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Adjunctive Aripiprazole in Treatment-Resistant Bipolar Depression

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Background. *There are limited management options for treatment-resistant depression in bipolar disorder (BD) patients.*
Method. *Open adjunctive aripiprazole was administered to outpatients with treatment-resistant depression assessed with the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation, and followed with the STEP-BD Clinical Monitoring Form.*
Results. *Thirty BD (11 type I, 15 type II, 4 NOS) patients (mean age 44.4 ± 17.0 years, 70% female) on a mean of 3.2 ± 1.6 other psychotropic and 2.3 ± 1.6 nonpsychotropic prescription medications received aripiprazole for a mean duration of 84 ± 69 days, with a mean final dose of 15.3 ± 11.2 (range 2.5–40) mg/day. Fourteen patients (47%) discontinued aripiprazole; due to inefficacy in 5/30 (17%), patient choice in 3/30 (10%), and adverse effects in 6/30 (20%). Aripiprazole yielded improvement in Clinical Global Impression–Severity (CGI–S, 4.4 ± 1.1 to 3.8 ± 1.2, $p < 0.01$), with 8/30 (27%) patients responding (CGI–S improvement > = 2), including 4/30 (13%) who remitted (final CGI–S < = 2). Global Assessment of Function, and depressed mood and suicidal ideation ratings also improved. Aripiprazole was generally well tolerated, with no significant change in mean adverse effect ratings or mean weight.*
Conclusion. *Aripiprazole appeared effective and generally well tolerated in treatment-resistant bipolar depression. Controlled trials are warranted to systematically explore these preliminary naturalistic observations.*

Keywords Bipolar disorder, Treatment, Depression, Aripiprazole

INTRODUCTION

Bipolar disorders are common conditions, affecting 1 to 3.5% of the population, and are characterized by recurrent episodes of depression and mood elevation. Although there has been much research that has yielded multiple treatment options for acute mania, until recently there has been much less emphasis on studies of acute bipolar depression, and treatment options for this phase of the illness remain limited (1). This is a substantial problem, as patients with bipolar disorders spend much more time struggling with symptoms of depression compared to mood elevation (2,3). To date, the combination of olanzapine and fluoxetine is only treatment that has received a United States Food and Drug Administration (FDA) indication for acute bipolar depression (4). However, controlled evidence also supports the utility of monotherapy with lithium (5), lamotrigine (6), and the atypical antipsychotics quetiapine (7), and (with a modest effect size) olanzapine (4). Although combining antidepressants with antimanic agents for bipolar depression is common in clinical practice, and some controlled trials suggest probable efficacy (8), large, multicenter, double-blind placebo controlled trials are needed to confirm the utility of this approach.

The biochemical pathophysiology underlying bipolar depression, and bipolar disorder in general remains to be established. Hypotheses regarding multiple neurotransmitter and intracellular signaling systems have been proposed (9,10). Evidence from clinical studies supports the hypothesis that altered dopaminergic neurotransmission may contribute to the pathophysiology of bipolar disorders. For example, cerebrospinal concentrations of the dopamine metabolite homovanillic acid (HVA) may be decreased in depression and increased in mania (11–13), although there is some variability in findings. As a class, atypical antipsychotics affect neurotransmission of dopamine as well as multiple other neurochemicals. These agents appear effective in bipolar disorders, with olanzapine

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(14,15), risperidone (16,17), quetiapine (18,19), ziprasidone (20,21), and aripiprazole (22,23) having received FDA indications for the treatment of acute mania, and olanzapine (24) and aripiprazole (25) having received FDA indications for maintenance treatment, and emerging data suggest potential utility for at least some such agents in acute bipolar depression (4,7).

Aripiprazole is an atypical antipsychotic that is a partial agonist at dopamine D2 (26,27) and serotonin 5-HT1A (28) receptors, and an antagonist at 5-HT2A (29) receptors, that has been shown to be effective for acute mania (22,23) and maintenance treatment (25). In an acute mania study, aripiprazole also attenuated depressive symptoms, yielding a mean Clinical Global Impression (CGI) Severity of Depression score decrease of 0.2 (compared to an increase of 0.1 with placebo, $p < 0.03$) (22). It may be that a dopamine partial agonist such as aripiprazole could offer benefit not only by attenuating putative excessive dopaminergic neurotransmission in mania, but also by enhancing putative deficient dopaminergic neurotransmission in bipolar depression.

In a recent report, open adjunctive aripirazole appeared to offer benefit in treatment-resistant unipolar depression (30). In order to provide a preliminary naturalistic assessment of the utility of this medication in bipolar depression, we explored the safety and tolerability of adjunctive treatment with open aripiprazole in patients with treatment-resistant bipolar depression.

METHODS

In 30 bipolar disorder outpatients with treatment-resistant bipolar depression treated at the Stanford Bipolar Disorders Clinic, data were prospectively collected using the Systematic Treatment Enhancement for Bipolar Disorders (STEP-BD) Affective Disorders Evaluation (for assessment at intake) and Clinical Monitoring Form (CMF, for longitudinal monitoring) (31). The STEP-BD protocol for prospective assessment and clinical monitoring was approved by the Stanford University Administrative Panel on Human Subjects, and all patients provided verbal and written informed consent prior to participation. In a naturalistic fashion, aripiprazole was added to prior treatment (including no prior treatment in one patient) and titrated gradually in efforts to minimize the risk of adverse effects. With the additional approval of the Stanford University Administrative Panel on Human Subjects, clinical responses to aripiprazole were retrospectively analyzed.

The primary outcome measure was change in mean Clinical Global Impression–Severity (CGI–S) score from baseline (just prior to addition of aripiprazole) to endpoint (last observation on aripiprazole). Secondary efficacy measures included response (CGI–S improvement of at least 2 points) and remission (final CGI–S of 2 or less) rates, and change from baseline to endpoint in mean Global Assessment of Function (GAF) and CMF depressed mood and suicidal ideation scores. Secondary safety and tolerability measures included change from baseline to endpoint in CMF adverse effect scores and weight, discontinuations for adverse effects, and serious adverse events.

The above data were analyzed by compiling descriptive statistics, and comparing measures at baseline and endpoint. Continuous variables were compared using t-statistics, and categorical parameters were compared using chi-square tests. Means (± standard deviations) are reported, and a significance threshold of $p < 0.05$ was used, with no correction for multiple comparisons.

RESULTS

Patients had a mean (±SD) age of 44.4 ± 17.0 years, and were 70% female, and 88% Caucasian. Eleven of thirty patients (37%) had bipolar I disorder, 15/30 (50%) had bipolar II disorder, and 4/30 (13%) had bipolar disorder not otherwise specified, with a mean onset age of 21.5 ± 12.4 years, and mean illness duration of 22.9 ± 16.1 years. Twenty-five of thirty patients (83%) had syndromal and 5/30 (17%) had subsyndromal depression. Comorbid conditions were common, including lifetime histories of anxiety disorders (11 patients with panic disorder, 10 with generalized anxiety disorder, 5 with post-traumatic stress disorder, 4 with social phobia, and 2 with obsessive-compulsive disorder), alcohol and substance abuse (6 patients), eating disorders (2 with bulimia, 1 with binge eating disorder), Cluster B personality disorders (2 patients) and attention-deficit/hyperactivity disorder (2 patients). In about one-third of these patients, comorbid conditions were active at the time aripiprazole was started.

When aripiprazole was started, patients were on a mean of 3.2 ± 1.6 other psychotropic prescription medications (including a mean of 0.6 ± 0.5 other atypical antipsychotics, 1.0 ± 0.8 mood stabilizers, 0.6 ± 0.7 antidepressants, and 0.7 ± 0.7 sedative/anxiolytics) and 2.3 ± 1.6 nonpsychotropic prescription medications. Nineteen patients were on other atypical antipsychotics, nine were on lithium (mean dose 808 ± 309 mg/day), six were on divalproex (mean dose 1042 ± 188 mg/day), 15 were on lamotrigine (mean dose 240 ± 166 mg/day), seven were on other anticonvulsants (three on gabapentin, three on topiramate, and one on oxcarbazepine), 14 were on antidepressants, and 18 were on sedative/anxiolytics, when aripiprazole was started.

Aripiprazole therapy was administered for a mean duration of 84 ± 69 days, with a mean starting dose of 6.1 ± 1.6 mg/day (range 5 to 10 mg/day), and a mean final dose of 15.3 ± 11.2 mg/day (range 2.5 to 40 mg/day). A total of 16/30 patients (53%) continued aripiprazole, including 8/30 (27%) responders, and 8/30 (27%) nonresponders who nevertheless had sufficient improvement to continue aripiprazole. A total of 14/30 patients (47%) discontinued aripiprazole, including 5/30 (17%) due to inefficacy, 3/30 (10%) due to patient choice, and 6/30 (20%) due to adverse effects. Patients who discontinued aripiprazole took it for a mean duration of 70 ± 62 days, with a mean final dose of 16.5 ± 13.9 mg/day, while patients who remained on aripiprazole took it for a mean duration of 98 ± 75 days, with a mean final dose of 14.3 ± 8.6 mg/day.

Aripiprazole therapy was associated with improvement in CGI–S scores (4.4 ± 1.1 to 3.8 ± 1.2, df = 29, t = 2.8,

p = 0.009), with 8/30 patients (27%) responding, 4/30 (13%) whom experienced remission. Aripiprazole also yielded improvement in GAF (52.4 ± 8.0 to 57.7 ± 8.3, df = 29, t = 3.2, p = 0.004), and depressed mood (0.85 ± 0.42 to 0.63 ± 0.52, df = 29, t = 2.9, p = 0.007) and suicidal ideation (0.37 ± 0.41 to 0.20 ± 0.33, df = 29, t = 3.1, p = 0.005) ratings on the CMF. Suicidal ideation ratings even decreased in the 22 nonresponders (0.36 ± 0.38 to 0.23 ± 0.36, df = 21, t = 2.4, p = 0.03).

Aripiprazole was generally well tolerated with no treatment-emergent mania, 5/30 patients (17%, all female age 27–54) switching into hypomania, and no significant change in mean CMF adverse effect ratings or mean weight (161.7 ± 42.8 lbs to 169.9 ± 39.9 lbs, p = NS). Four of thirty patients (13%) had greater than 7% weight gain, and 1/30 (3%) had greater than 7% weight loss. Mild sedation, nausea, and constipation were the most common adverse effects. Six of 30 patients (20%) discontinued aripiprazole due to adverse effects, including 3/30 (10%) due to agitation, 2/30 (7%) for cognitive problems, and 1/30 (3%) due to hypomania. Only 1/30 (3%) experienced a serious adverse event (cholecystectomy and medical hospitalization).

DISCUSSION

In this naturalistic study, adjunctive aripiprazole appeared effective and well tolerated in treatment-resistant bipolar depression. Aripiprazole was associated with improvement in global symptom, global function, depression, and suicidal ideation scores. Eight of thirty patients (27%) responded, and 4/30 (13%) remitted. There were no cases of treatment-emergent mania, and no significant changes in mean adverse effect ratings or mean weight.

Our findings are consistent with the hypothesis that atypical antipsychotics in general and aripiprazole in particular may have utility in bipolar depression. The mechanism(s) contributing to such putative antidepressant effects remain to be determined. If the entire class of atypical antipsychotics eventually proves effective in bipolar depression, then biochemical commonalities among these agents such as antagonist effects at serotonin 5-HT2A receptors could merit assessment in relationship to antidepressant actions. If only some atypical antipsychotics ultimately prove useful in bipolar depression, or if some of these medications yield more robust antidepressant effects than others, then mechanistic dissociations could be relevant. In this regard, relationships between the novel partial agonist effects of aripiprazole at dopamine D2 and serotonin 5-HT1A receptors and antidepressant actions could eventually be worth exploring.

This study has noteworthy strengths and limitations. The sample was derived from a heterogeneous cohort of bipolar disorder patients with diverse clinical presentations, comorbidities, and medication regimens (31), suggesting more generalizability than might be inferred from controlled trials with restrictive inclusion and exclusion criteria. In particular, aripiprazole was added to an average of 3.2 psychotropic and 2.3 nonpsychotropic prescription medications, reflecting the sort of combination pharmacotherapies used in clinical settings. However, the findings of this study need to be approached with considerable caution in view of important limitations. The open adjunctive administration of aripiprazole and absence of a control condition raise the possibility that placebo response, spontaneous remission, or delayed response to prior pharmacotherapies could account for the observed improvement with aripiprazole, although the treatment-resistant nature of our sample suggests that the impact of such confounds ought to be modest. In addition, the small (30 patient) size of our sample provides insufficient statistical power to detect uncommon adverse effects.

Nevertheless, our observations support the contention that more research is indicated. Specifically, double-blind, placebo-controlled studies appear warranted to confirm these preliminary findings suggesting that aripiprazole may be effective and well-tolerated in patients with treatment-resistant bipolar depression.

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