Aripiprazole Augmentation of Selective Serotonin Reuptake Inhibitors for Treatment-Resistant Major Depressive Disorder

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Background: Due to their favorable side effect profile, atypical antipsychotic agents offer important therapeutic advantages in mood disorders. Aripiprazole, an atypical antipsychotic agent with partial dopaminergic and serotonin 1_A receptor agonist activity, may be particularly useful when used in conjunction with standard antidepressants in treatment-resistant depression. The purpose of this study was to test this hypothesis in depressed outpatients who have not experienced significant clinical improvement following an adequate trial of a selective serotonin reuptake inhibitor (SSRI).

Method: 12 patients (mean ± SD age = 46.6 ± 11.3 years, 66.7% female) with major depressive disorder (MDD) diagnosed by use of the Structured Clinical Interview for DSM-IV–Axis I Disorders, who had failed to experience a clinical response following an adequate trial of an SSRI, were treated with open-label aripiprazole in addition to their SSRI for 8 weeks. Clinical response was defined as a 50% or greater decrease in depressive symptoms during the course of the trial (baseline–endpoint) as measured by the 17-item Hamilton Rating Scale for Depression total score. Data were collected from August 2003 to July 2004.

Results: 9/12 (75.0%) patients completed the trial. Using a completer analysis, 5/9 (55.6%) patients were classified as responders. An intent-to-treat (ITT) analysis resulted in 7 responders (58.3%). The overall proportion of remitters was 3/9 (33.3%) using a completer analysis and 5/12 (41.7%) using the ITT analysis. Aripiprazole administration appeared safe, with no severe adverse events observed in any of the study participants.

Conclusions: These results suggest a possible augmentation role for aripiprazole when used in conjunction with SSRIs in SSRI-resistant MDD.

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Treatment-resistant depression (TRD) is fairly common, with anywhere from 25% to 50% of depressed patients enrolled in a clinical trial showing inadequate response following antidepressant treatment.[1] In parallel, it has recently been reported that as many as half of all patients treated in 2 academic-based depression specialty clinics did not achieve remission despite receiving numerous adequate antidepressant trials.[2] In addition, among responders to antidepressant treatment, residual symptoms are common[3,4] and associated with a greater likelihood of relapse[5] as well as poorer psychosocial functioning.[6]

Due to their relatively favorable side effect profile compared to typical antipsychotic drugs, atypical antipsychotic agents may offer important therapeutic advantages in mood disorders. In fact, following the publication of a case study in which 8 outpatients with TRD were reported to achieve remission within 1 week following the addition of risperidone to their selective serotonin reuptake inhibitor (SSRI) regimen,[7] uncontrolled trials for ziprasidone,[8] risperidone,[9] and olanzapine[10] and a positive, placebo-controlled trial for olanzapine[11] as adjuncts in TRD have been published. Although preliminary, the sum of these studies supports the potential utility of atypical antipsychotic agents for TRD.

Aripiprazole is a quinoline derivative and the first of a new class of atypical antipsychotics.[12] Due to its unique receptor-affinity profile, aripiprazole may be particularly effective as an adjunct to SSRIs for the treatment of major depressive disorder (MDD). Specifically, aripiprazole is a potent dopamine D_2 receptor partial agonist, blocking

D_2 receptors under hyperdopaminergic conditions while acting as a D_2 agonist under hypodopaminergic conditions.[13–17] As a result, administration of aripiprazole has been shown to increase dopamine release in the prefrontal cortex and hippocampus of animals.[18] In addition to being a D_2 receptor partial agonist, aripiprazole acts as a 5-HT_{1A} autoreceptor agonist,[19,20] and also demonstrates significant antagonism for the 5-HT_{2A} and 5-HT_7 receptors.[20]

The main obstacles for the use of atypical antipsychotic agents while treating patients with refractory mood and/or anxiety disorders are the potential risks of extrapyramidal symptoms (EPS), cardiac adverse events such as QTc prolongation, and neuroendocrine/metabolic side effects including weight gain, hyperprolactinemia, dyslipidemia, and diabetes. While treatment with aripiprazole has been reported to result in small (0.7–1.2 kg) but statistically significant weight gain compared to placebo acutely (3–4 weeks) among patients with schizophrenia[21–23] but not among patients with bipolar mania,[24] this increase in weight relative to placebo does not appear to be sustained during long-term (26 weeks') treatment.[25] In parallel, treatment with aripiprazole has not been reported to result in greater increases in serum prolactin levels than placebo.[21–25] In fact, 2 trials demonstrate significant decreases in serum prolactin levels relative to placebo among aripiprazole-treated patients,[22,24] which may be explained by the partial agonist properties of aripiprazole at the D_2 receptor. Interestingly enough, treatment with aripiprazole also did not appear to result in greater incidence/severity of EPS than placebo,[21–23,25] even though doses used in those trials (15–30 mg) have been shown to result in greater than 85% striatal D_2 occupancy in vivo.[26] Finally, treatment with aripiprazole also does not appear to be associated with increases in serum lipids, fasting blood glucose levels,[22–25] or the QTc interval.[21–25] The most common side effects reported during treatment with aripiprazole include sedation, insomnia, fatigue, headache, tremor, akathisia/restlessness, and nausea.[21,24]

In summary, aripiprazole appears to be safe and well tolerated, with a very low likelihood of sedation, weight gain, prolactin elevation, or extrapyramidal side effects. Due to its unique receptor-affinity profile, it has been hypothesized that aripiprazole may be particularly useful when used in conjunction with standard antidepressants in treatment-resistant MDD. In fact, the results of a recent case report[27] as well as a retrospective chart review[28] suggest that adjunctive treatment with aripiprazole may result in significant improvement of mood and/or anxiety symptoms among outpatients with SSRI-resistant mood or anxiety disorders. The goal of this study was to assess, in a prospective, open-label fashion, the efficacy of aripiprazole augmentation in the management of depression resistant to SSRIs.

METHOD

Subject Selection

Data were collected from August 2003 to July 2004. Study subjects were recruited through general newspaper and radio advertisements that listed common symptoms of depression or through clinical referrals. Men and women, ages 18 to 65, with MDD diagnosed by the use of the Structured Clinical Interview for DSM-IV–Axis I Disorders[29] and with an initial 17-item Hamilton Rating Scale for Depression (HAM-D-17) score[30] ≥ 14, were eligible for the study. All patients had been treated with an adequate trial of an SSRI prior to study entry, defined as a *minimum dose* of 10 mg/day for escitalopram; 20 mg/day for fluoxetine, paroxetine, and citalopram; or 50 mg/day for sertraline, for a *minimum duration* of 6 weeks. All patients were taking an SSRI at the time of study enrollment, and had been at that dose for at least 4 weeks. All patients continued their SSRI medication at the same dose throughout the study.

The following patients were excluded: pregnant women, patients who posed a serious suicidal or homicidal risk, and patients with organic mental disorders, an active substance or alcohol use disorder within the last 3 months, schizophrenia, delusional disorder, mood-congruent or -incongruent psychotic symptoms, bipolar disorder, antisocial personality disorder, or a history of an allergy to the study drug or a history of multiple drug allergies. Patients with significant cardiac conduction problems on screening electrocardiogram, electrolyte abnormalities, significant cardiovascular disease, or a history of QTc prolongation, or who were taking medications that prolong the QTc, were also excluded. Finally, patients who during the course of their current major depressive episode (MDE) had failed to respond to 4 or more adequate antidepressant trials, or patients who had had electroconvulsive therapy within 6 months of study enrollment, were excluded.

Study Procedures

A total of 12 subjects were enrolled at the Depression Clinical and Research Program at Massachusetts General Hospital (Boston, Mass.) (N = 10) and the Anxiety Disorders Research Program at Cambridge Health Alliance (Cambridge, Mass.) (N = 2). Institutional Review Board–approved written informed consent was obtained before any protocol-specified procedures were carried out. Patients were seen weekly for the first 6 weeks, then at week 8 for the final visit. The following instruments were administered during each visit by experienced psychiatrists and psychologists who were trained in their use: the HAM-D-17 and the Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales.[31] During the first visit, all patients were instructed to take 1 tablet of the study medication containing aripiprazole

15 mg daily if they were taking citalopram, escitalopram, or sertraline. Since aripiprazole is metabolized by the cytochrome P450 2D6 enzyme,[32] patients taking either fluoxetine or paroxetine, both inhibitors of that enzyme, were instructed to take 1 tablet containing aripiprazole 10 mg instead to avoid a considerable increase in blood aripiprazole levels. Starting with week 2, the medication dosage was increased by 10- to 15-mg/week increments up to a daily dose of 30 mg, or until patients experienced a clinical response or significant side effects. Clinicians also had the option of decreasing the dose for patients who could not tolerate higher doses. Compliance with aripiprazole was assessed on the basis of pill count and office appointments. Acceptable compliance necessary for a patient to be able to continue participating in the study was defined as no less than 85% compliance from visit to visit, including no more than 3 consecutive days without medication (aripiprazole). At the conclusion of the trial, responders and nonresponders were offered the option of up to 3 months' free follow-up.

Statistical Tests

The primary test of outcome was based on the assessment of the difference between baseline and endpoint in depression severity following treatment with aripiprazole. Clinical response was defined as a 50% or greater reduction in HAM-D-17 score from baseline to endpoint. Remission was defined as a final HAM-D-17 score ≤ 7. A paired t test was used to assess the changes in depression severity between the baseline HAM-D-17 score and the endpoint HAM-D-17 score. Two analyses were completed: (1) a completer analysis of all patients finishing the trial and (2) an intent-to-treat (ITT) analysis examining all patients enrolled in the trial, using the last recorded HAM-D-17 score as the endpoint.[33]

RESULTS

The mean ± SD age for all patients was 46.6 ± 11.3 years, and the gender distribution was 8/12 women (66.7%). The mean duration of the current MDE was 20.0 ± 23.0 months, while the mean age at onset of MDD was 29.0 ± 15.1 years. The mean number of lifetime MDEs was 4.1 ± 5.7. The mean number of adequate antidepressant trials failed during the current MDE was 2.2 ± 0.7. The mean total HAM-D-17 and CGI-S scores during the baseline visit were 22.8 ± 4.5 (range, 16–32) and 4.9 ± 0.6, respectively. Overall, 1 patient enrolled had an MDE resistant to fluoxetine (20 mg), 2 to citalopram (40 mg each), and 9 to escitalopram (mean dose 23.3 ± 5.0 mg; range, 20–30 mg). The mean duration of the SSRI-augmented trial was 9.7 ± 5.1 weeks (range, 6–24 weeks). Of note, all but 1 patient failed to respond to SSRI doses higher than the required minimum for enrollment in the study (20 mg of fluoxetine, 20 mg of citalopram, or 10 mg of escitalopram was the minimum daily dosage to meet criteria for enrollment in the study), and all but 4 patients failed to respond to an SSRI trial longer than the required minimum for enrollment (6 weeks was the minimum duration).

Table 1. Common Side Effects[a] in 12 Patients With SSRI-Resistant MDD Treated With Adjunctive Aripiprazole for 8 Weeks

Side Effect	% (N)
Nervous	
Fatigue/sedation	58.3 (7)
Restlessness	16.7 (2)
Poor concentration	16.7 (2)
Gastrointestinal	
Nausea	25.0 (3)
Diarrhea	25.0 (3)

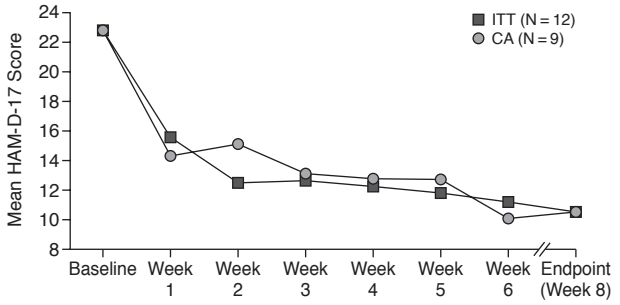
[a]Defined as reported by 2 or more patients.
Abbreviations: MDD = major depressive disorder, SSRI = selective serotonin reuptake inhibitor.

Nine (75.0%) of 12 patients completed the 8-week trial. The reasons for premature discontinuation were intolerance (2/12 or 16.7%—reasons were restlessness in 1 patient who had not responded to treatment and fatigue in a second patient who had achieved remission—patients discontinued during weeks 2 and 6, respectively) and loss to follow-up in a remitter (1/12 or 8.3%—discontinued during week 6). Adverse events (defined as events that, in the opinion of the evaluating clinician, were more likely to be attributed to aripiprazole rather than to SSRI treatment or disease state) reported by 2 or more patients are listed in Table 1. No patient experienced a severe adverse event. There was no change in mean QTc (0.422 ± 0.015 msec versus 0.421 ± 0.016 msec, respectively, $p > .05$ paired t test), serum cholesterol levels (5.1 ± 1.2 mmol/L versus 5.2 ± 0.9 mmol/L, $p > .05$ paired t test), serum glucose levels (5.6 ± 0.7 mmol/L versus 5.3 ± 0.9 mmol/L, $p > .05$ paired t test), or weight (180.8 ± 60.2 lb versus 183.9 ± 60.0 lb, $p > .05$ paired t test) from baseline to week 8. Using a completer analysis, 5/9 (55.6%) patients were classified as responders. An ITT analysis resulted in 7 responders (58.3%). The overall proportion of remitters was 3/9 (33.3%) using a completer analysis and 5/12 (41.7%) using the ITT analysis. There was also a significant reduction in mean CGI-S (4.9 ± 0.6 to 2.7 ± 1.4, $p = .0002$) and HAM-D-17 (22.8 ± 4.5 to 10.5 ± 5.0, $p < .0001$) scores during the trial in the ITT sample (N = 12). The mean daily maximum aripiprazole dose was 22.8 ± 4.5 mg. Figure 1 presents mean HAM-D-17 scores by week for ITT and completer group samples.

DISCUSSION

The present findings suggest the potential usefulness of aripiprazole as an augmentation to SSRIs in TRD. Among 12 patients with an MDE resistant to an adequate trial of an SSRI, 7 responded (58.3%), 5 (41.7%) of whom

Figure 1. HAM-D-17 Scores of Patients With SSRI-Resistant MDD Treated With Adjunctive Aripiprazole for 8 Weeks



Abbreviations: CA = completer analysis, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, ITT = intent-to-treat analysis, MDD = major depressive disorder, SSRI = selective serotonin reuptake inhibitor.

achieved remission, following adjunctive treatment with aripiprazole. In addition, when we examined the rate of change of depressive symptoms over time, improvement with aripiprazole appeared robust and rapid, with a considerable proportion of overall improvement having occurred within the first week of treatment (see Figure 1). This is in accordance with 3 other studies reporting rapid improvement in depressive symptoms with ziprasidone,[8] olanzapine,[11] and risperidone[9] augmentation of SSRIs. Finally, given the small sample size, it is difficult to draw definitive conclusions on the overall tolerability of aripiprazole augmentation in MDD, although statistically significant increases in QTc, serum cholesterol, plasma glucose, or weight during the course of treatment were not observed. However, fatigue was reported in as many as 58.3% of patients. Other common adverse events included restlessness, poor concentration, nausea, and diarrhea.

The major limitation of this study was the absence of placebo, which would help control for nonspecific treatment effects of the trial. Without the use of placebo, it is impossible to separate augmentation drug response from clinical response due to continued administration of the SSRI. However, given that the present sample consisted of patients with TRD, it is reasonable to assume that the placebo response rate would be much lower, perhaps as low as 10% according to some authors,[34] and as suggested by a recent placebo-controlled trial of refractory depression conducted by our group.[35] In this context, a response rate of 58.3% is likely to be clinically significant.

While it is important to keep in mind that the relatively short *minimal* adequate duration of 6 weeks for an SSRI trial as a criterion for study entry may have been responsible for considerable response to continued treatment with the SSRI, in reality, most (8/12) patients enrolled in the present trial had actually been treated with an SSRI for 8 weeks or more. An additional limitation is the definition of *minimal* adequate SSRI dose for study entry as an equivalent of 20 mg of fluoxetine, 10 mg of escitalopram, or 20 mg of citalopram, although 11 of 12 enrolled patients had failed higher doses. A further limitation is the definition of minimal severity for entry into the study as baseline HAM-D-17 score ≥ 14, although all patients enrolled had a HAM-D-17 score at baseline greater than 14 (mean HAM-D-17 score at baseline was 22.8 ± 4.5; range, 16–32).

CONCLUSION

More than half of all patients with depression resistant to an adequate trial of SSRIs responded when aripiprazole was added to their antidepressant regimen, with most responders experiencing complete remission by the end of the trial. If the present results are supported by larger, double-blind, placebo-controlled studies, aripiprazole augmentation should be among the options considered after a patient does not respond to an adequate SSRI trial.

Drug names: aripiprazole (Abilify), citalopram (Celexa and others), escitalopram (Lexapro), fluoxetine (Prozac and others), olanzapine (Zyprexa), paroxetine (Paxil and others), risperidone (Risperdal), sertraline (Zoloft), ziprasidone (Geodon).

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