Switching Outpatients With Bipolar or Schizoaffective Disorders and Substance Abuse From Their Current Antipsychotic to Aripiprazole

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Objective: Substance abuse is extremely common in patients with bipolar disorders, although minimal data are available on the treatment of this important clinical population. Aripiprazole is an atypical antipsychotic that is approved for the treatment of mania and that has a novel mechanism of action, acting as a dopamine-2 receptor partial agonist, thereby increasing dopamine release in some parts of the brain and decreasing dopamine release in other brain regions. Dopamine release is implicated in substance use, and both dopaminergic agonists and antagonists have been examined for the treatment of substance abuse. To our knowledge, dopamine receptor partial agonists have not been investigated for treatment of substance abuse in humans.

Method: Twenty antipsychotic-treated patients with bipolar or schizoaffective disorder and current substance abuse were switched to open-label aripiprazole using an overlap and taper method. At baseline, diagnoses were confirmed using the Mini-International Neuropsychiatric Interview based on DSM-IV criteria. Psychiatric symptoms, side effects, and substance use and craving were assessed over 12 weeks. Psychiatric symptoms were assessed with the Hamilton Rating Scale for Depression (HAM-D), Young Mania Rating Scale (YMRS), and Brief Psychiatric Rating Scale (BPRS). Substance craving was assessed with visual analogue scales, and side effects were monitored using the Abnormal Involuntary Movement Scale, Simpson-Angus Scale, Barnes Akathisia Scale, and patient report. Study enrollment was from April 2003 to February 2004.

Results: Significant baseline-to-exit improvement in HAM-D ($p = .002$), YMRS ($p = .021$), and BPRS ($p = .000$) scores were observed without a significant change in antipsychotic-induced side effect scales. In 17 participants with current alcohol dependence, significant reductions in dollars spent on alcohol ($p = .042$) and alcohol craving ($p = .003$) were found. In 9 participants with cocaine-related disorders, significant reductions in cocaine craving ($p = .014$), but not use, were found.

Conclusion: A change to aripiprazole was associated with symptomatic improvement. Limitations of the study include a small sample size, high attrition, and an open-label design. Controlled trials in dual-diagnosis patients are needed to confirm these findings.

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Bipolar disorders are common and severe psychiatric illnesses with 1.3% to 1.7% prevalence in the general population.[1,2] Substance abuse in people with bipolar disorder is common.[3] Regier et al.[1] found a 61% lifetime prevalence of substance abuse in people with bipolar I disorder and a 48% prevalence in people with bipolar II disorder. Therefore, useful treatments for both mood symptoms and substance abuse in patients with bipolar disorders and comorbid substance abuse disorders are of great interest. However, minimal data are available on the treatment of this population.

Atypical antipsychotics have become first-line treatments for bipolar and schizoaffective disorders. Some retrospective and anecdotal data suggest that clozapine and risperidone may be useful in dual-diagnosis patients.[4,5] Our group has reported promising results with quetiapine in studies of patients with major psychiatric illnesses and drug or alcohol use.[6–8] To our knowledge, these are the only reports on the use of antipsychotics in patients with bipolar disorder and substance abuse.

Both dopaminergic agonists and antagonists, in theory, are potential treatments for substance abuse.[9] Dopamine receptor partial agonists increase dopamine in areas of the brain low in dopamine and decrease dopamine in areas of the brain with high dopamine,[10] but despite promising findings in animal models,[11,12] to our knowledge they have not been explored in humans with substance-related disorders.

Aripiprazole is a dopamine-2 receptor partial agonist that is U.S. Food and Drug Administration (FDA)–approved for the treatment of schizophrenia and mania.[13] In addition to a unique mechanism of action, aripiprazole

differs from many other currently available atypical antipsychotics by producing less somnolence.[14] Casey et al.[15] examined the safety of 3 methods of switching patients with schizophrenia from another antipsychotic to aripiprazole: (1) initiation and discontinuation, (2) initiation and 2-week taper, and (3) gradual upward titration and gradual taper. All 3 methods appeared to be safe and well tolerated. To our knowledge, no data are available on switching patients with bipolar disorders from another antipsychotic to aripiprazole. However, given data suggesting that sudden discontinuation of lithium can be associated with relapse in patients with bipolar disorders,[16] overlap and taper methods are sometimes recommended.

In this report, data are presented from an open-label pilot study examining the impact on psychiatric symptoms and substance use and craving of switching 20 patients with bipolar disorders or schizoaffective disorder, bipolar type from their current antipsychotic to aripiprazole using an overlap and taper method.

METHOD

Study enrollment was from April 2003 to February 2004. A total of 20 participants were enrolled after signing an institutional review board–approved informed consent form. Inclusion criteria were age of 18 to 65 years; fluency in English or Spanish; diagnosis of bipolar I, II, not otherwise specified, or schizoaffective, bipolar type disorders; current abuse of or dependence on cocaine, amphetamines, cannabis, opiates, or alcohol with use within 7 days prior to enrollment; and current treatment with an antipsychotic other than aripiprazole. Exclusion criteria were life-threatening medical conditions; current active suicidal ideation; severe cognitive impairment; current pregnancy or nursing; and a history of allergic reaction to, poor response to, or lack of tolerability with aripiprazole.

At baseline, diagnoses were confirmed using the Mini-International Neuropsychiatric Interview (MINI) based on DSM-IV criteria,[17] and psychiatric symptoms were assessed with the 17-item Hamilton Rating Scale for Depression (HAM-D),[18,19] the Young Mania Rating Scale (YMRS),[20] and the 18-item Brief Psychiatric Rating Scale (BPRS).[21] Substance craving was assessed with 100-mm visual analogue scales (VAS) asking about intensity of craving in the past week. Substance use (days of use in the past week and dollar amount spent on substances in the past week) was assessed, and urine drug screens were obtained. Side effects were monitored with the Abnormal Involuntary Movement Scale (AIMS),[22] Simpson-Angus Scale (SAS),[23] and Barnes Akathisia Scale (BAS)[24] and by patient report. Aripiprazole was initiated at 15 mg/day, and the baseline antipsychotic was tapered and discontinued over a period of up to 6 weeks. Aripiprazole could be increased at any follow-up appointments to 30 mg/day based on clinician judgment. Participants returned weekly for assessments for 12 weeks and were paid $10 at each visit.

Statistical Analysis

Baseline-to-exit change in mean scores for the psychiatric symptom scales, side effect scales, craving, and substance use were assessed in all participants with baseline and at least 1 postbaseline assessment (intent-to-treat sample) using 2-sided, paired t tests. Urine drug screen results (positive vs. negative) were analyzed using a χ^2 analysis. Changes in frequency and amount of alcohol and cocaine use were assessed in those with dependence on these substances. These substances were selected for analyses as they were the most commonly abused in the sample. Significance was set at $\alpha = .05$ for all comparisons.

RESULTS

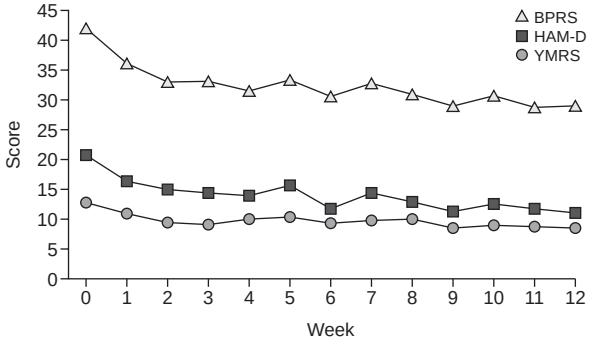
Demographic information on the participants is given in Table 1. A total of 19 participants had bipolar I or II disorders, and 1 participant had schizoaffective disorder, bipolar type. The mean (± SD) length of participation was 7.1 (± 4.9) weeks, with 35% of participants (7/20) completing the 12-week study. The majority were depressed at baseline. All participants were receiving at least 1 atypical antipsychotic at baseline. Three participants were taking 2 antipsychotics at baseline. A strong effort was made to completely discontinue the baseline antipsychotic no later than week 4. However, 1 participant taking 600 mg/day of quetiapine took 6 weeks to discontinue the quetiapine. Most participants were taking 30 mg of aripiprazole at study exit (Table 1). Concomitant psychiatric medications at study entry, in addition to the antipsychotics, included selective serotonin reuptake inhibitors (N = 11), anticonvulsants (N = 6), trazodone (N = 6), bupropion (N = 5), lithium (N = 5), benzodiazepines (N = 3), and anticholinergics (N = 1). Psychiatric medication changes, other than the addition of aripiprazole and discontinuation of other antipsychotics, included the addition of hydroxyzine at baseline for anxiety, the addition of diazepam at week 9 for sleep, the addition of benztropine at week 11 for restlessness thought to be akathisia after a reduction in aripiprazole dose from 30 mg to 15 mg at week 10 did not lead to resolution of the symptoms, the addition of zolpidem at week 2 for sleep, and the addition of paroxetine at week 3 (the participant's final week in the study) for an increase in depressive symptoms.

In the intent-to-treat sample (N = 19), with at least 1 postbaseline visit, significant baseline-to-exit improvement on the HAM-D (20.6 ± 7.1 to 10.9 ± 7.1, p = .002), YMRS (13.3 ± 6.9 to 8.0 ± 7.8, p = .021), and BPRS (42.1 ± 7.2 to 29.5 ± 8.3, p = .000) were observed (Figure 1). No significant change in score on the AIMS (0.8 ± 1.8

Table 1. Demographic Characteristics of Outpatients With Bipolar or Schizoaffective Disorders and Substance Abuse Switched to Aripiprazole From Other Antipsychotics (N = 20)

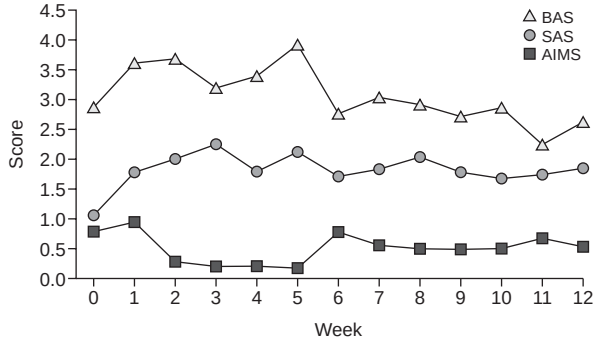
Characteristic	Value
Age, mean (± SD), y	40.6 (8.9)
Gender, N (%)	
Male	11 (55)
Female	9 (45)
Race, N (%)	
White	15 (75)
African American	3 (15)
Hispanic	2 (10)
Marital status, N (%)	
Single/divorced	16 (80)
Married/living with someone	4 (20)
Household income, N (%)	
≤ $15,000 per year	15 (75)
> $15,000 per year	5 (25)
Education, N (%)	
≥ Some college	12 (60)
≤ High school/trade school	8 (40)
Primary diagnosis, N (%)	
Bipolar I disorder without psychotic features	16 (80)
Bipolar I disorder with psychotic features	2 (10)
Bipolar II disorder	1 (5)
Schizoaffective disorder, bipolar type	1 (5)
Baseline antipsychotic, N (%)	
Quetiapine	9 (45)
Olanzapine	5 (25)
Risperidone	3 (15)
Quetiapine and haloperidol	1 (5)
Quetiapine and ziprasidone	1 (5)
Quetiapine and olanzapine	1 (5)
Substance abuse/dependence diagnosis, N (%)	
Alcohol dependence	17 (85)
Cocaine dependence	9 (45)
Opioid dependence	3 (15)
Cannabis abuse	2 (10)
Cocaine abuse	1 (5)
Cannabis dependence	1 (5)
Baseline mood state, N (%)	
Depressed	11 (55)
Mixed	6 (30)
Manic	2 (10)
Did not meet criteria for current mood state	1 (5)
Additional diagnosis, N (%)	
Generalized anxiety disorder	8 (40)
Social phobia	6 (30)
Posttraumatic stress disorder	6 (30)
Antisocial personality disorder	6 (30)
Panic disorder	5 (25)
Obsessive-compulsive disorder	3 (15)
Length of participation, mean (± SD), wk	7.1 (4.9)
Aripiprazole dose at exit, N (%)	
30 mg	12 (60)
15 mg	8 (40)
Aripiprazole dose at exit, mean (± SD), mg/d	24.0 (7.5)

Figure 1. Weekly Mean HAM-D, YMRS, and BPRS Scores in Intent-to-Treat Sample of Outpatients With Bipolar or Schizoaffective Disorders and Substance Abuse Switched to Aripiprazole From Other Antipsychotics (N = 19, LOCF)



Abbreviations: BPRS = Brief Psychiatric Rating Scale, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, YMRS = Young Mania Rating Scale.

Figure 2. Weekly Mean Antipsychotic Side Effect Scale Scores in Intent-to-Treat Sample of Outpatients With Bipolar or Schizoaffective Disorders and Substance Abuse Switched to Aripiprazole From Other Antipsychotics (N = 19, LOCF)



Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, LOCF = last observation carried forward, SAS = Simpson-Angus Scale.

to 0.5 ± 1.1, NS), SAS (1.1 ± 1.4 to 1.8 ± 3.1, NS), or BAS 2.9 ± 2.0 to 2.6 ± 3.4, NS) was found, but small, nonsignificant increases in the BAS and SAS were observed during the overlap and taper period (Figure 2).

As alcohol and cocaine were the most common substances of abuse in our sample, analysis of change in use and craving of these substances was conducted in participants meeting criteria for their dependence. In the 17 participants with alcohol dependence, significant reductions were found in alcohol craving on the VAS (62.6 ± 33.9 to 28.1 ± 35.6, p = .003) and in dollars spent/week on alcohol (28.6 ± 31.9 to 13.8 ± 15.2, p = .042) but not days/week of alcohol use (3.2 ± 2.5 to 2.3 ± 2.7, NS). In the 9 participants with cocaine dependence, significant reduction in craving on the VAS (52.64 ± 39.7 to 20.6 ± 34.6, p = .014) but not in dollars spent (83.3 ± 160.5 to 16.7 ± 50.0, NS) or days used (2.1 ± 2.5 to 0.8 ± 0.0, NS) was found. The number of cocaine-positive urine screens decreased from 7/9 to 6/9 (χ^2, NS) from baseline to exit.

Somatic symptoms reported by participants included insomnia (N = 9), stiffness (N = 6), tremors (N = 4), dry mouth (N = 4), increased salivation (N = 4), headaches

(N = 3), sedation (N = 2), restlessness (N = 2), sweating (N = 1), sore throat (N = 1), nausea (N = 1), diarrhea (N = 1), dizziness (N = 1), and blurred vision (N = 1). These symptoms were generally mild. To our knowledge, only 1 participant self-discontinued from the study secondary to a medication-related side effect.

DISCUSSION

The findings from this pilot study suggest that in patients with bipolar or schizoaffective disorders and substance abuse who were actively using substances, a change from their current antipsychotic to aripiprazole was associated with improvement in psychiatric symptoms and in some cases a reduction in substance use and craving. Aripiprazole is FDA approved for mania. Thus, the reduction in YMRS scores is not surprising. However, most of the participants were depressed at baseline, and the decrease in HAM-D scores is noteworthy. Additional research examining whether aripiprazole is effective for bipolar depression seems warranted.

Significant reductions in dollars spent on alcohol and alcohol craving were found in those with alcohol dependence at baseline. This finding is potentially important given that alcohol appears to be the most frequently abused substance in people with bipolar disorder, and minimal treatment data are available. A significant decrease in cocaine craving, but not use, was found. However, the numerical decrease in dollars spent and days of cocaine use was large. Cocaine-positive urine screens also decreased, but not significantly. The small number of participants with cocaine-related disorders limited our ability to detect significant differences in cocaine use. Other substances were abused by very small numbers of participants; thus, we did not conduct separate analyses.

The switch from the baseline antipsychotic to aripiprazole was generally, but not always, well tolerated. As can be seen in Figure 1, participants as a whole showed an improvement in HAM-D, YMRS, and BPRS scores. Thus, the antipsychotic switch using an overlap and taper appeared to be generally safe in terms of psychiatric symptom change.

A potential concern in switching from one antipsychotic to another using an overlap and taper is that side effect burden might increase due to the combination antipsychotic therapy during the overlap period. As can be seen in Figure 2, scores on the BAS and SAS tended to increase slightly during the overlap period in weeks 1 to 4. Interestingly, the AIMS scores tended to decrease during this same time period. BAS scores decreased to levels similar to those at baseline in later weeks, but SAS scores remained slightly higher than at baseline throughout the study. One participant complained of akathisia-like symptoms of sufficient severity that a decrease in aripiprazole dose from 30 mg to 15 mg was made. As the symptoms did not abate, benztropine was added, and the symptoms resolved. Two participants complained of insomnia and were given hypnotics that relieved this symptom. Thus, insomnia may occur in switching a patient from a sedating to a nonsedating antipsychotic but can be relieved with adjunctive medication.

A number of caveats are in order. The study had an open-label design without a control group. Therefore, we cannot rule out improvement in psychiatric symptoms due to nonspecific effects of treatment (i.e., placebo effect). The study was conducted in participants with active substance use at baseline, which is a strength of the design in that it allows data collection in a "real world" setting in patients with at least 2 serious psychiatric illnesses. However, the criteria selected for a treatment-resistant sample in terms of substance use during antipsychotic therapy. Thus, as the participants were nonresponders in terms of substance use on their current antipsychotic, they might be likely to improve with a change in antipsychotic. An alternative interpretation would be that, as they had not responded to their current antipsychotic in terms of substance use, they would be unlikely to respond to another antipsychotic, making the observed improvement more noteworthy. Although participants were actively using substances at baseline, we did not attempt to quantify symptoms of either substance intoxication or withdrawal. Therefore, specific changes in these substance use symptoms are not available.

Another limitation of the study is the sample heterogeneity in terms of mood state and substances used. As this is a pilot study, we allowed broad inclusion criteria with the goal of finding subgroups with particularly favorable responses. On the basis of our findings, patients with bipolar depression or cocaine abuse may be promising groups for future research with aripiprazole.

The high attrition rate was also a limitation, with only 7 of 20 participants completing the 12-week study. As some participants were lost to follow-up, we cannot rule out the possibility that these participants discontinued themselves from the study due to a worsening of psychiatric symptoms or substance use. High attrition rates, although undesirable, are almost inherent in work with dual-diagnosis patients. Recent reports by our group on quetiapine in outpatients recruited from referral sources similar to those in the present study had completion rates of 41%[7] and 58%.[6] However, the high attrition limits our ability to assess efficacy and tolerability of aripiprazole and raises concerns about whether side effects or a worsening in symptoms may have resulted in participant discontinuation.

Finally, participants were taking a variety of concomitant medications that could have influenced changes in mood symptoms or substance use patterns. At baseline, 5 participants were taking bupropion, a medication that is FDA approved for smoking cessation. However, con-

comitant medications generally remained constant during the study. Only 5 changes in concomitant medications occurred during the study (1 addition of medication for anxiety at baseline, 2 additions of medications for sleep, 1 addition of a side effect medication, and 1 addition of an antidepressant at the last study assessment). Thus, the only consistent change in medication was the switch to aripiprazole.

CONCLUSION

Results from this pilot study suggest that the switch to aripiprazole in some cases is accompanied by clinical improvement in mood and substance use. Larger, controlled trials are needed to confirm these preliminary observations.

Drug names: aripiprazole (Abilify), benztropine (Cogentin and others), bupropion (Wellbutrin and others), clozapine (Clozaril, FazaClo, and others), diazepam (Valium and others), haloperidol (Haldol and others), hydroxyzine (Atarax, Vistaril, and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), paroxetine (Paxil and others), quetiapine (Seroquel), risperidone (Risperdal), trazodone (Desyrel and others), ziprasidone (Geodon), zolpidem (Ambien).

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