Adjunctive Aripiprazole in Major Depressive Disorder: Analysis of Efficacy and Safety in Patients With Anxious and Atypical Features

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Objective: To evaluate the efficacy of adjunctive aripiprazole to standard antidepressant therapy (ADT) for patients with DSM-IV major depressive disorder with anxious/atypical features at baseline.

Method: Data from 2 identical 14-week studies (an 8-week prospective ADT treatment phase and a 6-week randomized, double-blind phase) of aripiprazole augmentation were pooled to evaluate efficacy and safety in the 2 subgroups. The primary efficacy endpoint was mean change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from end of ADT treatment to end of randomized treatment (last observation carried forward). Anxious depression was defined by a Hamilton Rating Scale for Depression anxiety/somatization factor score ≥ 7, and atypical depression was defined by previously described criteria on the Inventory of Depressive Symptomatology–Self-Report. Both anxious and atypical subtypes were defined based on symptoms at entry into prospective ADT (week 0). Patients were enrolled between June 2004 and April 2006 in one study and from September 2004 to December 2006 in the other (total randomized population, N = 742; anxious/nonanxious population, N = 740; atypical/nonatypical population, N = 737).

Results: Completion rates were between 84% and 90% and comparable across all subgroups, with low discontinuations due to adverse events. Patients receiving adjunctive aripiprazole demonstrated significantly greater improvement in MADRS total score versus patients receiving adjunctive placebo, starting at week 1 or week 2 and continuing through to endpoint (anxious: –8.72 vs. –6.17, $p \leq .001$; nonanxious: –8.61 vs. –4.97, $p \leq .001$; atypical: –9.31 vs. –5.15, $p \leq .001$; nonatypical: –8.08 vs. –6.22, $p < .05$). At endpoint, remission rates were also significantly higher with adjunctive aripiprazole versus adjunctive placebo ($p < .05$) in all subgroups. Treatment emergent adverse event profile was similar in all subgroups and comparable to the total population. Reporting of akathisia and weight gain on aripiprazole treatment did not differ between subgroups.

Conclusion: Adjunctive aripiprazole is an effective treatment for patients with major depression presenting with either anxious or atypical features.

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Unresolved or residual symptoms are common among individuals treated for major depressive disorder (MDD) and are associated with an increased risk of relapse and poor psychosocial functioning.[1,2] When first-line strategies are ineffective, clinicians frequently switch antidepressants or use an augmentation agent. Several augmentation and combination strategies have been used to try to improve outcomes in patients who show an inadequate response to antidepressant treatment.[3] Treatment is further complicated by the heterogeneity of the syndrome. Specifically, there are several clinically

relevant subtypes of depression that do not respond uniformly to standard antidepressant treatments. For example, significant proportions of patients with MDD manifest anxious or atypical features or both. Depending on the clinical criteria used, up to 46% of MDD patients meet criteria for anxious depression[4] and up to 36% of patients have atypical features.[5] These subtypes may also be associated with poorer long-term prognosis. For example, anxious depression has been shown to be associated with greater symptom severity, suicidality, worse functioning, and poorer acute outcomes.[6–8] Furthermore, depression with atypical features may also show a differential response to treatment. Atypical depression was less responsive to tricyclic antidepressants than monoamine oxidase inhibitors[5]; however, newer antidepressants, such as fluoxetine, may be as effective for depression with atypical features.[9] Since remission is the goal for treatment, there is a need for better understanding of medications that can improve and remit core depressive symptoms such as sadness, lack of energy/fatigue, lack of interest, and inability to enjoy daily activities in these difficult to treat populations with anxious or atypical features.

Aripiprazole is approved for use as an adjunctive treatment to antidepressant therapy (ADT) in adults with MDD and has a unique pharmacology that may make it effective as an augmentation agent for the treatment of depression, with partial agonist activity at dopamine D_2 and D_3 receptors[10,11] and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors.[12,13] Based on the results from 2 identical, large, multicenter, randomized, double-blind, placebo-controlled trials, aripiprazole has been shown to be relatively well tolerated, safe, and effective as adjunctive treatment to ADT in patients who demonstrated an inadequate response to at least 1 historical and 1 prospective 8-week trial of antidepressant therapy.[14,15] In this analysis, data were pooled from these identical studies of aripiprazole augmentation to evaluate the efficacy and safety of adjunctive aripiprazole to standard ADT for the subgroups of patients with anxious and atypical depression.

METHOD

Data were pooled from 2 placebo-controlled studies conducted at multiple sites within the United States.[14,15] Both studies were conducted in accordance with the Declaration of Helsinki and received appropriate approval by the institutional review board or independent ethics committee. Written informed consent was obtained from all participants before study entry. Patients were enrolled between June 2004 and April 2006 in one study[14] and from September 2004 to December 2006 in the other.[15]

Study Design

Details of the primary study methods have been described previously.[14,15] Briefly, 2 identical multicenter, randomized, double-blind, placebo-controlled studies were conducted to investigate the efficacy and safety of adjunctive aripiprazole or placebo with standard ADT in patients with major depression who showed an inadequate response to at least one historical and one 8-week prospective antidepressant treatment. The treatment protocol consisted of 3 phases: a 7- to 28-day screening phase, an 8-week prospective treatment phase to establish inadequate antidepressant response with standard ADT (escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine, based on clinician choice), and a 6-week randomized, double-blind treatment phase (actual study visits, week 9 to week 14) in which patients with inadequate response at the end of prospective treatment were randomly assigned (1:1) to continue the same antidepressant treatment plus either adjunctive placebo or adjunctive aripiprazole (2–20 mg/day or 2–15 mg/day for patients taking fluoxetine and paroxetine). Inadequate response to the prospective trial was defined as a 17-item Hamilton Rating Scale for Depression (HAM-D)[16] total score that represented a less than 50% reduction in symptoms during prospective ADT, a HAM-D total score ≥ 14, and a Clinical Global Impressions-Improvement[17] score ≥ 3. All patients received single-blind placebo during the prospective treatment phase in order to blind patients to the transition to the randomization phase. Most psychotropic drugs, including benzodiazepines and other hypnotic agents, were discontinued during the screening phase.

Study Population

Study inclusion and exclusion criteria were identical among the 2 trials. Patients included outpatients aged 18 to 65 years who met the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) criteria for a major depressive episode[18] that had lasted ≥ 8 weeks. In addition, patients were required to have a history of inadequate response to at least 1 (and no more than 3) adequate ADT trials in the current depressive episode. Historical nonresponse was defined as < 50% reduction in severity of depressive symptoms across at least 6 weeks of treatment at therapeutic doses, as determined by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.[19] Patients were excluded if they had a current Axis I (DSM-IV-TR) diagnosis of delirium, dementia, amnestic or other cognitive disorder, schizophrenia or other psychotic disorder, bipolar I or II disorder, eating disorder (including anorexia nervosa or bulimia), obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, or a clinically significant current Axis II (DSM-IV-TR) diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder. Further details of inclusion and exclusion criteria have been reported elsewhere.[14]

Anxious/Atypical Features Subgroups

For the purpose of this subanalysis, the randomized (N = 742), efficacy (N = 723), and safety (N = 736) populations of both studies were pooled to evaluate efficacy and safety of adjunctive aripiprazole in subgroups of patients with major depression with (1) anxious features or (2) atypical features. Anxious and atypical subgroups were determined, post hoc, using patients who entered the prospective treatment phase of the study at week 0. Using the same criteria as those used in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study,[4,6] anxious depression was defined as MDD with high levels of anxiety symptoms and a HAM-D anxiety/somatization factor score ≥ 7. The HAM-D anxiety/somatization factor includes the following 6 items from the 17-item HAM-D version: anxiety (psychic), item 10; anxiety (somatic), item 11; somatic (gastrointestinal), item 12; somatic (general), item 13; hypochondriasis, item 15; and insight, item 17. Atypical depression, as in the STAR*D trial, was defined as MDD with atypical features, as defined by following the Inventory of Depressive Symptomatology–Self-Report (IDS-SR)[20] criteria, which requires a score of 0, 1, or 2 for mood reactivity (item 8) plus at least 2 of the following symptoms: a score of 2 or 3 for hypersomnia (item 4), a score of 2 or 3 for increased appetite (item 12) or increased weight (item 14), a score of 3 for interpersonal sensitivity (item 29), or a score of 2 or 3 for leaden paralysis (item 30). Patients meeting criteria for anxious or atypical depression were then compared to those with nonanxious and nonatypical depression, respectively, as outlined below.

Assessments

Patients were evaluated weekly for the 6-week duration of double-blind treatment. The efficacy of study medication for reducing symptoms of depression in this post hoc analysis was measured using the mean change from the end of the prospective treatment phase (week 8) to the end of the randomized, double-blind phase (week 14) in the Montgomery-Asberg Depression Rating Scale (MADRS)[21] total score. Additional efficacy measures included mean change in MADRS total score from baseline to each weekly visit during double-blind treatment and response and remission rates. 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 by an absolute MADRS total score of ≤ 10 and at least 50% reduction in MADRS total score relative to the end of the prospective treatment phase. Survival analysis was performed using the Kaplan-Meier method; nonresponder or nonremitter was censored. The aripiprazole treatment group was defined as 0 while the placebo group was defined as 1 when hazard ratios (HRs) were generated.

Safety was evaluated by monitoring of adverse events and body weight. Akathisia events were assessed using the Barnes Akathisia Rating Scale.[22]

Statistical Analyses

The primary efficacy outcome, adjusted mean change from the end of the prospective treatment phase to the end of the randomized, double-blind treatment phase in MADRS total score, was evaluated using the last-observation-carried-forward data set, by analysis of covariance (ANCOVA), with treatment and study as main effects and end of prospective treatment phase score as covariate. To investigate interaction of treatment with subgroups, an interaction test at week 14 was performed using the ANCOVA model, with double-blind treatment, study, and subgroup as main effects; end of prospective treatment assessment as covariate; and subgroup-by-treatment as interaction effect. Treatment comparisons of response and remission rates were evaluated by a Cochran-Mantel-Haenszel General Association Test, controlling for study. Odds ratios and 95% confidence intervals for the differences in MADRS response and remission between anxious and nonanxious (or atypical and nonatypical) depression at week 14, were calculated using a logistic regression model controlling for study and treatment. Time to response and remission between treatment groups for each subgroup were compared using Kaplan-Meier survival curves. Kaplan-Meier curves were compared statistically using the Wilcoxon test considering the greater possibility of an earlier event in response and remission. A logistic regression model was also used to estimate the odds ratio and 95% confidence intervals for the differences in adverse events (akathisia and restlessness) between anxious and nonanxious (or atypical and nonatypical), controlling for study and treatment. All statistical tests are interpreted at the 5% significance level.

RESULTS

Patient Population

At week 0, mean (SD) HAM-D anxiety/somatization factor scores in nonanxious patients were 5.33 (0.79) and 5.32 (0.85) in those receiving adjunctive aripiprazole and adjunctive placebo, respectively, and in anxious patients were 7.89 (1.09) and 7.95 (1.06), respectively. At week 0, mean (SD) IDS-SR item 8 scores in nonatypical patients were 1.75 (0.91) and 1.71 (0.87) in those receiving adjunctive aripiprazole and adjunctive placebo, respectively, and in atypical patients were 1.52 (0.68) and 1.56 (0.62), respectively. Mean (SD) IDS-SR scores for the other items in nonatypical patients were 0.78 (0.83) and 0.80 (0.71) in those receiving adjunctive aripiprazole and adjunctive placebo, respectively, and in atypical patients were 2.53 (0.69) and 2.47 (0.66), respectively.

Table 1. Baseline Demographic and Disease Characteristics by Subgroup of Patients With MDD (randomized sample)[a]

	Anxious		Nonanxious		Atypical		Nonatypical	
Characteristic	Adjunctive Placebo (N = 232)	Adjunctive Aripiprazole (N = 218)	Adjunctive Placebo (N = 136)	Adjunctive Aripiprazole (N = 156)	Adjunctive Placebo (N = 172)	Adjunctive Aripiprazole (N = 176)	Adjunctive Placebo (N = 195)	Adjunctive Aripiprazole (N = 196)
Age, mean (SD), y	43.7 (10.5)	45.3 (10.4)	45.1 (11.2)	46.1 (11.4)	42.7 (10.7)	44.4 (11.5)	45.6 (10.6)	46.7 (10.1)
Sex, % male	28.5	32.1	44.1	41.0	26.7	27.3	40.5	43.9
Race, % white	92.7	87.6	87.5	89.1	93.6	88.6	88.7	88.3
Weight, mean (SD), kg	86.1 (22.0)	83.6 (18.9)	88.7 (22.1)	88.2 (21.5)	86.6 (23.4)	86.7 (18.9)	87.3 (20.8)	84.5 (21.2)
Duration of current episode, mean (SD), mo	32.7 (62.2)	29.6 (30.5)	51.1 (78.5)	30.4 (34.7)	45.1 (87.8)	34.1 (38.6)	35.0 (52.0)	26.0 (24.4)
Depressive episodes, %								
Single	20.7	18.4	30.2	20.5	22.1	13.6	26.2	24.5
Recurrent	79.3	81.7	69.9	79.5	77.9	86.4	73.9	75.5
Previous ADT trials in current episode, %[b]								
1	67.1	69.7	66.9	67.7	66.1	70.1	67.7	67.4
2	25.5	25.7	27.9	24.5	27.5	24.6	25.6	25.5
3	7.4	4.1	5.2	7.7	6.4	4.6	6.7	6.6
MADRS total score, mean (SD)[c]	27.1 (6.2)	26.4 (6.3)	25.6 (5.6)	24.5 (5.7)	27.3 (6.3)	26.6 (6.0)	25.8 (5.7)	24.8 (6.1)

[a]Demographics were assessed at screening.
[b]Two adjunctive aripiprazole patients (1 anxious and 1 nonatypical) had > 3 previous ADT trials in the current episode.
[c]All baseline comparisons per subgroup of MADRS total scores aripiprazole versus placebo, p > .05.
Abbreviations: ADT = standard antidepressant therapy, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder.

Table 2. Patient Disposition by Subgroup (randomized sample[a])

	Anxious		Nonanxious		Atypical		Nonatypical	
Patient Status	Adjunctive Placebo, N (%)	Adjunctive Aripiprazole, N (%)	Adjunctive Placebo, N (%)	Adjunctive Aripiprazole, N (%)	Adjunctive Placebo, N (%)	Adjunctive Aripiprazole, N (%)	Adjunctive Placebo, N (%)	Adjunctive Aripiprazole, N (%)
Randomized	232	217	136	155	172	176	195	194
Discontinued	31 (13.4)	34 (15.7)	15 (11.0)	17 (11.0)	18 (10.5)	23 (13.1)	28 (14.4)	28 (14.4)
Lack of efficacy	4 (1.7)	4 (1.8)	1 (0.7)	2 (1.3)	2 (1.2)	4 (2.3)	3 (1.5)	2 (1.0)
Adverse event	3 (1.3)	9 (4.2)	3 (2.2)	4 (2.6)	2 (1.2)	8 (4.6)	4 (2.1)	5 (2.6)
Withdrew consent	8 (3.5)	5 (2.3)	6 (4.4)	3 (1.9)	6 (3.5)	3 (1.7)	8 (4.1)	5 (2.6)
Lost to follow-up	8 (3.5)	7 (3.2)	3 (2.2)	3 (1.9)	4 (2.3)	2 (1.1)	7 (3.6)	8 (4.1)
Other[b]	8 (3.5)	9 (4.2)	2 (1.5)	5 (3.2)	4 (2.3)	6 (3.4)	6 (3.1)	8 (4.1)
Completed randomization phase	201 (86.6)	183 (84.3)	121 (89.0)	138 (89.0)	154 (89.5)	153 (86.9)	167 (85.6)	166 (85.6)

[a]Total randomized population, N = 742; anxious/nonanxious population, N = 740; atypical/nonatypical population, N = 737. Data are missing for 2 patients; 3 atypical/nonatypical patients had no week 0 Inventory of Depressive Symptomatology–Self-Report score.
[b]Other includes poor/noncompliance, subject no longer meets study criteria, other known cause.

Baseline (week 8) characteristics for the pooled subgroups are shown in Table 1. There were no significant differences in demographic characteristics between the anxious and nonanxious and atypical and nonatypical groups, with the exception of the nonanxious and nonatypical groups, which had higher proportions of males than the anxious and atypical subgroups. Patient disposition by subgroup is shown in Table 2. Completion rates were comparable across all subgroups, and discontinuations due to adverse events were low.

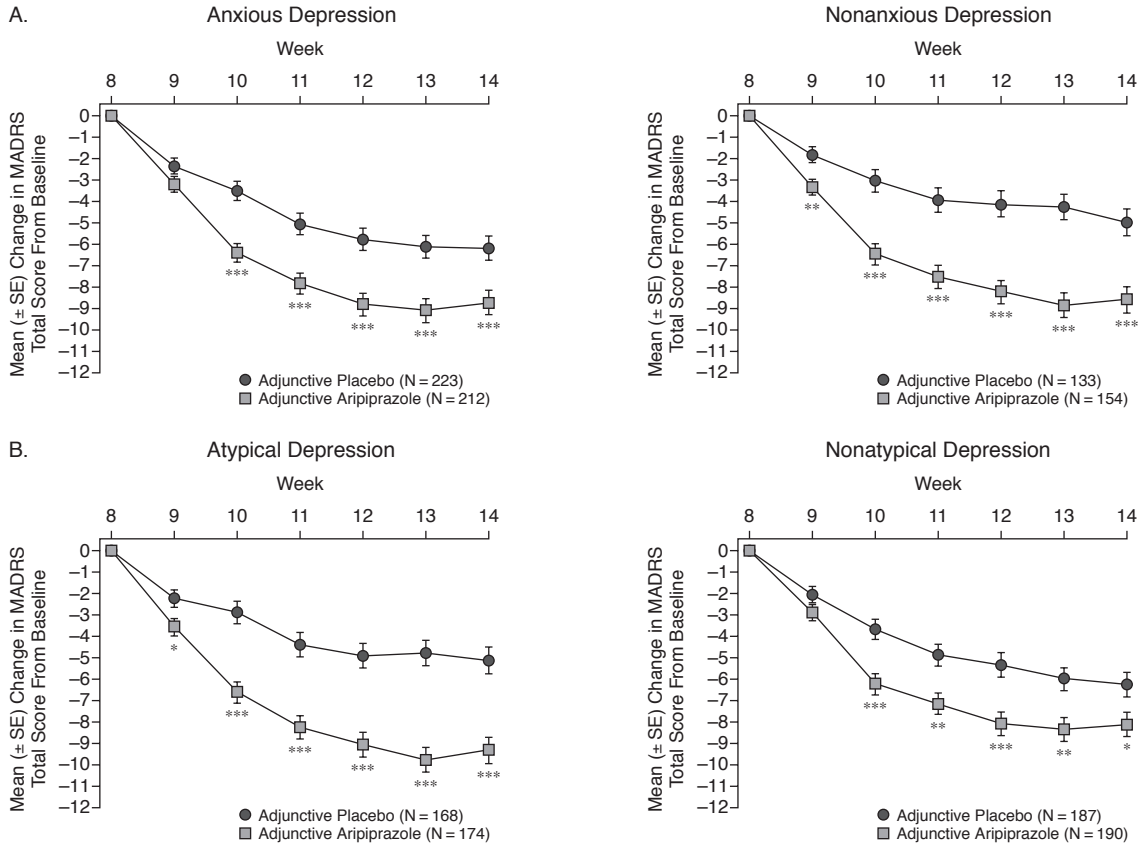
Efficacy of Aripiprazole in Total Population (randomized adjunctive phase week 9 to week 14)

In the pooled overall population (N = 723, efficacy sample), patients treated with adjunctive aripiprazole demonstrated improvements in depressive symptoms as early as the first week of adjunctive treatment (week 9) compared to patients in the adjunctive placebo group, and this improvement was maintained until endpoint. At endpoint, aripiprazole-treated patients had a mean change in MADRS score of –8.67 points compared with a mean change of –5.73 points in placebo-treated patients ($p \leq .001$).

Efficacy of Aripiprazole in Anxious/Nonanxious Depression (randomized adjunctive phase week 9 to week 14)

At endpoint (week 14), the mean change in MADRS total score from baseline (end of week 8) was significantly greater in both anxious and nonanxious patients receiving adjunctive aripiprazole (–8.72 and –8.61, respectively) than in those receiving adjunctive placebo (–6.17 and –4.97, respectively; $p \leq .001$ for both comparisons; Figure 1A). The difference in reduction in MADRS scores between aripiprazole and placebo was statistically significant by the second week of adjunctive treatment

Figure 1. Mean ± Standard Error (SE) Change in MADRS Total Score[a] During Double-Blind Treatment Phase in Patients Classified at Baseline With (A) Anxious/Nonanxious Depression or (B) Atypical/Nonatypical Depression



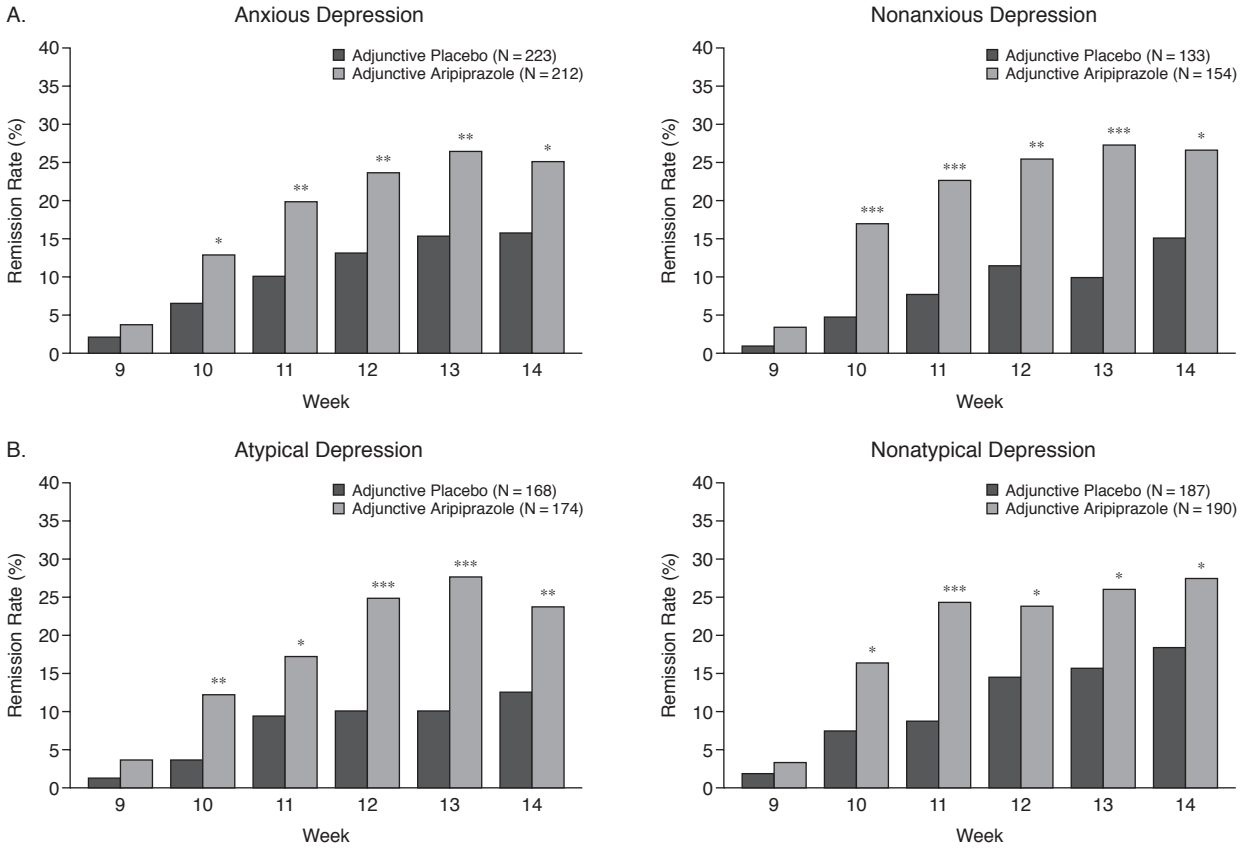
[a]Mean MADRS total scores at week 8: anxious depression, aripiprazole = 26.4, placebo = 27.0; nonanxious depression, aripiprazole = 24.4, placebo = 25.6; atypical depression, aripiprazole = 26.7, placebo = 27.3; nonatypical depression, aripiprazole = 24.6, placebo = 25.8.
*p < .05 versus placebo.
**p ≤ .01 versus placebo.
***p ≤ .001 versus placebo.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

(week 10) in anxious patients and by the first week of adjunctive treatment (week 9) in nonanxious patients, with continued improvement through to endpoint (Figure 1A). Test for interaction on MADRS scores at endpoint showed no difference in the efficacy of aripiprazole augmentation between patients with anxious depression and nonanxious depression (p = .434).

Compared with adjunctive placebo, adjunctive aripiprazole produced significantly greater remission rates in patients with either anxious or nonanxious depression from the second week of adjunctive treatment onward (Figure 2A). At endpoint, adjunctive aripiprazole produced significantly greater remission rates than adjunctive placebo in both patients with anxious (25.0% vs. 15.7%; p < .05) and patients with nonanxious (26.6% vs. 15.0%; p < .05) depression. There was no difference in MADRS remission rates between anxious and nonanxious patients at endpoint (OR = 0.97; 95% CI = 0.67 to 1.40). At endpoint, response rates were also significantly greater with adjunctive aripiprazole versus adjunctive placebo in patients with both anxious (33.0% vs. 20.6%; p < .01) and nonanxious (33.1% vs. 20.3%; p < .05) depression. Response rates in anxious patients treated with aripiprazole were significantly greater than placebo from the second week of adjunctive treatment (p ≤ .001) through to endpoint. For patients with nonanxious depression, response rates were significantly greater for adjunctive aripiprazole versus adjunctive placebo from the first week of adjunctive treatment (p < .05) through to endpoint. Similar to remission, there was no difference in MADRS response rates between anxious and nonanxious patients at endpoint (OR = 1.01; 95% CI = 0.72 to 1.42).

Response was achieved significantly earlier in both anxious (Wilcoxon p = .030; HR = 0.83; 95% CI = 0.61 to 1.12) and nonanxious (Wilcoxon p = .009; HR = 0.71;

Figure 2. Remission Rates[a] During Double-Blind Treatment Phase in Patients Classified at Baseline With (A) Anxious/Nonanxious Depression or (B) Atypical/Nonatypical Depression



[a]Montgomery-Asberg Depression Rating Scale (MADRS) remission = a MADRS total score of ≤ 10 and a ≥ 50% reduction in MADRS total score from end of prospective treatment.
*p < .05 versus placebo.
**p ≤ .01 versus placebo.
***p ≤ .001 versus placebo.

95% CI = 0.48 to 1.06) patients with aripiprazole treatment compared to placebo. Remission occurred significantly earlier in aripiprazole-treated patients compared to placebo-treated patients in the nonanxious depression group (Wilcoxon p = .002; HR = 0.73; 95% CI = 0.47 to 1.14), although there was no significant difference between aripiprazole and placebo in the anxious depression group (Wilcoxon p = .166; HR = 0.82; 95% CI = 0.58 to 1.15).

Efficacy of Aripiprazole in Atypical/Nonatypical Depression (randomized adjunctive phase week 9 to week 14)

At endpoint (week 14), the mean change in MADRS total score from baseline was significantly greater in both atypical (–9.31 vs. –5.15, p ≤ .001) and nonatypical (–8.08 vs. –6.22, p < .05) patients receiving adjunctive aripiprazole than in those receiving adjunctive placebo (Figure 1B). The mean change in MADRS total score was significantly greater with adjunctive aripiprazole versus adjunctive placebo from the first week of adjunctive treatment (week 9) in patients with atypical depression and from the second week of adjunctive treatment (week 10) in patients with nonatypical depression, with continued improvement to endpoint in both groups (Figure 1B). Test for interaction at endpoint on MADRS scores suggested a trend for greater improvement among patients with atypical depression, although the interaction did not reach statistical significance (p = .065).

Remission rates were significantly greater with adjunctive aripiprazole versus adjunctive placebo in both atypical (23.6% vs. 12.5%; p < .01) and nonatypical (27.4% vs. 18.2%; p < .05) patients at endpoint. Compared with adjunctive placebo, adjunctive aripiprazole produced significantly greater remission rates in patients with atypical or nonatypical depression from the second week of adjunctive treatment onward (Figure 2B). There was no difference in MADRS remission rates between

Table 3. Incidence of Treatment-Emergent Adverse Events in Patients by Subgroup (≥ 5% of adjunctive aripiprazole–treated patients and twice the placebo rate; safety sample)

	Anxious, %		Nonanxious, %		Atypical, %		Nonatypical, %		Total Population, %	
Adverse Event	Adjunctive Placebo (N = 230)	Adjunctive Aripiprazole (N = 216)	Adjunctive Placebo (N = 136)	Adjunctive Aripiprazole (N = 154)	Adjunctive Placebo (N = 171)	Adjunctive Aripiprazole (N = 176)	Adjunctive Placebo (N = 194)	Adjunctive Aripiprazole (N = 192)	Adjunctive Placebo (N = 366)	Adjunctive Aripiprazole (N = 370)
Akathisia	5.2	25.5	2.9	23.4	6.4	27.3	2.6	22.4	4.4	24.6
Restlessness	1.7	15.3	2.2	7.1	2.3	11.4	1.5	12.5	1.9	11.9
Fatigue	2.6	6.9	…	…	3.5	8.0	3.6	8.3	3.6	8.1
Insomnia	1.3	5.6	2.9	10.4	1.8	8.0	2.1	7.3	1.9	7.6
Blurred vision	1.3	5.6	0	5.8	1.8	6.8	…	…	1.1	5.7
Constipation	0	5.1	…	…	0	5.7	…	…	…	…
Somnolence	…	…	1.5	9.1	…	…	2.6	5.7	…	…
Arthralgia	…	…	…	…	1.2	5.7	…	…	…	…
Disturbance in attention	…	…	…	…	1.2	5.1	…	…	…	…
Tremor	…	…	…	…	2.3	5.1	…	…	…	…

Symbol: … = incidence of treatment-emergent adverse event did not occur in ≥ 5% of adjunctive aripiprazole–treated patients or at twice the placebo rate.

atypical and nonatypical patients at endpoint (OR = 0.75; 95% CI = 0.52 to 1.08).

Response rates were significantly greater with adjunctive aripiprazole versus adjunctive placebo at endpoint in patients with atypical depression (34.5% vs. 17.3%; $p < .001$). Improvement in response rates in atypical patients treated with aripiprazole was significantly greater than placebo from the second week of adjunctive treatment ($p \leq .01$) through to endpoint. For patients with nonatypical depression, response rates were significantly greater for adjunctive aripiprazole versus adjunctive placebo in the initial 4 weeks of adjunctive treatment (all $p < .05$), although the difference between treatments did not reach significance at endpoint (31.6% vs. 23.5%; $p = .073$). There was no difference in MADRS response rates between atypical and nonatypical patients at endpoint (OR = 0.91; 95% CI = 0.65 to 1.27).

Response was achieved significantly earlier in nonatypical patients with aripiprazole treatment compared to placebo (Wilcoxon $p = .002$; HR = 0.65; 95% CI = 0.47 to 0.91), although time to response in atypical depression (Wilcoxon $p = .121$; HR = 0.93; 95% CI = 0.65 to 1.34), and time to remission in both atypical (Wilcoxon $p = .132$; HR = 0.84; 95% CI = 0.56 to 1.26) and nonatypical (Wilcoxon $p = 0.053$; HR = 0.75; 95% CI = 0.52 to 1.08) depression, showed no significant difference between aripiprazole and placebo.

Adverse Events

The treatment-emergent adverse events that occurred in ≥ 5% of patients in any group and twice the placebo rate are reported in Table 3 for patients with and without anxious or atypical depression. Logistic regression analysis examining the association between anxious and atypical depression showed that reported akathisia rates were similar between anxious and nonanxious patients (OR = 1.22; 95% CI = 0.79 to 1.90) and atypical and nonatypical patients (OR = 1.49; 95% CI = 0.97 to 2.30). Akathisia with adjunctive aripiprazole treatment was generally mild (anxious, 43.6%; nonanxious, 41.7%; atypical, 41.7%; nonatypical, 44.2%) or moderate (anxious, 47.3%; nonanxious, 52.8%; atypical, 47.9%; nonatypical, 51.2%) in severity in all patient subgroups and resolved before study endpoint in approximately half of patients (resolution rates of akathisia: anxious, 49.1%; nonanxious, 55.6%; atypical, 54.2%; nonatypical, 48.8%).

Analysis of weight change over the course of double-blind treatment showed that for all subgroups of depression, mean (± SE) weight change in the adjunctive aripiprazole group (range [kg]: +1.61 ± 0.19 to +1.83 ± 0.15) was statistically significantly greater than in the adjunctive placebo group (range [kg]: +0.22 ± 0.21 to +0.48 ± 0.15; all $p < .001$). Tests for interaction showed that weight gain did not differ between anxious and nonanxious patients (interaction test, $p = .866$) or atypical and nonatypical patients (interaction test, $p = .984$).

DISCUSSION

The results of this analysis of pooled data from the 2 multicenter, double-blind, placebo-controlled clinical trials of aripiprazole augmentation of ADT suggest that this strategy is effective and relatively well tolerated in patients with either anxious or atypical features of MDD and is comparable to that seen in patients without anxious or atypical features. Similar improvement in symptoms was demonstrated by rapid improvements in MADRS total scores as early as the first 2 weeks of adjunctive aripiprazole treatment, with continued improvement to study endpoint in all populations analyzed. Adjunctive aripiprazole treatment was also associated with significantly higher remission rates than adjunctive placebo from the second week of the adjunctive treatment phase (week 10) onward in all patient subgroups. These data indicate that when

using aripiprazole as an adjunctive medication in patients with MDD who have failed to achieve an adequate response to previous ADT treatment, symptomatic outcomes are comparable, irrespective of whether patients have anxious or atypical features.

Adjunctive aripiprazole was relatively well tolerated in patients with either anxious or atypical depression. Completion rates were high across all subgroups, and discontinuations due to adverse events were low. The treatment emergent adverse events profile was similar in all subgroups and comparable to the total population. Although adjunctive aripiprazole was associated with a higher rate of akathisia than adjunctive placebo in all patient subgroups, the rates of akathisia in these subgroups were similar to those reported with adjunctive aripiprazole in the total population of patients with MDD.[14,15] Furthermore, depressive subtype did not have an impact on the occurrence of akathisia events. As seen previously, akathisia was generally mild to moderate in severity, regardless of patient subgroup, a finding that has been confirmed by the Barnes Akathisia Rating Scale global item scores. However, unlike akathisia and weight gain, restlessness was more common in anxious than nonanxious patients and may reflect that patients with anxious features are more sensitive to adverse events than those with nonanxious depression.[6]

Previous research has suggested that patients with anxious features of depression may be less responsive to treatment with antidepressants than those without anxious features.[23–25] This has been confirmed in recent analysis of data from the STAR*D, which showed that patients with anxious depression were less likely to achieve remission or respond to treatment than those with nonanxious depression in both level 1 (citalopram) and level 2 (switch to sustained-release bupropion, sertraline, extended-release venlafaxine; or augmentation with sustained-release bupropion or buspirone) of STAR*D, regardless of treatment assignment in level 2.[6] These findings are in contrast to those reported here, which have shown that adjunctive aripiprazole produced comparable response and remission rates in patients with or without anxious depression who had failed to achieve an adequate response to previous ADT treatment. Time to response was also significantly faster with adjunctive aripiprazole as compared with the antidepressant alone in patients with or without anxious depression.

Also of interest is the observation that rates of atypical and anxious depression reported here are somewhat higher than would be expected in outpatient populations.[23] This may reflect the relative enrichments of patients with atypical or anxious features in subpopulations that have not responded to 2 or more adequate treatment trials prior to randomization.

Strengths of this analysis include the relatively large numbers of patients with both anxious and atypical depression who participated in the 2 trials and the use of both historical and prospective antidepressant trials in determining antidepressant nonresponse. However, the findings of this analysis should also be considered in light of several limitations. First, although this analysis is based on pooled data from large placebo-controlled trials, the post hoc nature of this analysis means that the results should be considered preliminary, and prospectively designed studies are needed to confirm these findings. Second, use of the HAM-D-17 anxiety/somatization factor to classify anxious depression may not capture all the symptoms of anxiety, and, similarly, use of the IDS-SR to identify atypical depression may also not identify all patients with atypical features. Finally, as this study was conducted in patients who showed an inadequate response to at least 1 historical and 1 prospective antidepressant treatment, it is unclear how these findings will generalize to patients with anxious or atypical depression who are treated earlier in the course of illness.

In conclusion, this analysis extends previous findings demonstrating that adjunctive aripiprazole improves core depressive symptoms as an augmentation strategy to standard ADT in patients with a history of an inadequate response to antidepressant medication to patients with either anxious or atypical depression.

Drug names: aripiprazole (Abilify), bupropion (Aplenzin, Wellbutrin, and others), buspirone (BuSpar and others), citalopram (Celexa and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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