between groups)*								
CGI-S								
Median	4	4	–	–	–	–	–	–
IQR	3–4	3–4	–	–	–	–	–	–
P-value	0.602		–		–		–	–
(between groups)***								
CGI-I								
Median	–	–	–	–	4	4	–	–
IQR	–	–	–	–	4–4	3.5–4	–	–
P-value	–		–		0.375		–	–
(between groups)***								

Notes: *Unpaired Student's *t*-test. **Repeated-measures analysis of variance. ***Mann–Whitney test.

Abbreviations: CGI-I, Clinical Global Impressions improvement subscale; CGI-S, Clinical Global Impressions severity subscale; HDL, high-density lipoprotein cholesterol; IQR, interquartile range; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Table 3 shows the analysis of completers versus noncompleters of the study. Twenty-six patients (100%) from stay group and 15 patients (42.8%) from the switch group met the modified NCEP ATP-III criteria for presence of metabolic syndrome ($P<0.001$) at the end of study.

Two patients from both groups experienced efficacy failure (ie, they were hospitalized). There were no differences between groups in psychopathology changes as measured by the PANSS total score at baseline and 24 weeks ($P=0.911$) and CGI-I scores at the end of study ($P=0.375$).

Table 3 Analysis of completers versus noncompleters of study

	Completers	Noncompleters	P-value
Group			
Stay, n	26	5	0.138
Switch, n	21	10	
Residence			
Rural, n	24	7	0.767
Urban, n	23	8	
Sex			
Male, n	26	13	0.029
Female, n	21	2	
Marital status			
Married, n	34	13	0.683
Unmarried, n	8	1	
Previously married, n	5	1	
Education			
Under matriculation, n	27	7	0.465
Matric and above, n	20	8	
Waist circumference, mean (SD)	91.00 (9.231)	93.00 (9.681)	0.473
Systolic blood pressure, mean (SD)	126.13 (11.369)	129.93 (9.422)	0.246
Diastolic blood pressure, mean (SD)	84.34 (10.192)	91.47 (12.106)	0.028
Fasting blood sugar, mean (SD)	113.09 (13.845)	119.20 (17.949)	0.172
Triglycerides, mean (SD)	192.04 (40.044)	197.07 (27.319)	0.653
HDL, mean (SD)	40.62 (8.631)	39.93 (7.941)	0.787
PANSS, mean (SD)	69.00 (4.482)	68.40 (5.950)	0.723
CGI-S, median (interquartile range)	4 (3–5)	4 (3–5)	0.761

Abbreviations: CGI-S, Clinical Global Impressions severity subscale; HDL, high-density lipoprotein cholesterol; PANSS, Positive and Negative Syndrome Scale; n, number; SD, standard deviation.

Discussion

Multiple trials over time have studied the metabolic derangements with second-generation antipsychotic medications. For example, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial found that, among the antipsychotic medications used, olanzapine was associated with highest risk for weight gain and dyslipidemia, especially elevated triglyceride levels.^{40–43} Various strategies have been adopted to counter these antipsychotic medication-induced metabolic derangements. Switching to antipsychotic medications with lesser metabolic side effects or adopting a lifestyle intervention focused on diet and exercise is the appropriate first step. Addition of statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) to the antipsychotic medication regimen tends to benefit low-density lipoprotein cholesterol and triglycerides rather than HDL or weight,⁴⁴ while adding metformin leads to weight reduction.^{45,46}

Switching from olanzapine to aripiprazole in our study was effective in helping many patients improve the results of various parameters of metabolic syndrome, while those who continued on olanzapine experienced further deterioration in these parameters. These findings are in accordance with

most of the studies conducted in this field.^{32,33,47,48} The fact that intergroup differences with respect to fasting levels of HDL cholesterol were statistically significant in our study as against the findings of Stroup et al³² could be explained by the fact that we shifted only olanzapine-treated schizophrenia patients to aripiprazole, whereas in the Stroup et al study patients were switched from olanzapine, quetiapine, or risperidone to aripiprazole. Olanzapine causes more metabolic derangements than quetiapine and risperidone,⁴⁹ and this could be the reason that switching produced more beneficial effects in results of fasting levels of HDL cholesterol in our study.

At the end of our study there were no statistically significant differences between groups in psychopathology changes as measured by the PANSS total score ($P=0.911$) and CGI-I scores ($P=0.375$) in completers of the study. Fleischhacker et al³⁰ found that olanzapine had a statistically significant efficacy advantage over aripiprazole, with more reduction in PANSS total score. McCue et al⁵⁰ also found that aripiprazole was significantly less able to get patients out of hospital in 3 weeks (the primary outcome measure) compared with olanzapine. In these studies, acute relapsing patients with schizophrenia were shifted to aripiprazole,

whereas in our study we switched only those patients with schizophrenia who were already stable on olanzapine. It is likely that patients with schizophrenia who are already stable on olanzapine maintain their remission even after switching to aripiprazole; even so, difference exists in acute psychotic episodes, where olanzapine is relatively superior in efficacy to aripiprazole.⁵⁰

Pae et al³¹ found that patients switched to aripiprazole with sudden discontinuation of the previous antipsychotic medication showed an increase in symptom severity during the first week of switching. In our study, slow cross-titration of antipsychotic medication can explain the reason why there was no significant clinical destabilization in the switch group. Takeuchi and Remington⁵¹ concluded in a recent systematic review that a small number of patients with schizophrenia or schizoaffective disorder risked an exacerbation of psychotic symptoms if aripiprazole was added to existing antipsychotic treatment. Many of the cases reported involved patients who were quite ill and had been exposed to long-term antipsychotic treatment; it is likely that aripiprazole was added to current treatment in patients with treatment-resistant schizophrenia, but in our study, patients with schizophrenia who were already stable on olanzapine were switched to aripiprazole. As our patients were already stable on olanzapine, this could be a reason for successful switching without much worsening in psychotic symptoms.

The difference in the metabolic derangements between the two groups can be explained by the differential receptor occupancy by aripiprazole and olanzapine. Aripiprazole is a partial agonist at D2 dopamine and 5HT1A serotonin receptors and an antagonist at 5HT2A serotonin receptors,⁵² whereas olanzapine is an antagonist at D2 dopamine, 5HT2A and 5HT2C serotonin, M1 muscarinic, and histamine-1 receptors.⁵³ Histamine-1 and 5HT2C receptor antagonism closely correlates with the weight-gaining potential of some antipsychotics like olanzapine^{54,55} and may interfere with leptin-mediated appetite suppression.^{55,56} Adiposity alone does not explain the diabetogenic potential of some atypical antipsychotic medications.⁵⁷ Significant insulin resistance, even with a single dose of olanzapine, has also been documented in nonobese individuals receiving olanzapine versus those receiving risperidone.^{58,59} Blocking M3 (type 3) muscarinic and 5HT1A receptors may be a factor in diminished pancreatic beta-cell responsiveness, and blocking 5HT2A receptor may suppress glucose uptake in skeletal muscle.⁵³

Treatment with olanzapine in patients with schizophrenia offers the advantage of effectiveness for both positive and negative symptoms, with the fewest extrapyramidal side effects.^{8–11} However, because of growing evidence of olanzapine-induced metabolic derangements, as is evident from our study also, a prescribing choice must be based on an assessment of each drug's efficacy as well as its potential to cause metabolic side effects. Because schizophrenia is a chronic illness that requires antipsychotic treatment for a prolonged period, an antipsychotic agent with fewer metabolic side effects, such as aripiprazole, can be used for maintenance, to prevent psychotic relapse and long-term deterioration. As is evident from our study, the dropout rate was higher in the switch group than in the stay group ($P=0.138$), which can be an impediment in stabilized schizophrenia patients while switching them to other antipsychotic medications and is something that clinicians will want to address. This problem can partially be addressed by slow cross-titration of drugs and close follow-up of such patients. Monitoring blood levels of aripiprazole is a meaningful option, because it seems to have a therapeutic window at 150–210 ng/mL.⁶⁰ Levels beyond 210 ng/dL will lead to more side effects, and levels below 150 ng/dL will show subtherapeutic response and thus lead to more dropouts.

Conclusion

Clinically stable patients with schizophrenia on olanzapine who have evidence of metabolic syndrome can be successfully switched to aripiprazole, with improvement in various parameters of metabolic syndrome and without any significant change in efficacy measures. Switching is an option if careful cross-titration and close monitoring is possible. Careful clinical monitoring after a switch to aripiprazole might have been the reason that those who switched did not experience a higher rate of efficacy failures, compared with those who stayed on olanzapine.

Disclosure

There are no financial or other relationships that might lead to a conflict of interest. The authors report no other conflicts of interest in this work.

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