The Efficacy and Safety of Aripiprazole as Adjunctive Therapy in Major Depressive Disorder: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study

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Objective: To assess the efficacy and safety of aripiprazole versus placebo as adjunctive treatment to standard antidepressant therapy (ADT) in patients with major depressive disorder (MDD) who showed an incomplete response to 1 prospective and 1 to 3 historical courses of ADT within the current episode.

Method: The study comprised a 7- to 28-day screening phase, an 8-week prospective treatment phase, and a 6-week double-blind treatment phase. Patients with DSM-IV-TR–defined MDD were enrolled between June 16, 2004, and April 27, 2006. During prospective treatment, patients received ADT: escitalopram, fluoxetine, paroxetine controlled-release, sertraline, or venlafaxine extended-release, each with single-blind, adjunctive placebo. Incomplete responders continued ADT and were randomly assigned to double-blind, adjunctive placebo or adjunctive aripiprazole (2–15 mg/day with fluoxetine or paroxetine; 2–20 mg/day with all others). The primary efficacy endpoint was the mean change from end of prospective treatment to end of double-blind treatment (week 14, last observation carried forward) in Montgomery-Asberg Depression Rating Scale (MADRS) total score (analysis of covariance).

Results: A total of 178 patients were randomly assigned to adjunctive placebo and 184 to adjunctive aripiprazole. Baseline demographics were similar between groups (mean MADRS total score of 26.0). Mean change in MADRS total score was significantly greater with adjunctive aripiprazole (–8.8) than adjunctive placebo (–5.8; $p < .001$). Adverse events (AEs) that occurred in ≥ 10% of patients with adjunctive placebo or adjunctive aripiprazole were akathisia (4.5% vs. 23.1%), headache (10.8% vs. 6.0%), and restlessness (3.4% vs. 14.3%). Discontinuations due to AEs were low with adjunctive placebo (1.7%) and adjunctive aripiprazole (2.2%); only 1 adjunctive aripiprazole–treated patient discontinued due to akathisia.

Conclusions: In patients with MDD who showed an incomplete response to ADT, adjunctive aripiprazole was efficacious and well tolerated.

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Despite advances in the understanding and treatment of depression over the past decades, failure to achieve an adequate treatment response remains a prominent clinical problem. Up to 60% of patients do not fulfill conventional remission criteria following treatment with at least 1 antidepressant of adequate dose and duration.[1] Many patients only achieve partial response (e.g., 25%–49% reduction in symptoms) or continue to experience residual symptoms.[2] This is of significant concern, as patients with residual symptoms have reduced functioning and a worse prognosis than patients who achieve remission. Determining how to manage such patients is complicated by the wide range of different augmentation and combination strategies available and by the paucity of research to guide clinicians on how best to increase their patients' chances of achieving and sustaining remission from depression. One treatment algorithm that has undergone validation testing is the 4-step treatment path used in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. Strategies used in this algorithm included switching antidepressants and adding adjunctive medication to an ongoing regimen. In this study, almost

two-thirds of patients did not demonstrate an adequate treatment response (i.e., not in remission) after the first antidepressant trial.[3] Furthermore, remission rates were significantly diminished in patients who did not demonstrate a response after 2 antidepressant trials, demonstrating that there is still a need to improve the treatment of depression.

The rationale for investigating the use of aripiprazole as an adjunctive agent in the treatment of depression is supported on both an empirical and a pharmacologic basis. Open-label studies with multiple atypical antipsychotics have demonstrated their efficacy as adjunctive therapy in the treatment of depression[4–7]; however, randomized, controlled trials have failed to show consistently positive results or demonstrate the superiority of one agent over another.[8–12]

Aripiprazole has been shown to provide efficacy in treating depression symptoms in patients with schizophrenia[13] and bipolar disorder.[14] In addition, recent open-label studies[15–19] and a retrospective chart review[20] have reported the efficacy of adjunctive aripiprazole in patients with either an inadequate response or treatment-resistant depression. The pharmacologic rationale for the potential efficacy of aripiprazole as an adjunctive agent relates to its distinct pharmacologic profile. Aripiprazole has potent partial agonist activity at the D_2 and D_3 receptors. Additionally, aripiprazole is a partial agonist at the serotonin-1A ($5\text{-}HT_{1A}$) receptor and is an antagonist at $5\text{-}HT_2$ receptors—effects that may contribute to potential antidepressant action.[21–25] For example, adjunctive therapy with buspirone ($5\text{-}HT_{1A}$ partial agonist) and pramipexole (D_3 agonist) has demonstrated efficacy in treatment-resistant depression.[26]

The aim of this study was to compare the efficacy, safety, and tolerability of aripiprazole (2–20 mg/day) versus placebo as adjunctive treatment to standard antidepressant therapy (ADT) in the treatment of a major depressive episode in patients who have shown an incomplete response to a prospective 8-week trial of the same antidepressant agent and at least 1 historical ADT trial.

METHOD

Patients

This multicenter, randomized, double-blind, placebo-controlled study enrolled patients from 24 sites in the United States between June 16, 2004, and April 27, 2006. In accordance with the Declaration of Helsinki, the ethics committee at each site approved the protocol. All study participants eligible for enrollment in the screening phase met *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (DSM-IV-TR) criteria for a major depressive episode[27] that had lasted ≥ 8 weeks prior to inclusion without an adequate response. An inadequate response to antidepressant treatment was defined as a < 50% reduction in depressive symptoms severity, as assessed by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ)[1] within the current depressive episode. Patients were characterized by having an inadequate response to at least 1, and no more than 3, adequate antidepressant trials (> 6 weeks' duration at adequate dose as specified in the ATRQ). Patients could enter the prospective treatment phase if they had a 17-item Hamilton Rating Scale for Depression (HAM-D-17)[28] total score ≥ 18 at the end of the screening phase. For continuation into the double-blind treatment phase, patients had to have a HAM-D-17 total score that represented a < 50% reduction in symptoms during prospective treatment, a HAM-D-17 total score ≥ 14, and a Clinical Global Impressions-Improvement (CGI-I)[29] score of ≥ 3. Most psychotropic medications, including benzodiazepines and other hypnotics, were discontinued during the screening phase.

Patients were outpatients aged 18 to 65 years who could understand and comply with protocol requirements and provide written informed consent. Patients were excluded if they had a current Axis I diagnosis of delirium, dementia, amnestic or other cognitive disorder, schizophrenia or other psychotic disorder, bipolar I or II disorder, eating disorder, obsessive-compulsive disorder, panic disorder, or posttraumatic stress disorder or a clinically significant current Axis II diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder. Patients experiencing hallucinations, delusions, or any psychotic symptomatology in the current depressive episode were also excluded, as were patients who had met DSM-IV-TR criteria for any significant substance use disorder within the past 12 months.

Other reasons for exclusion included known allergy, hypersensitivity, or previous unresponsiveness to aripiprazole or known intolerance to other study medications. Patients were also excluded if they had participated in a clinical trial with aripiprazole or any other investigational product within the past month; had a history of thyroid pathology, neuroleptic malignant syndrome, or serotonin syndrome; had a significant history of seizure disorder; or had a positive screen for drugs of abuse. Also excluded were patients who had received adjunctive antipsychotic plus antidepressant for ≥ 3 weeks during the current episode and those who had received electroconvulsive therapy (ECT) for the current episode. Inadequate response to previous ECT in any episode also led to exclusion.

Additionally, patients were excluded if they posed a suicidal risk, were likely to require prohibited concomitant therapy during the trial, had received treatment with a monoamine oxidase inhibitor within 2 weeks prior to enrollment, or had been hospitalized within 4 weeks of the screening visit.

Study Design

The study comprised a 7- to 28-day screening phase, an 8-week prospective treatment phase, and a 6-week randomized, double-blind treatment phase (actual study visits week 8 to week 14). The prospective treatment phase was included to establish inadequate antidepressant response prior to randomization to study treatment. During this phase, patients experiencing a major depressive episode received single-blind (the investigator, but not the patient, knew of the treatment assignment), adjunctive placebo plus 1 of the following open-label standard ADTs according to label guidelines and were required to reach a target dose by the end of the third week: escitalopram (10 or 20 mg/day), fluoxetine (20 or 40 mg/day), paroxetine controlled-release (CR) (37.5 or 50 mg/day), sertraline (100 or 150 mg/day), or venlafaxine extended release (150 or 225 mg/day). Assignment of ADT was based on investigator assessment of clinical factors (e.g., prior antidepressant use, response, and tolerability), although use of any single ADT was limited to < 40% of patients. Patients who had only 1 adequate antidepressant trial in the current episode could not be assigned that antidepressant for prospective treatment. Investigators were encouraged to distribute their antidepressant choices equally and were required not to assign any one ADT to more than two fifths of their patients. Single-blind placebo treatment during this phase was used to blind patients to the transition into the randomization phase.

Patients who met the study criteria for incomplete response at the end of the prospective treatment phase were eligible to enter the double-blind, randomized treatment phase. Double-blind treatment was randomly allocated according to a permuted block design with a fixed block size of 4, stratified by study center, in a 1:1 ratio to either adjunctive placebo or adjunctive aripiprazole, in addition to continuation of the same antidepressant from the previous phase. Patients who responded to prospective treatment, and therefore were not eligible to enter the double-blind treatment phase, were assigned to 6 weeks of treatment with single-blind adjunctive placebo plus the assigned ADT taken during the prospective treatment phase. These patients were followed with fewer study visits than patients randomly assigned to double-blind treatment (data to be reported separately).

Dosing Schedule for Double-Blind Treatment

During the double-blind treatment phase, patients continued to receive the same fixed-dose ADT that they were receiving at the end of the prospective treatment phase. Dose adjustment of ADT was not permitted during the double-blind treatment phase; patients not tolerating treatment were discontinued from the study. Patients randomly assigned to receive adjunctive aripiprazole were treated with a starting dose of 5 mg/day, which could be increased weekly in 5 mg/day increments to a maximum dose of 15 mg/day (patients receiving fluoxetine or paroxetine CR, due to their cytochrome P450 2D6 inhibition increasing aripiprazole levels) or 20 mg/day (all other patients) based on assessment of tolerability and clinical response. Doses could be decreased at any visit, based on tolerability; patients unable to tolerate 5 mg/day could have their dose decreased to 2 mg/day. No dose increase was permitted in the last week of the study.

Assessments

Screening assessments included a standard medical, psychiatric, and antidepressant (ATRQ) history, physical examination, 12-lead electrocardiography (ECG), clinical laboratory tests, pregnancy test (where applicable), vital signs, and drug screens. During the 8-week prospective treatment phase, patients were seen weekly for the first 4 weeks and every 2 weeks thereafter to assess efficacy and safety. Patients were then assessed weekly for the 6-week duration of double-blind treatment.

The primary efficacy endpoint was the mean change in Montgomery-Asberg Depression Rating Scale (MADRS)[30] total score from the end of prospective treatment (week 8 visit) to the end of double-blind treatment (week 14, last observation carried forward [LOCF]). The key secondary endpoint was the mean change from the end of the prospective treatment phase to the end of the double-blind treatment phase (week 14 visit, LOCF) in the Sheehan Disability Scale (SDS) mean score. The SDS is a 3-item patient-rated instrument used to assess the impact of illness-related impairment in 3 domains of functioning (work/school, social life, and family life/home responsibilities), with each item scored from 0 (not at all) to 10 (extreme).[31] Additional efficacy measures included mean change in MADRS total score by week, mean change in Clinical Global Impressions-Severity of Illness (CGI-S)[29] score, mean change in Inventory of Depressive Symptomatology Self-Report Scale (IDS-SR)[32] total score, and CGI-I endpoint score. Furthermore, response and remission rates were assessed. Response was defined as a reduction in MADRS total score of at least 50% relative to the end of the prospective treatment phase. Remission was defined as response plus an absolute MADRS total score of ≤ 10. Clinical Global Impressions-Improvement response was defined as a CGI-I score of 1 or 2 (very much improved or much improved).

Subgroup analyses of change from end of the prospective treatment phase in MADRS total score to every study week in the randomized, double-blind phase were performed by gender, by ADT, by age group, and by response on the MADRS at the end of the prospective treatment phase relative to baseline.

Safety assessments included spontaneous reporting of adverse events (AEs), physical examination, measurement of vital signs and body weight, and 12-lead ECG. Laboratory assessments included hematologic evaluations, fast-

ing serum chemistries, urinalysis, urine screen for drugs of abuse, blood alcohol level, and pregnancy testing. Extrapyramidal symptom (EPS)-related AEs were assessed using the Abnormal Involuntary Movement Scale (AIMS),[33] Simpson-Angus Scale (SAS),[34] and Barnes Akathisia Rating Scale (BARS).[35] Sexual functioning was evaluated using the Sexual Function Inventory (SFI) questionnaire. The SFI is a self-report instrument to assess changes in multiple aspects of sexual functioning (interest, arousal, ability to achieve orgasm, satisfaction, overall improvement, and, in men, erectile function).[36]

Statistics

Patient samples and analysis data sets. Safety summaries include all randomized patients who received double-blind study medication, whereas efficacy analyses include all patients who received double-blind study medication and who had at least 1 post-randomization efficacy evaluation in the double-blind treatment phase. The LOCF data for each visit included the data recorded at that visit, or otherwise the data carried forward from the last visit in the double-blind phase. All efficacy analyses presented are based on LOCF.

Primary and secondary outcome measures. The primary endpoint, mean change in MADRS total score from the end of prospective treatment to end of double-blind treatment, was assessed by analysis of covariance (ANCOVA), with the score at the end of prospective treatment as a covariate and treatment and study center as main effects. For all the primary and secondary endpoints, change is determined relative to the end of the prospective phase of treatment. Mean change in MADRS total score within subgroups was evaluated for gender, ADT, age group (4 levels defined by quartiles), and MADRS response at the end of the prospective treatment phase (< 25% and ≥ 25%). ANCOVA models were applied to each of the 13 subgroups, including the MADRS total score at the end of the prospective treatment phase as covariate and treatment as main effect. To investigate interactions of treatment with subgroups, ANCOVA models were applied including the MADRS total score at the end of the prospective treatment phase as covariate, treatment and subgroup as main effects, and a treatment-by-subgroup interaction term. The key secondary outcome measure was the mean change in the SDS mean score from the end of the prospective treatment phase to the end of the double-blind treatment phase. Changes in SDS mean score, in CGI-S score, and in IDS-SR total score were evaluated using ANCOVA, with the score at the end of the prospective treatment phase as covariate and with treatment and study center as main effects. Clinical Global Impressions-Improvement mean score was evaluated using ANCOVA, with the CGI-S score at the end of the prospective treatment phase as covariate and with treatment and study center as main effects. Response and remission rates were evaluated using a Cochran-Mantel-Haenszel (CMH) general association test, controlling for study center.

Safety analyses. Mean changes in SAS and AIMS total scores and in BARS Global Clinical Assessment of Akathisia score were assessed by ANCOVA, with the score at the end of prospective treatment as covariate and treatment and study center as main effects. Mean changes in SFI scores were assessed by ANCOVA, with the end of prospective treatment score as covariate and treatment, gender, and study center as main effects. Mean change in body weight was assessed by ANCOVA, with weight at the end of prospective treatment as covariate and treatment as main effect. The proportions of patients with at least 7% weight gain were evaluated using a CMH general association test. No formal statistical testing was applied to incidences of patients with AEs or potentially clinically significant abnormalities in vital signs, ECGs, or laboratory measurements.

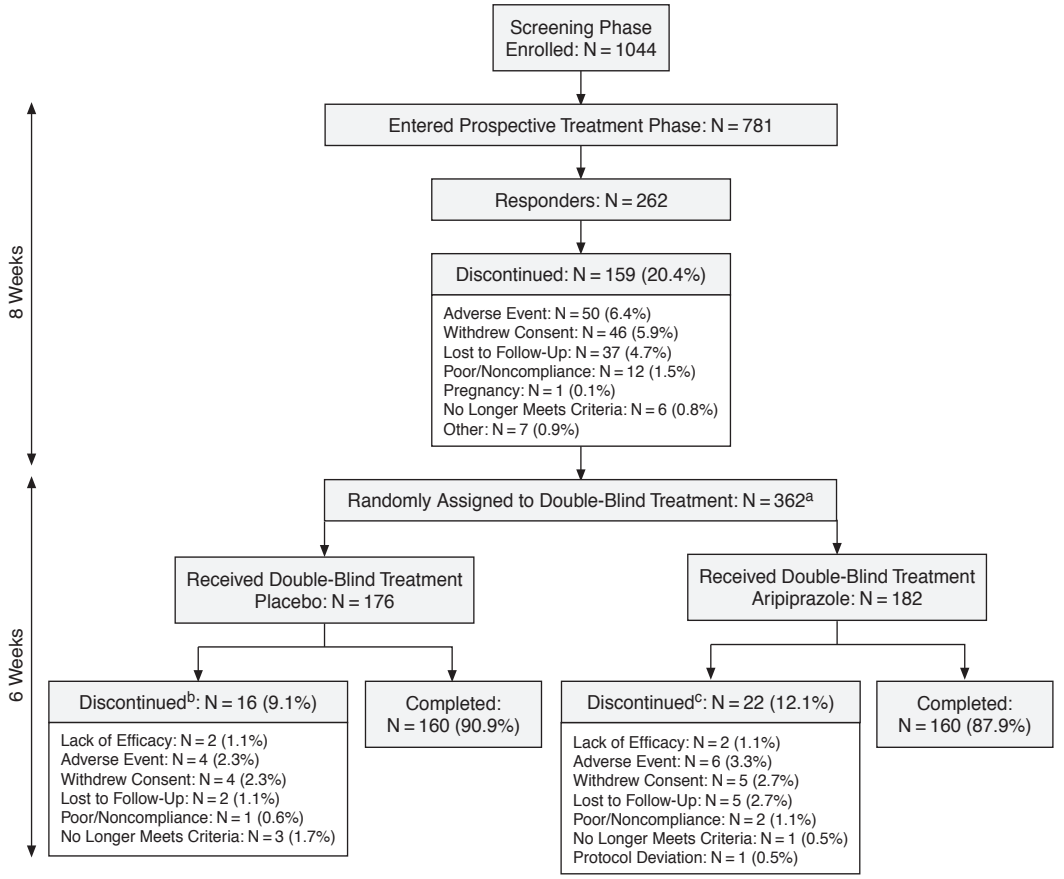
RESULTS

Patient Disposition and Characteristics

A total of 1044 patients were screened in this study, of whom 781 were eligible for enrollment and continuation into the prospective treatment phase (Figure 1). Of these, 159 patients (20.4%) discontinued treatment during the prospective treatment phase. Of the 622 patients who completed the prospective treatment phase, 42% met the criteria for response (HAM-D-17 improvement ≥ 50%; or HAM-D-17 score < 14; or CGI-I score < 3). In total, 362 patients were randomly assigned to adjunctive placebo (N = 178) or adjunctive aripiprazole (N = 184). This included 2 patients, both randomly assigned to aripiprazole, who had discontinued already during the prospective treatment phase but were randomly assigned in error, and a further 2 patients, both randomly assigned to placebo, who were lost to follow-up before receiving double-blind study medication. Safety results included all patients who received double-blind treatment (adjunctive placebo N = 176; adjunctive aripiprazole N = 182). During the double-blind treatment phase, the rate of treatment discontinuations among those patients who received double-blind study medication was similar in the adjunctive placebo and adjunctive aripiprazole groups (placebo 9.1%; aripiprazole 12.1%). In both groups, the most common reasons for discontinuation were AEs (placebo 2.3%; aripiprazole 3.3%), withdrawal of consent (placebo 2.3%; aripiprazole 2.7%), and loss to follow-up (placebo 1.1%; aripiprazole 2.7%).

Table 1 summarizes the characteristics of patients treated with double-blind study medication. Baseline demographics were similar between treatment groups. The duration of current illness in each group was also comparable and underscores the chronicity of the study population. Both groups were similar with regard to number of previous adequate antidepressant trials.

Figure 1. Patient Disposition



[a]Four randomly assigned patients were never treated with double-blind study medication.
[b]In the placebo group, 4 patients discontinued prior to undergoing any efficacy assessment.
[c]In the aripiprazole group, 1 patient discontinued prior to undergoing any efficacy assessment.

Treatment and Dosing

The distribution of each ADT at randomization to double-blind treatment was as follows: escitalopram, 29.6%; fluoxetine, 14.2%; paroxetine, 8.9%; sertraline, 19.8%; venlafaxine, 27.4%. This was similar to the distribution during the prospective treatment phase. The mean dose of adjunctive aripiprazole was 11.8 mg/day during the last week of double-blind treatment and was similar between ADT treatment groups: escitalopram 11 mg/day; fluoxetine 11 mg/day; paroxetine 10 mg/day; sertraline 14 mg/day; venlafaxine 12 mg/day. Among those patients who demonstrated a treatment response at endpoint with adjunctive aripiprazole, the distribution of doses at endpoint was as follows: 2 mg/day, 7%; 5 mg/day, 20%; 10 mg/day, 23%; 15 mg/day, 31%; and 20 mg/day, 20%. The dose equivalent in the placebo group was slightly higher: 15.7 mg/day.

Efficacy

At endpoint, the mean change in MADRS total score was significantly greater in patients receiving adjunctive aripiprazole (–8.8) than in those who received adjunctive placebo (–5.8, $p < .001$; Figure 2), providing a standardized treatment effect size of 0.39 in favor of aripiprazole. The difference in reduction of MADRS total score between treatment groups was already apparent by week 2 of double-blind treatment (adjunctive placebo –3.4 vs. adjunctive aripiprazole –6.3, $p < .001$), and the adjunctive aripiprazole group continued to show improvement throughout the study. Compared with adjunctive placebo, adjunctive aripiprazole also produced significantly greater remission rates during double-blind treatment from week 3 (8.7% vs. 18.8%, $p = .006$) through to endpoint (15.7% vs. 26.0%, $p = .011$) (Figure 3), providing a number needed-to-treat for remission of 10. Compared with adjunctive placebo, adjunctive aripiprazole provided significantly greater response rates from week 1 (1.8% vs. 6.2%, $p = .025$) through to endpoint (23.8% vs. 33.7%, $p = .027$) (Figure 4).

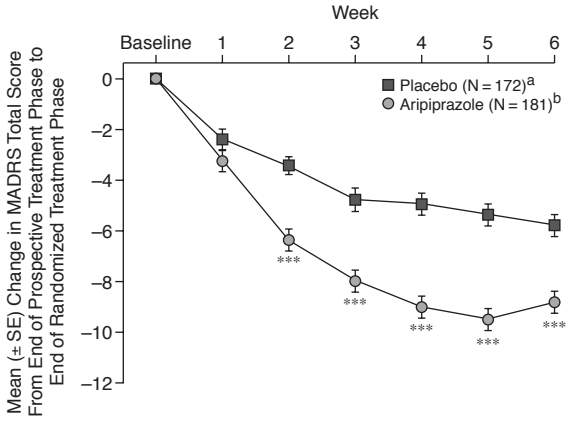
The mean change in SDS total scores showed a nonsignificant trend toward greater improvements in impairment

Table 1. Baseline Demographic and Disease Characteristics of Patients Treated With Double-Blind Study Medication

Characteristic	Placebo (N = 176)	Aripiprazole (N = 182)
Gender, N (%)		
Male	63 (35.8)	70 (38.5)
Female	113 (64.2)	112 (61.5)
Age, mean (SD), y	44.2 (10.9)	46.5 (10.6)
Race, N (%)		
White	163 (92.6)	159 (87.4)
Black/African American	10 (5.7)	15 (8.2)
Asian	0 (0)	3 (1.6)
American Indian/Alaska Native	0 (0)	1 (0.5)
Native Hawaiian/ other Pacific Islander	0 (0)	1 (0.5)
Other	3 (1.7)	3 (1.6)
Weight, mean (SD), kg	86.2 (20.7)	84.5 (19.5)
Duration of current episode, mo		
Mean (SD)	43.6 (53.8)	38.6 (59.0)
Median (range)	23.1 (3.0–328.7)	21.0 (1.7–474.1)
No. of prior adequate antidepressant trials in current episode, N (%)		
1 trial	117 (66.5)	121 (66.5)
2 trials	45 (25.6)	45 (24.7)
3 trials	14 (8.0)	16 (8.8)
Depressive episode, N (%)		
Single	53 (30.1)	39 (21.4)
Recurrent	123 (69.9)	143 (78.6)
MADRS total score, mean (SD)	25.9 (6.5)	26.0 (6.1)

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, SD = standard deviation.

Figure 2. Mean Change (± SE) in MADRS Total Score During Double-Blind Treatment Phase (LOCF)



[a]In the placebo group, 4 patients discontinued prior to undergoing any efficacy assessment.
[b]In the aripiprazole group, 1 patient discontinued prior to undergoing any efficacy assessment.
***p < .001 vs. placebo.
Abbreviations: LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, SE = standard error.

among adjunctive aripiprazole–treated patients than adjunctive placebo–treated patients (Figure 5). Statistically significant differences between adjunctive aripiprazole and placebo were observed on 2 of the 3 domains: family/home responsibilities and social activities (Figure 5).

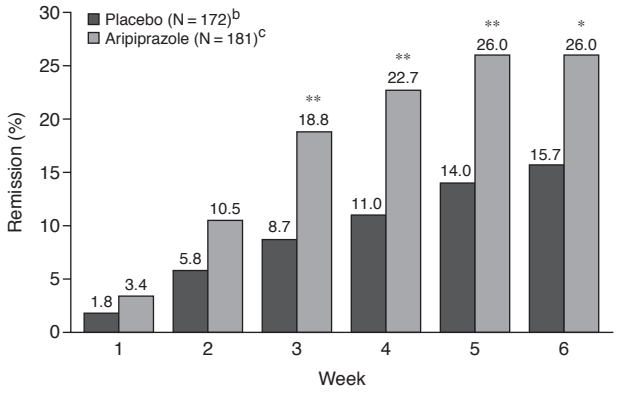
For additional secondary efficacy measures, adjunctive aripiprazole demonstrated a significantly greater decrease in CGI-S score at endpoint compared with adjunctive placebo (Table 2). Endpoint CGI-I scores and CGI-I response both showed significantly greater improvement with adjunctive aripiprazole than adjunctive placebo. The early separation of the 2 groups on the CGI-I response by week 2 is reflective of the findings on the primary endpoint. While differences on the IDS-SR were significant at weeks 2, 3, 4, and 5, significance was not shown at endpoint (p = .076).

Analyses were performed on multiple prespecified subgroups defined by psychiatric and demographic variables. Results across each of these subgroups consistently favored aripiprazole over placebo, with the only exception being the subgroup of men. The treatment difference in endpoint MADRS mean change scores favored aripiprazole over placebo in women, with a treatment difference of –5.00, while in men a treatment difference in MADRS total score of 0.48 favored placebo over aripiprazole. Although the treatment-by-gender interaction term was significant in the ANCOVA model (p = .002), an additional test (Gail-Simon test[37]) was performed to test for a qualitative interaction, and this test was not statistically significant (p = .359), indicating a lack of evidence of a directionally different treatment effect between men and women. In addition, this observed differential response was only seen in the last 2 weeks of the study. During the first 4 weeks of the double-blind, randomization phase, treatment differences between adjunctive aripiprazole– and adjunctive placebo–treated patients continuously increased, favoring adjunctive aripiprazole, for both men and women. However, in the last 2 weeks of the study, men in the adjunctive placebo group showed a substantial increase in response, while the change in MADRS total score in men who received adjunctive aripiprazole and in both female groups stayed the same or slightly worsened.

Tolerability

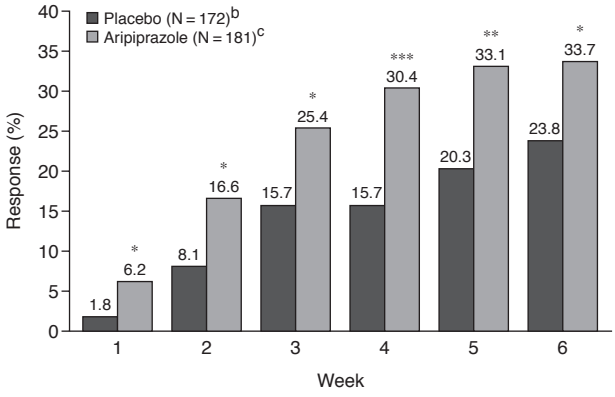
During the double-blind phase, 110 (62.5%) of 176 patients receiving adjunctive placebo and 149 (81.9%) of 182 patients receiving adjunctive aripiprazole reported at least 1 AE. Adverse events occurring at an incidence ≥ 5% in either treatment group are shown in Table 3. The most commonly reported AEs (incidence ≥ 10% of patients) in either the adjunctive placebo or adjunctive aripiprazole group included akathisia (adjunctive placebo 4.5%; adjunctive aripiprazole 23.1%), restlessness (3.4% and 14.3%), and headache (10.8% and 6.0%). By the last visit, continuing akathisia was reported in 19 patients (10% of the entire aripiprazole-treated sample), for whom this was mostly regarded as mild (79%) compared to moderate (16%) or severe (5%). Only 1 subject discontinued

Figure 3. Remission[a] Rates With Adjunctive Placebo or Adjunctive Aripiprazole During the Double-Blind Treatment Phase (LOCF)



[a]Remission defined as MADRS total score of ≤ 10 and ≥ 50% reduction in MADRS total score from end of prospective treatment. Rates presented are non-cumulative.
[b]In the placebo group, 4 patients discontinued prior to undergoing any efficacy assessment.
[c]In the aripiprazole group, 1 patient discontinued prior to undergoing any efficacy assessment.
*p < .05 vs. placebo.
**p < .01 vs. placebo.
Abbreviations: LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 4. Response[a] Rates With Adjunctive Placebo or Adjunctive Aripiprazole During the Double-Blind Treatment Phase (LOCF)



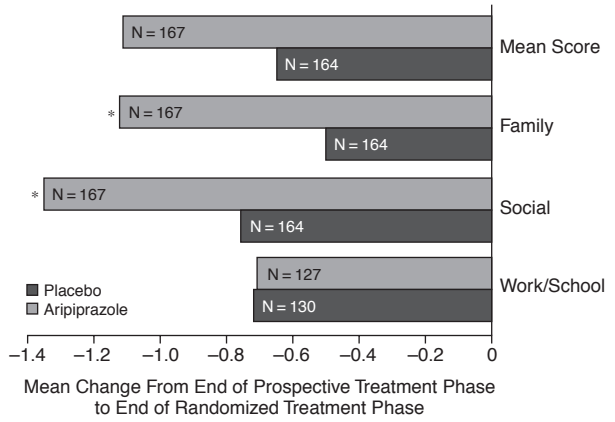
[a]Response defined as ≥ 50% decrease in MADRS total score from end of prospective treatment. Rates presented are non-cumulative.
[b]In the placebo group, 4 patients discontinued prior to undergoing any efficacy assessment.
[c]In the aripiprazole group, 1 patient discontinued prior to undergoing any efficacy assessment.
*p < .05 vs. placebo.
**p < .01 vs. placebo.
***p < .001 vs. placebo.
Abbreviations: LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

due to akathisia. Overall EPS–related AEs were reported by 9.7% of placebo-treated patients and 27.5% of aripiprazole-treated patients. Akathisia was reported in 4.5% of adjunctive placebo–treated patients compared with 23.1% of adjunctive aripiprazole–treated patients. Non-akathisia EPS-related AEs occurred in 5.1% of adjunctive placebo–treated and 4.4% of adjunctive aripiprazole–treated patients. During the double-blind randomized treatment phase, 2 AEs related to suicide (specifically, suicidal ideation) were reported, both in subjects who were randomly assigned to adjunctive placebo. Serious AEs (SAEs) occurred in 3 adjunctive placebo–treated patients (1.7%). One patient had exostosis, the second patient had cellulitis and staphylococcal abscess, and the third had SAEs reported of contusion and physical assault. Serious AEs were reported in 2 adjunctive aripiprazole–treated patients (1.1%). One patient had pneumonia, and the other had staphylococcal cellulitis.

The rate of discontinuation due to any AEs was low and similar in both groups (adjunctive placebo 1.7%; adjunctive aripiprazole 2.2%). Of the AEs that occurred in ≥ 10% in either treatment group, apart from the single patient (0.5%) who discontinued due to akathisia, 1 patient discontinued due to insomnia (0.5%).

Analysis of mean weight change from the end of prospective treatment to the end of double-blind treatment showed that patients treated with adjunctive aripiprazole had a significantly greater mean weight gain (+2.01 ± 0.17 kg) than patients treated with adjunctive placebo (+0.34 ± 0.18 kg; p < .001). There was also a significant difference in the proportion of patients showing ≥ 7% weight gain (adjunctive placebo 1.2%; adjunctive aripiprazole 7.1%; p = .008).

Figure 5. Mean Change in SDS Mean Score and Family, Social, and Work/School Items (LOCF)



*p < .05 vs. placebo.
Abbreviations: LOCF = last observation carried forward, SDS = Sheehan Disability Scale.

During the double-blind phase, minimal mean changes from the end of the prospective treatment phase were

Table 2. Secondary Efficacy Endpoints (LOCF) in the 6-Week Double-Blind Phase

Rating Scale	Placebo (N = 172)[a]	Aripiprazole (N = 181)[a]	p Value[b]
CGI-S			
Score at randomization, mean (SE)	4.11 (0.05)	4.08 (0.04)	
Change to week 6, mean (SE)	–0.64 (0.08)	–1.03 (0.08)	< .001
CGI-I			
Score at endpoint, mean (SE)	2.81 (0.09)	2.49 (0.08)	.003
Response, %[c]			
Week 1	12.2	18.3	.123
Week 2	22.7	35.0	.010
Week 3	28.5	45.3	< .001
Week 4	31.4	52.5	< .001
Week 5	32.6	51.4	< .001
Week 6	37.2	53.0	.002
IDS-SR			
Total score at randomization, mean (SE)	34.0 (1.1)	34.4 (1.0)	
Change to week 6, mean (SE)	–5.2 (0.8)	–7.0 (0.8)	.076

[a]Four patients treated with placebo and 1 patient treated with aripiprazole did not have efficacy assessments on double-blind treatment.
[b]p Values were based on analysis of covariance models (F-tests) in analyses of change from end of prospective treatment phase and on the Cochran-Mantel-Haenszel general association test in analyses of CGI-I response.
[c]Percentage of CGI-I responders (rating of "very much improved" or "much improved").
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, IDS-SR = Inventory of Depressive Symptomatology Self-Report Scale, LOCF = last observation carried forward, SE = standard error.

Table 3. Adverse Events Occurring During the Double-Blind Phase at an Incidence of ≥ 5% in Either Treatment Group, N (%)

Adverse Event	Placebo (N = 176)	Aripiprazole (N = 182)
Any adverse event	110 (62.5)	149 (81.9)
Akathisia	8 (4.5)	42 (23.1)
Restlessness	6 (3.4)	26 (14.3)
Upper respiratory tract infection	7 (4.0)	15 (8.2)
Insomnia	4 (2.3)	14 (7.7)
Vision blurred	3 (1.7)	12 (6.6)
Fatigue	6 (3.4)	11 (6.0)
Headache	19 (10.8)	11 (6.0)
Diarrhea	10 (5.7)	6 (3.3)
Dry mouth	11 (6.3)	6 (3.3)
Nausea	9 (5.1)	5 (2.7)

noted in SAS total score (0.08 vs. 0.28 at endpoint, for placebo and aripiprazole, respectively) and in AIMS total score (0.01 vs. 0.04 at endpoint for placebo and aripiprazole, respectively). However, the treatment difference at study endpoint in mean change from the end of the prospective treatment phase in BARS Global Clinical Assessment of Akathisia score (0.02 vs. 0.24 for placebo and aripiprazole, respectively) was statistically significant ($p < .001$).

During the double-blind randomization phase, both the placebo and aripiprazole groups generally reported minimal improvement in multiple domains of sexual functioning, as assessed by the SFI. Between-group differences favored aripiprazole on each of the 6 items (range, 0.05–0.22), but were not statistically significant.

There were no clinically meaningful differences between adjunctive placebo and adjunctive aripiprazole in vital signs, ECGs (including QTc findings), or laboratory abnormalities.

DISCUSSION

This is the first large-scale, randomized, prospective, double-blind, placebo-controlled trial to evaluate the efficacy and tolerability of aripiprazole augmentation in a well-defined population of patients with major depressive disorder (MDD) who have not achieved an adequate response after 2 to 4 adequate courses of antidepressant treatment in the current episode. Consistent with findings from previous small open-label studies,[16–20,38] the addition of aripiprazole to standard antidepressant treatment resulted in clinically meaningful improvements in depression symptoms compared with placebo. This was demonstrated by rapid improvements in MADRS total scores as early as week 2, with continued improvement in the aripiprazole group. Aripiprazole augmentation was also associated with significantly greater response and remission rates than placebo augmentation, as early as weeks 1 and 3, respectively. These results indicate that patients with MDD who show an incomplete response to standard antidepressant regimens may benefit from augmentation with aripiprazole.

Approximately 1 in 4 patients who had shown unresponsiveness to at least 2 previous antidepressant treatments achieved remission at the end of a 6-week treatment period with aripiprazole adjunctive to standard ADT. To put this finding into context, it should be considered that recently published results from the STAR*D study—the first large-scale study to examine the effectiveness of different treatment strategies for patients who did not become symptom-free after initial medication—have shown that lower acute remission rates are to be expected when more treatment steps are required.[3] The STAR*D study included a broadly representative population of nonpsychotic patients with MDD who initially received citalopram, but could then receive up to 3 additional treatment steps if they did not achieve remission or could not tolerate any given step. Acute remission rates were 37%, 31%, 14%, and 13% following treatment steps 1, 2, 3, and 4, respectively. Although there are inherent limitations in comparing results from studies using different methodologies and outcome measures, the remission rate of 26% achieved with aripiprazole augmentation in the study presented herein would seem favorable, given that the study population would correspond to step 3 in the STAR*D study, with regard to

previous treatment with at least 2 other agents before randomization.

With regard to other efficacy measures, CGI-S and CGI-I findings also showed that aripiprazole augmentation was significantly superior to placebo augmentation, confirming the efficacy of aripiprazole for the reduction of depressive symptoms. Importantly, given the impact of residual depression symptoms on psychosocial functioning,[2,39] patients receiving adjunctive aripiprazole reported significantly less impairment in family/home responsibilities and social activities than those who received adjunctive placebo, as rated using the SDS, although overall SDS scores were not significantly different.

Approximately half of the patients who completed the study and showed a response to adjunctive aripiprazole were receiving a dose of 10 mg/day or less. The starting dose of aripiprazole in this study was 5 mg/day, and the mean dose at the end of double-blind treatment was 11.8 mg/day, suggesting that the effective dose for many patients is lower than those recommended for schizophrenia and bipolar disorder. In the current study, the dose was increased to 10 mg/day as tolerated, with further adjustments based on efficacy. Given this obligatory titration based on tolerability, the true efficacious dose for some patients may have been lower. While some open-label studies support the effective use of lower doses,[17] others employed a dosing similar to that of the current study.[5,15,16,19,20]

The statistically significant interaction observed between response and gender at endpoint was an unexpected finding given the literature suggesting minimal[40] or modest[41] gender effects in nonresistant populations. It is possible that symptom improvement in placebo-treated men during the last 2 weeks may have contributed to the lack of a significant endpoint treatment effect, as differences were statistically significant at week 4. Further studies with adjunctive aripiprazole may help to clarify the significance of this interaction and whether it represents a type I error.

Aripiprazole augmentation was well tolerated. Despite a higher incidence of AEs with adjunctive aripiprazole than adjunctive placebo, completion rates were high and similar in both groups. No serious AEs were considered to be related to study medication, and the types of AEs reported here were consistent with those seen previously with aripiprazole. Although akathisia was the most common AE reported with adjunctive aripiprazole, in approximately half of the patients akathisia resolved before the end of the study. In the remaining cases, most often akathisia was reported to be mild, and only 1 patient discontinued treatment due to this AE. With regard to impact on sexual functioning, results on the SFI suggest that adjunctive aripiprazole does not confer adverse effects.

Aripiprazole augmentation was associated with greater weight gain than placebo during the 6-week treatment period; however, the overall magnitude of mean weight change with aripiprazole and the proportion of patients showing clinically significant weight gain are consistent with those observed in placebo-controlled studies of patients with schizophrenia.[42,43] Patients treated with olanzapine/fluoxetine combination have been shown to have significantly greater baseline-to-endpoint mean ± SD weight change than patients treated with fluoxetine alone (+4.9 ± 3.5 kg vs. +0.4 ± 2.3 kg; $p < .001$) during 8 weeks of treatment.[12]

The positive findings in this study are strengthened by the demonstration of both historical and prospective unresponsiveness to standard antidepressant treatment. One limitation of this study design is the lack of randomization to ADT during prospective treatment, which could have led to differences in representation of ADTs across the study population. These factors were minimized, as investigators were advised to try to evenly distribute their choice of ADT and were not permitted to assign more than 2 out of every 5 patients to any one ADT without permission from the study sponsors. It could, however, be argued that allowing physicians to assign ADT based on antidepressant history and clinical judgment is more closely representative of real-world practice, allowing more individualized therapy than would usually be seen in a clinical trial setting. This may, in fact, enhance the validity of the study findings, as patients who are poorly responsive to individualized treatment are more likely to be truly treatment resistant than patients who simply received a randomly assigned ADT. A further limitation is that sample sizes for each antidepressant assignment were too small to detect meaningful differences between antidepressant groups.

In conclusion, adjunctive aripiprazole as a short-term augmentation strategy to conventional ADT is efficacious and well tolerated in patients with MDD who showed an incomplete antidepressant response. It remains to be determined whether these improvements will translate into long-term improvements in remission rates in this difficult-to-treat population, and the long-term safety profile of aripiprazole in this population remains to be clarified. Ongoing studies may clarify some of these questions.

Drug names: aripiprazole (Abilify), buspirone (BuSpar and others), citalopram (Celexa and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), olanzapine/fluoxetine combination (Symbyax), paroxetine (Paxil, Pexeva, and others), pramipexole (Mirapex), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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