Examining the Efficacy of Adjunctive Aripiprazole in Major Depressive Disorder: A Pooled Analysis of 2 Studies

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Background: Patients with major depressive disorder (MDD) who fail to achieve complete remission with antidepressant therapy may benefit from augmentation therapy with an atypical antipsychotic.

Method: A pooled analysis was performed on 2 identical 14-week studies (8-week prospective antidepressant therapy treatment phase followed by 6-week randomized double-blind phase) evaluating the efficacy of adjunctive aripiprazole (2–20 mg/day) in DSM-IV-TR–defined MDD patients with an inadequate response to antidepressant therapy. Primary efficacy endpoint was the mean change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from end of the prospective phase (week 8) to end of randomized phase (week 14, last observation carried forward). Subgroup analyses were performed. The key secondary endpoint was mean change in Sheehan Disability Scale (SDS) mean score.

Results: At endpoint, mean change in MADRS total score was significantly greater with adjunctive aripiprazole (–8.7) than with adjunctive placebo (–5.7; $p < .001$). Except for a differential treatment-by-sex interaction, change in MADRS total scores were consistently greater with adjunctive aripiprazole than with adjunctive placebo, regardless of race, age, episode duration, prior antidepressant therapy response, number of historical treatment failures, severity of depressive symptoms, and antidepressant. At endpoint, MADRS remission rates were significantly greater with adjunctive aripiprazole than with placebo (25.7% vs. 15.4%; $p < .001$). Adjunctive aripiprazole also demonstrated significantly greater improvements in mean change from baseline in SDS total score than adjunctive placebo (–1.2 vs. –0.6; $p = .001$).

Conclusion: Augmentation of antidepressant therapy with the atypical antipsychotic aripiprazole resulted in significant efficacy benefits across a range of subgroups of patients with MDD. Further study of a treatment-by-sex interaction is needed.

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Major depressive disorder (MDD) is a common, disabling illness presenting challenges in patient management. The ultimate goal of treatment is not simply to reduce symptoms but to help patients to reach and sustain remission.[1–3] Despite the growing number of antidepressant therapies available, approximately two thirds of patients do not achieve remission after an adequate course of at least 1 antidepressant and a significant number of patients do not remit after multiple courses of pharmacotherapy.[4–6] There are numerous problems associated with incomplete or partial remission of depression, including an increased likelihood of relapse/recurrence, chronicity, and suicide, as well as poorer health, and reduced quality of life.[7–12] The importance of remission (not simply response) was highlighted by the results of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial in which higher rates of relapse were observed for those who were not in remission at entry into the follow-up phase compared with those who had achieved remission.[5]

It is now recognized that, in the event of an inadequate response or partial response to antidepressant monotherapy, sequenced treatment steps using augmentation strategies may prove to be beneficial for patients with MDD. Rational pharmacotherapy would suggest the use

of agents with novel mechanisms of action to address the issue of unresolved symptoms.[13] One strategy is to use adjunctive atypical antipsychotics.[14–17] Aripiprazole, an atypical agent with a distinct pharmacologic profile, is the first medication that has received U.S. Food and Drug Administration (FDA) approval as an adjunctive treatment to antidepressant therapy in patients with MDD. Its potent partial agonism at the D_2 and D_3 receptors and partial agonism at the 5-HT_{1A} receptor, coupled with antagonism at the 5-HT_{2A} receptor, may contribute to the antidepressant effect as an adjunctive therapy to antidepressants.[18–20]

The efficacy and tolerability of aripiprazole as adjunctive therapy to antidepressants has been demonstrated in 2 large, identical, randomized, double-blind, placebo-controlled trials involving patients who presented with a history of inadequate response to at least 1 trial of antidepressant therapy and who exhibited an inadequate response to a prospective 8-week trial of a different antidepressant therapy.[21,22] In both studies, significant improvements in depressive symptoms were seen by the second week of randomized treatment in patients in the adjunctive aripiprazole group compared with those receiving antidepressants alone. Although these studies were designed to test the efficacy of adjunctive aripiprazole therapy versus adjunctive placebo (antidepressant therapy alone), neither study had adequate statistical power to test differential response in relation to relevant clinical characteristics and subgroups of patients with MDD. Here, we present pooled data from these studies to further assess the efficacy of aripiprazole as augmentation therapy to standard antidepressants in patients with MDD in an array of demographic subgroups. Data from a pooled safety analysis of these 2 studies are presented elsewhere.[23]

METHOD

Study Design

Details of the study methods have been described previously.[21,22] Briefly, 2 identical multicenter, randomized, double-blind, placebo-controlled studies (CN138-139 and CN138-163) were conducted in the United States (2004–2006) to investigate the efficacy and safety of adjunctive aripiprazole with standard antidepressant therapy in patients with DSM-IV-TR–defined MDD. Patients must have reported an inadequate response to at least 1 historical, adequate antidepressant trial (> 6 weeks duration) as defined by < 50% reduction in severity of depressive symptoms—determined by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.[6] Details of inclusion and exclusion criteria have been reported previously.[21,22]

Both studies comprised 3 phases: a screening phase (7–28 days), in which prohibited medications (benzodiazepines and hypnotic agents) were discontinued; a prospective antidepressant therapy phase (8 weeks); and a 6-week randomization phase (actual study visits, weeks 9–14). During the prospective antidepressant therapy phase, patients with major depression (17-item Hamilton Rating Scale for Depression [HAM-D-17] total score ≥ 18) received 8 weeks of therapy with escitalopram, fluoxetine, paroxetine CR, sertraline, or venlafaxine extended release (XR), per investigator choice under standard dosing guidelines, as well as an adjunctive placebo. Neither patients nor study physicians knew when the second phase ended and the third phase began. Patients with an inadequate response at the end of the second phase (< 50% reduction in HAM-D-17 total score, HAM-D-17 score ≥ 14 and Clinical Global Impressions-Improvement scale [CGI-I] score ≥ 3) were randomly assigned in a double-blind fashion to either continued adjunctive placebo or substitution of placebo with adjunctive flexible-dose aripiprazole (2–20 mg/day; starting dose, 5 mg/day) for 6 additional weeks of therapy. For patients who received aripiprazole as an adjunct to paroxetine CR and fluoxetine, 15 mg/day was the maximum dose of aripiprazole. Aripiprazole dose was capped at 15 mg/day when administered with potent cytochrome P450 2D6 (CYP2D6) inhibitors; paroxetine and fluoxetine, as CYP2D6 inhibitors would be expected to raise aripiprazole concentrations.

Statistical Analyses

As the studies were identical in design and methods, the data were pooled in this analysis to further evaluate efficacy in relevant subgroups of patients. Subgroup analyses for sex, responder status at the end of the prospective phase (< 25% [minimal responder] or ≥ 25%–< 50% [partial responder] improvement from baseline [Week 0] in Montgomery-Asberg Depression Rating Scale [MADRS] total score), and type of antidepressant therapy (chosen by investigators at the start of the study and to which aripiprazole or placebo was administered adjunctively) were prespecified to be performed on the primary efficacy outcome measure in the original study reports. Additional subgroup analyses for MADRS total score at the end of the prospective phase (≤ median, > median), age (≤ 50 years, > 50 years), race, ethnicity, number of previous adequate antidepressant therapies in current episode (1, 2, ≥ 3), duration of current depressive episode (≤ median, > median), and in the subgroup of patients treated with selective serotonin reuptake inhibitors (SSRIs) (i.e., all antidepressant therapies except venlafaxine XR) reported here were planned for FDA filing before completion of the second study (CN138-163). The efficacy measurement used for the pooled total population and subgroups reported above was the mean change in MADRS total score from end of prospective treatment to end of randomized treatment; the last-observation-carried-forward (LOCF) method was used to account for the outcomes of participants who did not complete the

Table 1. Disposition of Patients Randomly Assigned to Aripiprazole or Placebo

Outcome	Placebo (N = 368)	Aripiprazole (N = 373)[a]
Discontinued, N (%)	46 (12.5)	51 (13.7)
Lack of efficacy	5 (1.4)	6 (1.6)
Adverse event	6 (1.6)	13 (3.5)
Subject withdrew consent	14 (3.8)	8 (2.1)
Lost to follow-up	11 (3.0)	10 (2.7)
Other[b]	10 (2.7)	14 (3.8)
Completed randomization phase, N (%)	322 (87.5)	322 (86.3)

[a]Two patients who discontinued during the prospective phase were randomly assigned in error and are not included in this table.
[b]Includes poor/no compliance, subject no longer meets study criteria, and other known cause.

Table 2. Demographics of Sample Randomly Assigned to Aripiprazole or Placebo

Demographic	Placebo (N = 368)	Aripiprazole (N = 375)
Age, mean ± SD, y	44.2 ± 10.8	45.6 ± 10.8
Male/female, %	34.2/65.8	36.0/64.0
Race, N (%)		
White	334 (90.8)	331 (88.3)
Black	24 (6.5)	29 (7.7)
Asian	4 (1.1)	6 (1.6)
Other	6 (1.6)	9 (2.4)
Ethnicity, N (%)		
Hispanic or Latino	31 (8.4)	17 (4.5)
Not Hispanic or Latino	337 (91.6)	358 (95.5)
Duration of current episode, mo		
Median	21.0	18.8
Mean ± SD	46.1 ± 73.8	41.1 ± 63.6
Depressive episodes, %		
Single	24.2	19.5
Recurrent	75.8	80.5
No. of previous ADT trials in current episode, %		
1	67.0	69.0
2	26.4	25.1
≥ 3	6.5	5.9
MADRS total score, mean ± SD[a]	26.5 ± 6.0	25.6 ± 6.1

[a]Mean ± SD MADRS total score at end of prospective treatment phase.
Abbreviations: ADT = antidepressant therapy, MADRS = Montgomery-Asberg Depression Rating Scale.

protocol. Mean change from the end of the prospective phase (week 8) to the end of the randomization phase (week 14 visit, LOCF) in Sheehan Disability Scale (SDS)[24] mean score and item scores of work/school, social life, and family life; MADRS response rate (defined as a reduction in MADRS total score of at least 50% relative to the end of the prospective treatment phase); and MADRS remission rate (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) were also calculated for the total pooled population. Change from baseline analyses involved analysis of covariance (ANCOVA) models with randomized treatment and study as main effects and the baseline score as covariate. Interaction effects of treatment by subgroup were assessed by ANCOVA with the end of the prospective phase measure as covariate; treatment, study, subgroup, as the main effects; and the treatment by subgroup as interaction effect. We evaluated differences between the 2 treatment groups in MADRS response and remission rates were evaluated using the Cochran–Mantel-Haenszel general association test, controlling for study. Relative risk and the 95% CIs for relative risk were calculated.

All statistical tests were interpreted at the 5% significance level and no correction was made for multiple comparisons. All analyses were performed using SAS Statistical Software, Version 8.2 or higher (SAS Institute Inc., Cary, NC).

Table 3. Antidepressant Therapy Assignment (efficacy sample)

Antidepressant Therapy	Placebo (N = 356)	Aripiprazole (N = 368)
Escitalopram		
N (%)	99 (27.8)	115 (31.3)
Dose, mean (range), mg/d	19.6 (10 or 20)	20.0 (10 or 20)
Fluoxetine		
N (%)	52 (14.6)	53 (14.4)
Dose, mean (range), mg/d	37.7 (20 or 40)	39.6 (20 or 40)
Paroxetine CR		
N (%)	27 (7.6)	31 (8.4)
Dose, mean (range), mg/d	46.8 (37.5 or 50.0)	48.4 (37.5 or 50.0)
Sertraline		
N (%)	74 (20.8)	69 (18.8)
Dose, mean (range), mg/d	143.9 (100 or 150)	141.3 (100 or 150)
Venlafaxine XR		
N (%)	104 (29.2)	100 (27.2)
Dose, mean (range), mg/d	214.2 (150 or 225)	215.3 (150 or 225)

Abbreviations: CR = controlled release, XR = extended release.

RESULTS

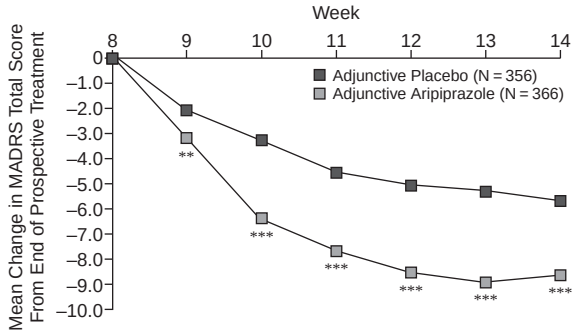
Subject Disposition and Baseline Demographics

In total, 741 patients had an inadequate response with the 8-week prospective treatment of antidepressant therapy and were randomly assigned to double-blind treatment with adjunctive aripiprazole (N = 373) or adjunctive placebo (N = 368). The completion rate was high and discontinuation due to adverse events was low in both groups (Table 1). The baseline demographic and clinical characteristics were similar between both treatment groups (Table 2). The mean duration of current episode was 43.6 (SD = 68.9) months and the median was 19.3 months. The MADRS total score for both groups at entry into the randomized phase was approximately 26. The majority of patients had only 1 historical treatment failure prior to entering the 14-week trial.

Characteristics of Study Treatment

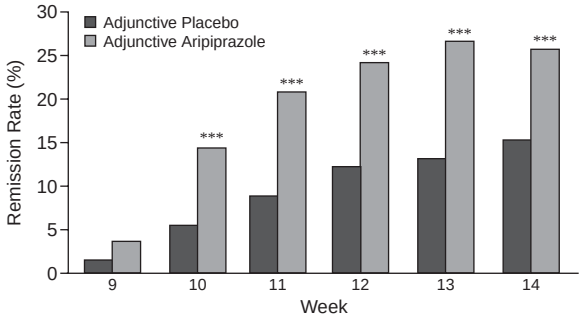
The aripiprazole and placebo groups were similar with respect to both the proportions of specific antidepressant

Figure 1. Mean Change in MADRS Total Score[a,b] During the Randomization Phase in Patients With Major Depressive Disorder Randomly Assigned to Adjunctive Aripiprazole or Adjunctive Placebo (efficacy sample; pooled data; ANCOVA; LOCF)



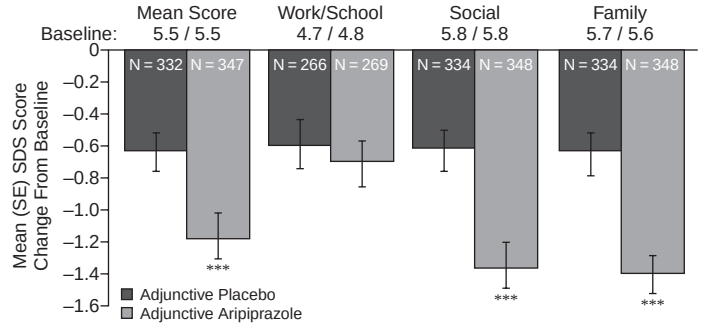
[a]MADRS total score is rated from 0 to 60; a negative change indicates an improvement.
[b]Baseline scores: placebo, 26.5; aripiprazole, 25.5.
**p < .01, ***p < .001 versus adjunctive placebo.
Abbreviations: ANCOVA = analysis of covariance, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 3. Remission[a] Rates in the Adjunctive Placebo and Adjunctive Aripiprazole Groups During Double-Blind Treatment



[a]Remission equals absolute Montgomery-Asberg Depression Rating Scale (MADRS) total score ≤ 10 and at least 50% reduction in MADRS total score relative to the end of the prospective treatment phase.
***p < .001 versus adjunctive placebo.

Figure 2. Mean Change in Sheehan Disability Scale (SDS) Mean Scores and Family, Social, and Work and School Items (LOCF) During Double-Blind Treatment



***p ≤ .001 versus adjunctive placebo.
Abbreviation: LOCF = last observation carried forward.

therapies as well as the doses received (Table 3). At entry into the randomization phase, the mean daily doses of the antidepressant therapies across both the placebo and aripiprazole arms were as follows: escitalopram, 19.9 mg; fluoxetine, 38.7 mg; paroxetine, 47.6 mg; sertraline, 142.7 mg; and venlafaxine, 214.7 mg. At study end, the mean (range) daily dose of aripiprazole at endpoint across all antidepressant therapies was 11.1 (2–20) mg/day. Considering each antidepressant therapy separately, the mean daily doses of aripiprazole for the following antidepressant groups were escitalopram, 11.1 mg/day; fluoxetine, 9.8 mg/day; paroxetine, 10.2 mg/day; sertraline, 12.4 mg/day; and venlafaxine, 11.0 mg/day.

Efficacy Analyses: Overall Pooled Population

At the end of the third (double-blind) phase, the mean change in the MADRS total scores was significantly greater in the patients receiving adjunctive aripiprazole (–8.7) than in those receiving adjunctive placebo (–5.7; p < .001). This change in MADRS corresponds to a treatment difference at week 14 (LOCF) between adjunctive aripiprazole and adjunctive placebo of –2.9 (95% CI = –4.1 to –1.8). Significant treatment differences in favor of aripiprazole were observed as early as the first week of double-blind treatment onward (Figure 1).

Patients treated with adjunctive aripiprazole showed greater reductions in the mean SDS score at endpoint (LOCF) than patients treated with placebo (–1.2 vs. –0.6; p = .001), a treatment difference (aripiprazole-placebo) of –0.5 (95% CI = –0.9 to –0.2) (Figure 2). Significant improvements over adjunctive placebo in the SDS item scores of social life and family life were also observed with adjunctive aripiprazole (Figure 2). The difference in the work/school item was not statistically significant (p = .576).

Remission rates were significantly higher in the adjunctive aripiprazole group than in the adjunctive placebo group for all time points from the second week of double-blind therapy onward (all p < .001; Figure 3). At endpoint (LOCF), the remission rates were 25.7% and 15.4% in adjunctive aripiprazole and adjunctive placebo groups, respectively; this difference was statistically significant (relative risk, 1.66; 95% CI = 1.23 to 2.24; p < .001). Re-

Table 4. Mean ± SE Change in MADRS Total Score in Subject Subpopulations (efficacy sample; pooled data; LOCF)

Variable	Placebo N	Placebo Mean ± SE	Aripiprazole N	Aripiprazole Mean ± SE	Treatment Comparison[a]: Aripiprazole-Placebo Difference (95% CI)	Interaction Test p Value[b]
Sex						
Male	119	–6.3 ± 0.7	132	–6.9 ± 0.7	–0.6 (–2.6 to 1.3)	
Female	237	–5.4 ± 0.5	234	–9.6 ± 0.5	–4.2 (–5.7 to –2.7)	.005
Age, y						
≤ 50	242	–5.5 ± 0.5	227	–8.4 ± 0.5	–2.9 (–4.3 to –1.4)	
> 50	114	–6.2 ± 0.8	139	–9.1 ± 0.7	–2.9 (–4.9 to –0.9)	.986
Race						
White	324	–5.7 ± 0.5	323	–8.7 ± 0.5	–3.0 (–4.3 to –1.8)	
Black	23	–7.2 ± 1.7	28	–9.5 ± 1.6	–2.3 (–6.9 to 2.4)	
Other	9	–4.7 ± 2.3	15	–6.1 ± 1.7	–1.4 (–7.3 to 4.6)	.927
MADRS score at end of prospective phase (median = 26)						
≤ 26	189	–4.9 ± 0.6	208	–8.1 ± 0.5	–3.2 (–4.7 to –1.7)	
> 26	167	–6.8 ± 0.7	158	–9.4 ± 0.7	–2.7 (–4.6 to –0.8)	.711
Response (MADRS) status at end of prospective phase						
< 25% (minimal responder)	262	–6.0 ± 0.5	238	–9.4 ± 0.5	–3.4 (–4.8 to –2.0)	
≥ 25%–< 50% (partial responder)	94	–5.4 ± 0.8	128	–7.2 ± 0.7	–1.8 (–3.9 to 0.2)	.242
No. of previous antidepressant trials in current episode						
1	237	–5.6 ± 0.5	249	–8.6 ± 0.5	–2.9 (–4.4 to –1.5)	
2	95	–6.1 ± 0.9	94	–9.3 ± 0.9	–3.2 (–5.5 to –0.8)	
≥ 3	23	–5.3 ± 1.5	22	–7.4 ± 1.6	–2.1 (–6.5 to 2.4)	.949
Duration of current episode, mo (median = 19.2)						
≤ 19.2	171	–6.0 ± 0.6	189	–8.2 ± 0.6	–2.3 (–3.9 to –0.6)	
> 19.2	185	–5.5 ± 0.6	177	–9.1 ± 0.6	–3.6 (–5.3 to –1.9)	.289
Antidepressant therapy						
Escitalopram	99	–4.9 ± 0.9	115	–8.3 ± 0.8	–3.4 (–5.7 to –1.2)	
Fluoxetine	52	–6.5 ± 1.1	53	–8.5 ± 1.1	–2.0 (–5.0 to 1.1)	
Paroxetine CR	27	–4.8 ± 1.4	30	–8.9 ± 1.4	–4.1 (–8.1 to –0.2)	
Sertraline	74	–5.9 ± 0.9	68	–9.3 ± 0.9	–3.4 (–5.9 to –0.9)	
Venlafaxine XR	104	–6.3 ± 0.8	100	–8.9 ± 0.8	–2.6 (–4.8 to –0.4)	.914

[a]Analysis of covariance, with double-blind treatment and study as main effects and end of prospective treatment phase assessment as covariate.
[b]Analysis of covariance, with double-blind treatment, study and subgroup as main effects, end of prospective treatment assessment as covariate, and treatment by subgroup as interaction effect.
Abbreviations: CR = controlled release, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, XR = extended release.

sponse rates were significantly higher in the adjunctive aripiprazole group than in the adjunctive placebo group for all time points from the first week on double-blind treatment ($p \leq .01$). At week 14 (LOCF), adjunctive aripiprazole produced significantly greater response rates than adjunctive placebo (33.1% vs. 20.5%); this difference also was significant (relative risk, 1.61; 95% CI = 1.25 to 2.07; $p < .001$). The number needed to treat (NNT) for response was 8 and the NNT for remission was 10.

Efficacy Analyses: Subgroup Analyses

With 1 exception, changes in MADRS total scores at endpoint (week 14, LOCF) were consistently greater with adjunctive aripiprazole than with adjunctive placebo in each of the subgroups investigated; efficacy was unrelated to race, age, duration of episode, response to prior antidepressant therapy, number of historical treatment failures, severity of depressive symptoms, and antidepressant (Table 4). In Hispanic patients, the mean improvement in MADRS total score in those receiving adjunctive aripiprazole (N = 16) was not greater than in those receiving adjunctive placebo (N = 30) (–5.6 vs. –6.5). The number of Hispanic patients was, however, small, and, with respect to ethnicity, the interaction test was not statistically significant ($p = .167$). In the subgroup of non-Hispanic patients, the treatment difference was similar to the treatment difference in the total patient sample (adjunctive aripiprazole, –8.8 vs. adjunctive placebo, –5.7). For the subgroup of patients treated with SSRIs (adjunctive aripiprazole, N = 266; adjunctive placebo, N = 252), adjunctive aripiprazole patients showed consistently greater reductions in the MADRS total score than adjunctive placebo patients (–8.6 vs. –5.5; treatment difference, –3.1; 95% CI = –4.5 to –1.7).

Patients receiving adjunctive aripiprazole versus those receiving placebo demonstrated significantly greater improvement in the MADRS total score versus adjunctive placebo in patients with 1 historical treatment failure (treatment difference, –2.9; 95% CI = –4.4 to –1.5; $p \leq .0001$) and >1 historical treatment failure (treatment difference, –3.0; 95% CI = –5.1 to –0.9; $p < .005$). A significant treatment-by-sex interaction was observed ($p = .005$); the treatment difference among females (–4.2; 95% CI = –5.7 to –2.7) was greater than that observed in the

males (–0.6; 95% CI = –2.6 to 1.3). This finding was driven by the results of 1 of the 2 studies (treatment-by-sex interaction study CN138-139; p = .002). The treatment-by-sex-interaction effect was not replicated in the second study (CN138-163; p = .374).

Safety

Detailed results of the pooled safety and tolerability data from the 2 randomized studies are reported elsewhere.[23] Briefly, adjunctive aripiprazole is relatively well tolerated in patients with MDD. Commonly observed adverse reactions (incidence ≥ 5% and at least twice that for placebo) with aripiprazole as adjunctive treatment to antidepressant therapy (N = 371) versus adjunctive placebo (N = 366) in adult patients with MDD include akathisia (25% vs. 4%), restlessness (12% vs. 2%), insomnia (8% vs. 3%), fatigue (8% vs. 4%), blurred vision (6% vs. 1%), and constipation (5% vs. 2%).[23] In clinical trials, akathisia is generally mild to moderate in severity and in these studies led to few discontinuations (N = 3). Akathisia resolved in 52% of the aripiprazole-treated patients with akathisia (47/91) by the end of the study. Interventions permitted and chosen for the management of akathisia included dose reduction (32%), the use of concomitant medications (benztropine [17%], propranolol [6%], or a combination of both [2%]), and a combination of dose reduction and concomitant medications (6%). No intervention was implemented for 39% of the akathisia events.[23] There were no deaths in the 2 trials, and the safety and tolerability profile did not differ across age, sex, or antidepressant therapy.

DISCUSSION

The results of this pooled analysis from 2 identically designed studies confirmed that the addition of aripiprazole to standard antidepressant therapy is significantly more effective than an antidepressant plus placebo for patients with MDD who had failed to achieve an adequate response following at least 1 historic and 1 prospective antidepressant trial during the current episode. Improvements in the depressive symptoms, as evidenced by the reduction in MADRS total score, were observed as early as the first week of randomized treatment and maintained at all time points throughout the study. A high completion rate was observed, which is reflected by a low discontinuation rate for adverse events, indicating that the adjunctive aripiprazole was well tolerated.

Aripiprazole was found to be effective, regardless of the antidepressant therapy chosen, with similar improvements in MADRS total score seen across all 5 antidepressants. Higher response and remission rates were also seen with adjunctive aripiprazole compared to adjunctive placebo, and, at endpoint, there was a 1.7-fold greater likelihood of achieving remission with adjunctive aripiprazole than placebo, confirming the clinical relevance of MADRS improvement. This significant difference in response and remission translates to a NNT of 8 and 10, respectively, meaning that for every 8 patients treated with adjunctive aripiprazole there will be 1 additional responding patient and for every 10 patients treated there will be 1 additional remitting patient.

In addition to symptomatic improvement in MADRS total scores, adjunctive aripiprazole also resulted in improvement in functioning as measured on the SDS mean score. Improvements observed in social and family items correspond to patients' self-reported improvement of their psychosocial functioning following addition of aripiprazole to their antidepressant treatment. The majority of patients with MDD report some level of functional impairment, which is greatest in the social domain.[25] Findings from this pooled analysis demonstrated that adjunctive aripiprazole improved both depressive symptoms and functioning.

The results of this pooled analysis also indicated that, with 1 exception, adjunctive aripiprazole was an effective treatment for a variety of patient subgroups. The 1 significant interaction reflected the observation that aripiprazole augmentation was more effective for women than men. Of note, this treatment-by-sex interaction was largely driven by results of 1 trial[21]; a significant treatment-by-sex interaction was not observed in the second trial.[22] Of note, in the first study the lack of a significant effect for adjunctive aripiprazole appeared to be largely due to a high placebo response in men. As there are a relatively small number of men even in this pooled data set, results of a recently completed third trial of adjunctive aripiprazole, using the same study design, will help to clarify the clinical significance of this unpredicted interaction.

Of particular note is the observation that adjunctive aripiprazole was effective in both patients with minimal response and in patients with partial response to the initial antidepressant treatment. In fact, the treatment difference in MADRS total scores favoring adjunctive aripiprazole over adjunctive placebo was almost twice as large among the subgroup of patients with only minimal MADRS response to the prospective course of antidepressant therapy as among those who had a partial MADRS response. Although augmentation strategies have commonly been used in partial responders, these data suggest that adjunctive aripiprazole therapy is also useful for minimal responders or nonresponders, and this information may be important when choosing adjunctive medications for patients who lack a significant response to antidepressant monotherapy.

Studies with atypical antipsychotic agents have shown that augmentation therapy with risperidone and olanzapine results in improvement in depressive symptoms in patients with at least 1 suboptimal response to antidepressant monotherapy.[17,26] The current analysis shows that

improvement in depressive symptoms following adjunctive aripiprazole is equally efficacious in patients who have had 1 or more treatment failures prior to the current episode. Thus, aripiprazole as an adjunctive therapy to an antidepressant is efficacious in patients that are more difficult to treat (i.e., > 1 treatment failure, minimal responders), as well as those who have had some success with antidepressant therapies (i.e., 1 treatment failure, partial responders).

Inhibition of noradrenergic neurons caused by serotonin reuptake inhibition[27] may explain the lack of optimal response to SSRIs in some patients. Given the important role of 5-HT_{2A} receptors in the interaction between the serotonin and norepinephrine systems in the brain,[28] it has been proposed that the beneficial action of atypical antipsychotics when used to augment SSRIs results from reversal of SSRI-induced inhibition of noradrenergic neurons via their 5-HT_{2A} antagonist action.[29,30] Serotonin-norepinephrine reuptake inhibitors (SNRIs) produce similar changes to serotonin neurotransmission as the SSRIs.[29] It is possible that the beneficial action of atypical antipsychotics when used with SNRIs also results from their effect on noradrenergic neurons through a cascade effect resulting from 5-HT_{2A} receptor blockage, although the exact basis for this interaction is currently unknown.

In addition to 5-HT_{2A} antagonism, aripiprazole also elicits partial agonism with high intrinsic activity at 5-HT_{1A}, similar to buspirone,[18,31,32] which can translate into increased dopamine release in the prefrontal cortex that is comparable to full 5-HT_{1A} agonists.[33] Currently, all other atypical antipsychotics are antagonists at D_2 receptors, and dopamine transmission, more specifically mediated by D_2 and D_3 receptors, has been implicated in the pathophysiology of major depression.[34,35] The serotonin activity of aripiprazole in combination with D_2/D_3 partial agonism may provide a unique synergistic approach to augment antidepressant response in patients with MDD.

Although the efficacy of adjunctive aripiprazole in MDD has been reported previously in small open-label studies,[36–40] pooling the data from identically designed studies has several uses. One of the strengths lies in the substantial number of patients included, which permits more precise estimates of treatment effects and provides greater power for subgroup analyses. Overall, these findings reinforce the benefits seen in the 2 individual studies, which both showed statistically significant findings on the primary endpoint, i.e., improvement of depressive symptoms in patients with MDD is optimized by using a combination of aripiprazole with an antidepressant. Another strength is in the study design. For instance, patients entered a 14-week trial, and, regardless of response during the second phase (week 0–week 8), all patients were followed for an additional 6 weeks. Patients were blinded to randomization so that this approach limited any possible confounding factor or patient bias arising from adding on an adjunctive treatment (i.e., aripiprazole). The trial design also confirms the benefits of augmenting antidepressant monotherapy with aripiprazole rather than extending exposure time of antidepressant monotherapy past the initial 8 weeks of treatment; adjunctive aripiprazole showed a greater improvement in depressive symptoms versus leaving the patient on antidepressant monotherapy plus placebo for the remainder of the trial (an additional 6 weeks).

However, it is also true that the value of pooled analyses is limited by their post hoc nature, and no correction was made for multiple comparisons. Although subgroup analyses were defined prior to completion of both studies, these results should be viewed as useful for generating hypotheses, not testing them. Finally, a prospective longer-term trial would be beneficial in further evaluating aripiprazole as an adjunctive therapy in MDD.

In conclusion, this pooled analysis extends previous findings from the individual trials by demonstrating that adjunctive aripiprazole is an efficacious strategy for a variety of subgroups of patients with MDD who had an inadequate response to a range of widely prescribed antidepressants.

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