

Aripiprazole Augmentation in Major Depressive Disorder: A Double-Blind, Placebo-Controlled Study in Patients with Inadequate Response to Antidepressants

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ABSTRACT

Introduction: Effective management of major depressive disorder (MDD) continues to be a challenging task for psychiatrists and primary care physicians. This trial evaluated the efficacy and safety of adjunctive aripiprazole versus antidepressant monotherapy in patients with MDD and independently replicated the positive findings of two similar trials.

Methods: Patients (N=1,147) with MDD experiencing a major depressive episode and a history of inadequate response to antidepressant monotherapy were enrolled (week 0); 827 received single-blind adjunctive placebo plus open-label antidepressant (escitalopram, fluoxetine, paroxetine controlled release, sertraline, or venlafaxine extended release) for 8 weeks to confirm inadequate response to antidepressants; 349 patients with inadequate response were randomized (1:1) to double-blind, adjunctive placebo (n=172) or adjunctive aripiprazole (n=177; 2–20 mg/day). Primary outcome was the mean change in Montgomery-Åsberg Depression Rating Scale (MADRS) Total score from baseline (week 8) to endpoint (week 14).

Results: Clinically significant improvements in depressive symptoms as assessed by decreases in the MADRS Total score were greater with adjunctive

FOCUS POINTS

- Depression is a leading cause of disease burden.
- Remission is an important goal for the treatment of patients with major depressive disorder (MDD); augmentation is one treatment strategy for achieving remission.
- Aripiprazole has demonstrated efficacy as augmentation therapy to antidepressants in two large registrational trials in patients with MDD who do not respond adequately to standard antidepressant monotherapy.
- This third consecutive trial demonstrates that aripiprazole augmentation to antidepressants is an efficacious and well-tolerated treatment for patients with MDD.

ive aripiprazole (–10.1) than placebo (–6.4; $P<.001$). Remission rates were greater for adjunctive aripiprazole than for adjunctive placebo (week 14, 36.8% vs 18.9%; $P<.001$). Completion rates with adjunctive aripiprazole and placebo were high (83% vs 87%) and discontinuations due to adverse events were low (6.2% vs 1.7%).

Conclusion: For some patients with MDD who do not obtain adequate symptom relief with antidepressant monotherapy, adjunctive therapies can significantly improve depressive symptoms. As reported, adjunctive aripiprazole was associated with a two-fold higher remission rate than adjunctive

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tive placebo. This, and previous studies, have shown that discontinuations due to adverse events were low and completion rates were high, and has indicated that both antidepressant and aripiprazole in combination were relatively well-tolerated and safe. This is the third consecutive clinical trial, in the absence of a failed trial, to demonstrate that aripiprazole augmentation to antidepressants is an efficacious and well-tolerated treatment for patients with MDD who do not respond adequately to standard antidepressant monotherapy (ClinicalTrials.gov study NCT00105196).

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INTRODUCTION

Depression is rated as the fourth leading cause of disease burden,¹ which affects 13–14 million adults in the United States in a given year² and impairs health to a substantially greater degree than chronic diseases, such as angina, asthma, and diabetes.³ In addition, depression is often comorbid with other chronic diseases, further worsening health outcomes compared with depression alone.³ Depression is one of the most common illnesses seen by primary care physicians (PCPs) and the majority of patients receive treatment in a primary healthcare setting.⁴ Not surprisingly, the disorder is increasingly recognized as an important public health issue, especially as inadequately treated depression is associated with increased healthcare service utilization.⁵

Treating to remission is increasingly seen as the goal of treatment for major depressive disorder (MDD) and means that the depressed individual has been able to return to a premorbid level of functioning. Despite the large number of antidepressants available, no single treatment is uniformly effective and more than one treatment step is often required in order to reach symptom remission. Currently, ~33% of patients achieve remission after an adequate course of at least one antidepressant,^{6,7} whether treated in a primary or specialist setting.⁸ Augmentation of antidepressant therapy is one approach to increasing the chances of achieving remission.

Background

Aripiprazole was the first medication to receive Food and Drug Administration approval for adjunctive treatment in patients with MDD. The results of two randomized clinical trials, using an innovative study design, demonstrated the benefits of adjunctive aripiprazole over antidepressant monotherapy in patients with MDD who have shown an inadequate response to at least one historic and one prospective course of antidepressant.^{9,10} The authors of this article report the results of a third consecutive, large, double-blind, placebo-controlled trial using the same study design, developed to ensure careful characterization of the inadequate response to antidepressant monotherapy and to enhance signal detection.

METHODS

Patients

Patients 18–65 years of age who met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision*¹¹ criteria for a major depressive episode lasting ≥ 8 weeks were enrolled in the trial. Patients must have reported an inadequate response to a previous antidepressant as defined by $< 50\%$ reduction in severity of depressive symptoms—determined by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire¹²—to 1–3 antidepressant trials of at least 6 weeks duration. All patients provided written informed consent. Patients were excluded if they had received antidepressant with an adjunctive antipsychotic for > 3 weeks during their current episode, experienced psychosis in the current episode, or previously could not tolerate any study antidepressants. Additional exclusion criteria have been reported previously.⁹

Study Design

This multicenter, randomized, double-blind, placebo-controlled trial was conducted at 36 sites in the US between March 2005 and April 2008 in accordance with the Declaration of Helsinki; the ethics committee at each site approved the protocol. All participants provided written informed consent.

The study consisted of three phases. Patients

entered a 7–28-day screening phase, in which prohibited psychotropics (benzodiazepines and other hypnotics) were discontinued. Patients experiencing an major depressive episode—defined as Total Score ≥ 18 on the 17-item Hamilton Rating Scale for Depression (HAM-D₁₇)—entered an 8-week, single-blind, prospective treatment phase designed to establish inadequate response to standard antidepressant. Patients received antidepressant in accordance with current product labeling guidelines and were titrated to the highest tolerated level achievable within 3 weeks, targeting the following doses: escitalopram (10 or 20 mg/day), fluoxetine (20 or 40 mg/day), paroxetine controlled release (CR) (37.5 or 50 mg/day; paroxetine 30 or 40 mg/day if paroxetine CR unavailable), sertraline (100 or 150 mg/day) or venlafaxine extended release ([ER] 150 or 225 mg/day). In addition, patients received single-blind, adjunctive placebo. Antidepressant dose decreases were allowed in the fourth week but not thereafter.

Patients meeting criteria for inadequate response ($<50\%$ reduction in the HAM-D₁₇ Total score from baseline to the end of the prospective treatment phase, a HAM-D₁₇ Total score ≥ 14 , and a Clinical Global Impressions-Improvement [CGI-I] score ≥ 3 at weeks 6 and 8) were eligible to enter a 6-week, double-blind phase, in which participants were randomized (1:1) to continue antidepressant treatment (no dose adjustment was permitted) plus either adjunctive placebo or aripiprazole (2–20 mg/day; maximum 15 mg/day in patients receiving fluoxetine or paroxetine). Patients randomized to receive aripiprazole started at 5 mg/day, with the possibility of decreasing to 2 mg/day if the original dose was not tolerated. Investigators could increase the dose by up to 5 mg/day/week, to a maximum of 20 mg/day. Allowable aripiprazole doses included 2, 5, 10, 15, and 20 mg/day. No aripiprazole dose increases were allowed after week 12 (ie, week 4 in double-blind treatment), although dose reduction for tolerability was permitted at any visit. Patients taking stable doses of hypnotics for insomnia, including benzodiazepines and other sleep aides, were required to discontinue medication at least 1 week prior to prospective treatment. All psychotropics (ie, mood stabilizers, neuroleptics) were prohibited. Treatment of extrapyramidal symptoms (eg, benzotropine

or propranolol) was permitted during the study except within 12 hours prior to administration of movement rating scales. Patients were blinded to the point of randomization and those not meeting criteria for randomization (due to response) continued antidepressant plus single-blind placebo.

Assessments

The primary efficacy endpoint was mean change from end of the prospective treatment to the end of randomized, double-blind treatment in the Montgomery-Åsberg Depression Rating Scale (MADRS) Total score.¹³ The key secondary endpoint was mean change from end of the prospective treatment to the end of randomized, double-blind treatment in the Sheehan Disability Scale (SDS) mean score.¹⁴ Other secondary efficacy measures included HAM-D₁₇ Total score, CGI-I and CGI-Severity of Illness,¹⁵ Inventory of Depressive Symptomatology Self-Report Scale (IDS-SR),¹⁶ the Quick Inventory of Depressive Symptoms Self-Report scale (QIDS-SR),¹⁷ a 16-item subscale of the IDS, and the Quality of Life Enjoyment and Satisfaction Questionnaire, Short Form.¹⁸ Response ($\geq 50\%$ decrease from end of prospective treatment phase in MADRS Total score) and remission (MADRS Total score of ≤ 10 and $\geq 50\%$ reduction in MADRS Total score from end of prospective treatment) were also assessed. Additional post-hoc analyses were performed using additional MADRS cut-off scores to define remission. Reported herein are the remission rates using a final score of MADRS Total ≤ 12 (previously used in antidepressant studies^{19,20}) and a final score of ≤ 8 (a more restrictive definition suggested by the findings of Mittmann and colleagues).²¹ Safety was evaluated by monitoring adverse events (AEs), body weight, vital signs, laboratory parameters, 12-lead electrocardiogram, and evaluation of extrapyramidal symptoms using the Simpson-Angus Scale (SAS),²² Abnormal Involuntary Movement Scale,²³ and Barnes Akathisia Clinical Assessment (BARS).²⁴ The self-reported Massachusetts General Hospital Sexual Functioning Inventory (SFI) scale was also evaluated.²⁵

Statistics

Safety analyses included all patients ran-

domized to treatment who received at least one dose of double-blind study medication (safety sample). Efficacy analyses included all patients in the safety sample who had at least one post-randomization efficacy evaluation (efficacy sample). Analyses were based on the last observation carried forward (LOCF) of data from double-blind treatment.

To summarize baseline information, means and standard deviations for continuous variables and frequencies (percentages) for discrete variables are presented. Analysis of covariance with end of prospective treatment phase score as covariate and treatment, and study center as main effects, was used to assess changes in MADRS Total scores and SDS mean scores. Secondary outcome measures and safety parameters were analyzed as previously described.⁹ Median change from end of prospective treatment was estimated for fasting lipids and glucose, and prolactin. Treatment comparisons were carried out using the Wilcoxon rank-sum test. A *P* value of <.05 was considered to indicate statistical significance. The hierarchy of analyses was prespecified.

RESULTS

Patient Disposition and Characteristics

Baseline characteristics, shown in Table 1, were similar between treatment groups with the exception of gender (more females randomized to adjunctive aripiprazole). Patient enrollment, randomization and disposition are shown in Figure 1. The randomized, double-blind treatment phase was completed by 83% of adjunctive aripiprazole patients and 87% of adjunctive placebo patients. Discontinuations due to AEs (randomized sample) had low incidence rates in both groups (adjunctive aripiprazole 6.2%, adjunctive placebo 1.7%).

Treatment and Dosing

The mean dose of aripiprazole at endpoint was 10.7 mg/day and was similar among antidepressant groups. In the placebo group, the mean "dose" equivalent was 13.9 mg/day. The distribution of adjunctive aripiprazole dosing at endpoint was as follows: 2 mg/day, 5.7%; 5 mg/day, 29.7%; 10 mg/day, 23.4%; 15 mg/day, 30.3%; and 20 mg/

day, 10.9%. The distribution of each antidepressant during randomization was similar between adjunctive aripiprazole (escitalopram: 33.9%; fluoxetine: 17.5%; paroxetine: 7.9%; sertraline: 11.9%; venlafaxine ER: 28.8%) and adjunctive placebo (escitalopram: 30.2%; fluoxetine: 14.5%; paroxetine: 11.6%; sertraline: 17.4%; venlafaxine ER: 26.2%). Antidepressant therapy doses were similar between treatment groups.

TABLE 1.
Baseline Demographic and Disease Characteristics of Randomized Patients

<i>Characteristic</i>	<i>Placebo</i>	<i>Aripiprazole</i>
Patients, n	172	177
Gender, n (%)		
Male	55 (32.0)	39 (22.0)
Female	117 (68.0)	138 (78.0)
Age, mean (SD), years	45.6 (11.3)	45.1 (10.6)
Weight,* mean (SD), kg	88.8 (22.8)	84.3 (21.0)
BMI,* mean (SD), kg/m ²	31.3 (8.0)	30.4 (7.2)
Race, n (%)		
White	149 (86.6)	155 (87.6)
Black	18 (10.5)	14 (7.9)
Asian	2 (1.2)	3 (1.7)
American Indian/ Alaskan native	1 (0.6)	0
Native Hawaiian/other Pacific Islander	0	1 (0.6)
Other	2 (1.2)	4 (2.3)
Duration of current episode (months)	17.2	18.8
Median (range)	(1.6–236.5)	(2.1–433.1)
Number of depressive episodes		
Mean (SD)	6.3 (10.0)	5.3 (8.2)
Median (range)	4.0 (0–99)	3.0 (1–99)
Single depressive episode, n (%)	20 (11.6)	26 (14.7)
Number of adequate trials in current episode, n (%)		
0	5 (2.9)	3 (1.7)
1	117 (68.0)	127 (71.8)
2	45 (26.2)	38 (21.5)
3	3 (1.7)	9 (5.1)
4	2 (1.2)	0
MADRS Total score*: mean (SD)	27.1 (5.8)	26.6 (5.8)

* Assessed at end of prospective treatment phase.

SD=standard deviation; BMI=body mass index; MADRS=Montgomery-Åsberg Depression Rating Scale.

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Efficacy

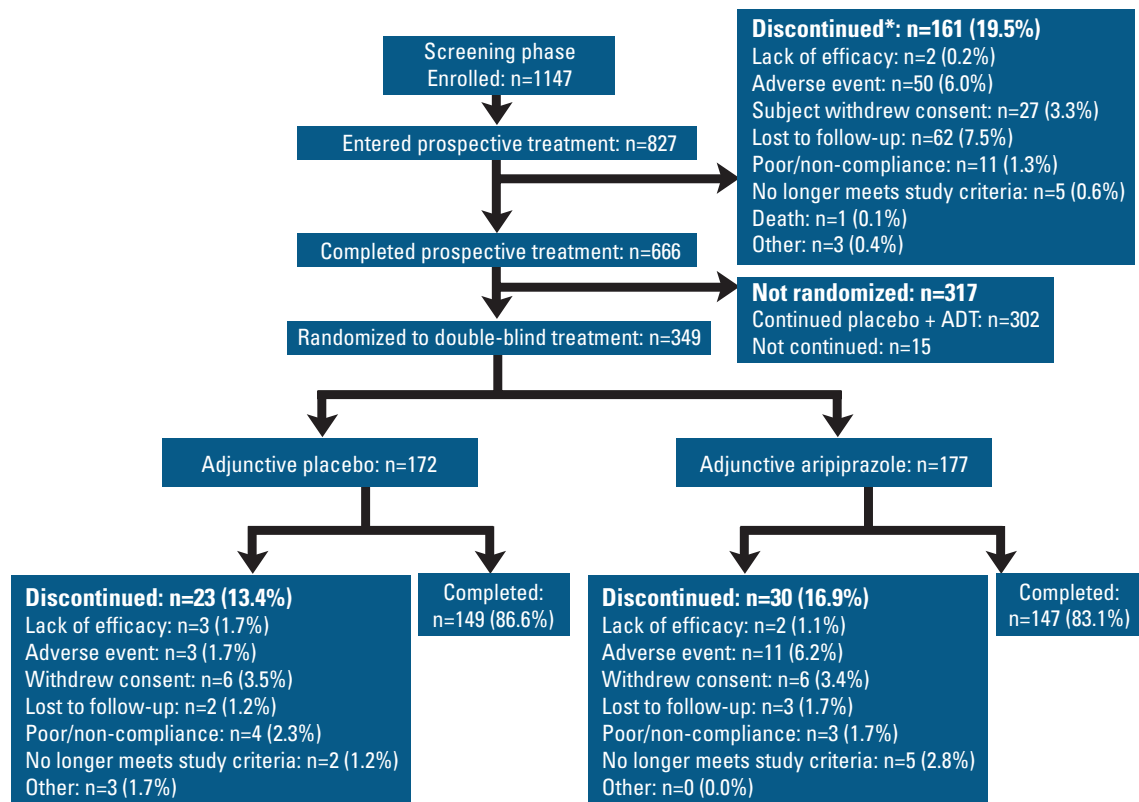
Patients randomized to adjunctive aripiprazole experienced a significantly greater improvement in MADRS Total score than those randomized to adjunctive placebo from the first week of double-blind phase to endpoint (−10.1 vs −6.4; $P<.001$; treatment difference −3.7; 95% CI −5.4, −2.0; Figure 2). A post-hoc analysis correcting for gender imbalance between treatment groups showed similar improvements at endpoint (−9.6 vs −6.1; $P<.001$; treatment difference −3.5; 95% CI −5.2, −1.8). Subgroup analysis of mean change in MADRS Total scores showed no statistically significant interaction effects for antidepressant ($P=.75$), age group (<37, ≤37 to <46, ≤46 to <53 and ≥53 years; $P=.74$), MADRS response (<25% vs 25% to <50% improvement during prospective phase; $P=.17$) or sex ($P=.62$). The treatment difference between adjunctive aripiprazole and

adjunctive placebo was −4.3 (95% CI −7.4, −1.3) in males and −3.3 (95% CI −5.5, −1.1) in females.

Adjunctive aripiprazole resulted in significantly greater remission (36.8% vs 18.9%; $P<.001$) and response (46.6% vs 26.6%; $P<.001$) rates than adjunctive placebo from the second week of double-blind phase to study endpoint (Figure 3). This produced a number needed-to-treat (NNT) for remission of 6 (95% CI 4-12) and for response of 5 (95% CI 4-10). Significantly greater rates of remission were also observed with adjunctive aripiprazole versus placebo in post-hoc analyses using alternative definitions of remission (MADRS total score ≤12: 43.7% vs 27.2%, $P<.001$; MADRS Total score ≤8: 27.6% vs 14.2%, $P<.01$).

Mean change in SDS mean score at endpoint was not statistically significantly different between adjunctive aripiprazole and adjunctive

FIGURE 1.
Enrollment, randomization, and disposition of patients



* Percentages based on number of patients who entered prospective treatment.
 † ADT=antidepressant therapy.

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placebo. A statistically significant treatment difference at endpoint in the change in Family Life subscore was observed in favor of adjunctive aripiprazole versus adjunctive placebo (Table 2). Other secondary efficacy endpoints, including improvement in quality of life assessments, are summarized in Table 2.

Tolerability

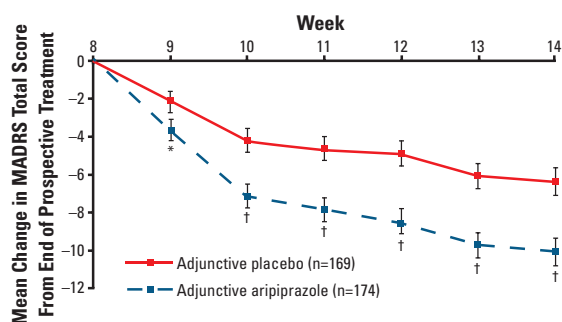
The number of patients with treatment-related AEs (incidence $\geq 5\%$ in either treatment group) and serious AEs during the randomized double-blind treatment phase are reported in Table 3. AEs (safety sample) reported after start of double-blind study medication and leading to discontinuation occurred in three patients (1.7%) in the placebo group and 10 patients (5.7%) in the adjunctive aripiprazole group. No patients died during randomized treatment, although one death was reported during the prospective treatment phase—a case of suicide considered unlikely to be related to study medication (paroxetine).

Akathisia was reported with adjunctive aripiprazole in 32/176 patients. The majority of cases was generally mild ($n=20/32$; 62.5%) or moderate ($n=9/32$; 28.1%) in severity; three patients reported akathisia as severe (9.4%). A total of 13 cases (40.6%) resolved by study endpoint, and the median time to resolution was 9 days (95% CI 8-16). Two adjunctive aripiprazole-treated

patients discontinued due to akathisia. During double-blind treatment, minimal changes from the end of prospective treatment were seen at endpoint (LOCF) on the SAS (placebo: 0.00; aripiprazole: 0.17, $P=.042$), AIMS (placebo: -0.05 ; aripiprazole: 0.00, $P=.23$), and BARS (placebo: 0.05; aripiprazole: 0.22, $P=.001$) scales.

There was no significant difference in weight gain between adjunctive aripiprazole and adjunctive placebo (+1.2 kg vs +0.8 kg; $P=0.14$; LOCF) or the number of patients experiencing clinically significant weight gain ($\geq 7\%$) at endpoint (adjunctive aripiprazole patients, 4.5% vs. adjunctive placebo 1.2%; $P=.08$; LOCF). There were no significant dif-

FIGURE 2.
Change in mean (\pm SE) MADRS Total score during the randomized, double-blind treatment phase (LOCF)



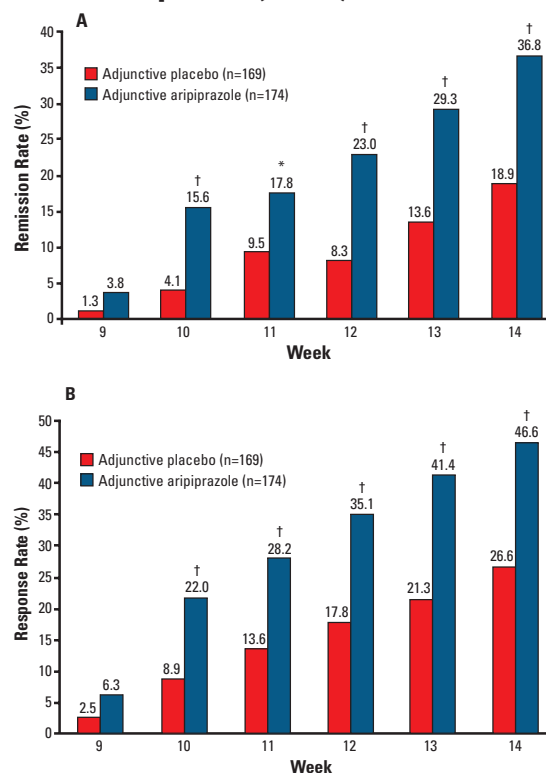
* $P < .05$ vs placebo.

† $P < .001$ vs placebo.

SE=standard error; MADRS=Montgomery-Åsberg Depression Rating Scale; LOCF=last observation carried forward.

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FIGURE 3.
Remission (A) and response (B) rates during the randomized, double-blind treatment phase (LOCF)



* $P < .05$ vs placebo.

† $P \leq .001$ vs placebo.

MADRS response= $\geq 50\%$ decrease from end of prospective treatment phase in MADRS Total score; MADRS remission=a MADRS Total score of ≤ 10 and $\geq 50\%$ reduction in MADRS Total score from end of prospective treatment.

LOCF=last observation carried forward; MADRS=Montgomery-Åsberg Depression Rating Scale.

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ferences between adjunctive aripiprazole versus adjunctive placebo in median changes in fasting levels of total cholesterol (1.0 vs 2.0 mg/dL [0.03 vs 0.05 mmol/L]; $P=.93$), triglycerides (7.0 vs 11.0 mg/dL [0.08 vs 0.12 mmol/L]; $P=.54$); HDL-C (2.0 vs 0.0 mg/dL [0.05 vs 0.00 mmol/L]; $P=.11$), LDL-C (−1.5 vs 0.0 mg/dL [0.04 vs 0.0 mmol/L]; $P=.85$), or fasting plasma glucose (0.0 vs 0.0 mg/dL [0.0 vs

0.0 mmol/L]; $P=.56$).

Adjunctive aripiprazole was associated with significantly greater improvements in sexual functioning versus adjunctive placebo as assessed by the overall improvement item of the SFI (treatment difference −0.3; $P=.03$; 95% CI −0.56, −0.04). The median change in prolactin level at endpoint was 0 ($P=.80$) in both

TABLE 2.
Mean Change From End of the 8-Week Prospective Treatment Phase (Double-Blind Baseline) to End of the Randomization Phase (Week 14, LOCF) in Secondary Efficacy Endpoints in the 6-Week Double-Blind Phase

<i>Rating Scale</i>	<i>Placebo</i>	<i>Aripiprazole</i>	<i>P</i>	<i>Rating Scale</i>	<i>Placebo</i>	<i>Aripiprazole</i>	<i>P</i>
<i>SDS mean score*</i>	n=160	n=160		<i>CGI-I score</i>	n=169	n=174	
Mean double-blind baseline (SE)	5.9 (0.2)	5.7 (0.2)		Mean endpoint score (SE)	2.8 (0.1)	2.4 (0.1)	.001
Mean change to week 14 (SE)	−0.8 (0.2)	−1.2 (0.2)	.08	<i>IDS-SR</i>	n=169	n=174	
<i>SDS Work/School item*</i>	n=126	n=115		Mean double-blind baseline (SE)	33.0 (1.1)	32.7 (1.1)	
Mean double-blind baseline (SE)	5.4 (0.3)	5.2 (0.3)		Mean change to week 14 (SE)	−5.4 (0.9)	−6.9 (0.9)	.12
Mean change to week 14 (SE)	−0.7 (0.3)	−0.8 (0.3)	.79	<i>QIDS-SR</i>	n=169	n=174	
<i>SDS Social Life item</i>	n=160	n=160		Mean double-blind baseline (SE)	12.8 (0.4)	13.0 (0.4)	
Mean double-blind baseline (SE)	6.1 (0.2)	5.9 (0.2)		Mean change to week 14 (SE)	−2.1 (0.3)	−2.8 (0.3)	.08
Mean change to week 14 (SE)	−0.7 (0.2)	−1.2 (0.2)	.05	<i>Q-LES-Q overall general subscore</i>	n=161	n=160	
<i>SDS Family Life item</i>	n=160	n=160		Mean double-blind baseline (SE)	44.3 (1.3)	43.8 (1.3)	
Mean double-blind baseline (SE)	5.9 (0.2)	5.7 (0.3)		Mean change to week 14 (SE) [†]	5.2 (1.4)	9.8 (1.4)	.004
Mean change to week 14 (SE)	−0.8 (0.2)	−1.4 (0.2)	.04	<i>Q-LES-Q satisfaction with medication</i>	n=153	n=146	
<i>HAM-D₁₇</i>	n=156	n=155		Mean double-blind baseline (SE)	3.0 (0.1)	3.1 (0.1)	
Mean double-blind baseline (SE)	20.0 (0.4)	19.8 (0.4)		Mean change to week 14 (SE) [†]	0.1 (0.1)	0.2 (0.1)	.26
Mean change to Week 14 (SE)	−5.1 (0.6)	−7.6 (0.6)	<.001	<i>Q-LES-Q overall life satisfaction</i>	n=161	n=160	
<i>CGI-S</i>	n=169	n=174		Mean double-blind baseline (SE)	2.6 (0.1)	2.6 (0.1)	
Mean double-blind baseline (SE)	4.2 (0.1)	4.1 (0.1)		Mean change to week 14 (SE) [†]	0.3 (0.1)	0.6 (0.1)	<.001
Mean change to week 14 (SE)	−0.7 (0.1)	−1.1 (0.1)	<.001				

* The SDS Work/School item score was missing for patients who neither worked nor went to school. For such patients the mean SDS score was the average of the remaining two item scores.

† Q-LES-Q positive change score signifies improvement.

LOCF=last observation carried forward; SDS=Sheehan Disability Scale; SE=standard error; HAM-D₁₇=17-item Hamilton Rating Scale for Depression; CGI=Clinical Global Impression; CGI-S=CGI-Severity of Illness; CGI-I=CGI-Improvement; IDS-SR=Inventory of Depressive Symptomatology-Self-Report; QIDS-SR=Quick Inventory of Depressive Symptomatology-Self Report version; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire Short Form; MADRS=Montgomery-Åsberg Depression Rating Scale.

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treatment groups.

DISCUSSION

Effective management of depression continues to be a challenging task for both psychiatrists and PCPs, despite the availability of a number of new antidepressants over the past 2 decades.²⁶ As illustrated by the results of this report, for some patients with MDD who do not obtain adequate symptom relief with antidepressant monotherapy, adjunctive therapies can significantly improve depressive symptoms. In this case, adjunctive aripiprazole was associated with a two-fold higher remission rate than adjunctive

placebo (36.8% vs 18.9%).

Findings from a broadly inclusive effectiveness trial conducted in both the PCP and psychiatric settings, the Sequenced Treatment Alternatives to Relieve Depression study,²⁷ have validated remission as the goal of treatment. This study has raised the question of whether augmentation strategies may be more effective than several sequenced monotherapy steps as an early treatment approach. The soon-to-be published third edition of the American Psychiatric Association practice guidelines for the treatment of patients with MDD will undoubtedly help guide treatment decisions toward achieving remission, and routine use of measurement-based tools to monitor symptoms and side effects of treatment will help to improve quality of care.²⁸ Given the importance of early symptom remission, there is a need to educate all healthcare providers on optimizing treatment for their MDD patients, especially PCPs who are well-positioned to provide evidence-based care earlier in treatment.

As reported earlier in 2008,²⁹ clinical trials in patients with MDD frequently fail to demonstrate the superiority of investigative agents over placebo. It is generally considered that as placebo response increases, the chance of missing a true treatment benefit also increases. As such, in the past, multiple clinical trials are often necessary in order to achieve the two positive trial results necessary for approval by the FDA.³⁰ In contrast, the study reported here is one of three consecutive studies in the absence of a failed trial that have consistently shown the superiority of adjunctive aripiprazole over antidepressant alone. The consistency of findings reported here can, in part, be attributed to a number of methodologic innovations used in this study, such as the modified sequential parallel comparison design, aimed at ensuring careful characterization of the inadequate response to antidepressant monotherapy and enhancing signal detection in an attempt to reduce the placebo response, which is common in affective disorder clinical trials.³⁰ Using this design, the status of adjunctive treatment was blinded to the patient across the entire 14-week treatment period and patients were only aware of the open-label antidepressant assigned. Furthermore, rater inflation was minimized by using different scales for baseline entry (HAM-D₁₇) and primary outcomes assess-

TABLE 3.
Treatment-Related and Serious Adverse Events (Safety Sample)

	<i>Adjunctive Placebo (n=172)</i>	<i>Adjunctive Aripiprazole (n=176)</i>
<i>Treatment-related adverse events occurring at an incidence of ≥5% in either treatment group during the randomized, double-blind treatment phase, n (%)</i>		
Akathisia	6 (3.5)	32 (18.2)
Headache	14 (8.1)	15 (8.5)
Somnolence	1 (0.6)	10 (5.7)
Dizziness	5 (2.9)	9 (5.1)
Restlessness	6 (3.5)	22 (12.5)
Insomnia	9 (5.2)	15 (8.5)
Constipation	6 (3.5)	10 (5.7)
Diarrhea	13 (7.6)	10 (5.7)
Nausea	10 (5.8)	7 (4.0)
Upper respiratory tract infection	13 (7.6)	13 (7.4)
Fatigue	8 (4.7)	16 (9.1)
Vision blurred	3 (1.7)	13 (7.4)
<i>Serious adverse events during the randomized, double-blind treatment phase, n (%)</i>		
Suicidal ideation	0	1 (0.6)
Arterial occlusive disease	1 (0.6)	0

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ments (MADRS). All three studies using this methodology demonstrated robust differentiation between active treatment (ie, adjunctive aripiprazole) and the adjunctive placebo arm, suggesting that these methodologies were successful in determining that augmentation strategies can be a safe and clinically effective approach to treating patients with MDD after an unsuccessful response with antidepressant monotherapy. Such methodologies should be considered for the future design of phase III clinical trials in patients with MDD.

The main limitation of this study is that robust clinical improvement on the primary efficacy measure, clinician-rated MADRS, did not translate into similar improvements with aripiprazole with the patient-rated IDS. This is consistent with the results of the previous two studies,^{9,10} and may be due to the fact that the IDS-SR has been shown to be less sensitive to change than the clinician-rated IDS in short-term studies.³¹ Additional limitations include the 6-week duration of adjunctive treatment preventing assessment of the long-term treatment benefits and the exclusion of patients with established medical comorbidities that are common in MDD—more research in these areas is warranted.

Finally, tolerability and side-effect burden are important factors when considering an augmentation treatment in MDD. This trial, in combination with previous studies,^{9,10} has shown that discontinuations due to AEs were low and completion rates were high, and has indicated that both antidepressant and aripiprazole in combination were relatively well-tolerated and safe during the treatment course. Even for the most common AE, akathisia, severity was usually mild to moderate and rarely led to discontinuation in each of the three studies. In this short-term setting, metabolic parameters did not change when adding aripiprazole to an antidepressant.

CONCLUSION

The results from this, and two other positive short-term studies,^{9,10} unequivocally support aripiprazole augmentation to standard antidepressant therapy in treating unresolved depressive symptoms in patients who have not achieved an adequate response to antidepressant monotherapy. In light of these findings, further studies are warranted to compare the effects of adjunctive

aripiprazole with other established augmentation strategies in patients with MDD. **CNS**

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