Efficacy of Dose Increase Among Nonresponders to Low-Dose Aripiprazole Augmentation in Patients With Inadequate Response to Antidepressant Treatment: A Randomized, Double-Blind, Placebo-Controlled, Efficacy Trial

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ABSTRACT

Objective: To examine the efficacy of a dose increase of aripiprazole to 5 mg/d in subjects with major depressive disorder (MDD) who did not respond to 4 weeks of treatment with aripiprazole 2 mg/d in a randomized, double-blind, placebo-controlled, parent study.

Method: 221 Subjects with Structured Clinical Interview for *DSM-IV* Axis I Disorders-Patient Edition–diagnosed *DSM-IV-TR* MDD (mean ± SD age, 45 ± 11 years; 64% women) with inadequate antidepressant response were recruited from September 2008–July 2009 and randomized to 60 days of double-blind augmentation with either aripiprazole or placebo in two 30-day phases. The study was performed across 8 academic hospital sites and 14 nonacademic (private clinic) sites throughout the United States. Randomization in a 2:3:3 ratio per sequential parallel comparison design was drug/drug (aripiprazole 2 mg/d in phase 1 and 5 mg/d in phase 2), placebo/placebo (placebo in both phases), and placebo/drug (placebo in phase 1 and aripiprazole 2 mg/d in phase 2). In phase 2, we examined efficacy of an aripiprazole dose increase to 5 mg/d in nonresponders to 2 mg/d by assessing response rates (≥ 50% reduction in Montgomery-Asberg Depression Rating Scale [MADRS] score [primary outcome measure]) and score changes in MADRS, Quick Inventory of Depressive Symptomatology-Self-Report, 9-item Patient Health Questionnaire (PHQ-9), the Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales, and patient-rated versions of the CGI-I and CGI-S scales.

Results: Response rate for aripiprazole 2 mg/d in phase 1 was 18.5% (n/n = 10/54). Among 39 nonresponders who increased their dose to 5 mg/d, response rate was 12.8% (95% CI, 4.30%–27.43%), with significant overall mean ± SD reductions in MADRS scores (−9.46 ± 7.83 [95% CI, −12.00 to −6.92]; $P < .0001$), Symptoms Questionnaire Distress scores (19.51 ± 17.73 [95% CI, 13.60 to 25.43]; $P < .0001$), PHQ-9 scores (−7.92 ± 5.92 [95% CI, −9.89 to −5.94]; $P < .0001$), and CGI-S scores (−0.86 ± 0.86 [95% CI, −1.15 to −0.58]; $P < .0001$). Differences in efficacy between drug and placebo groups were nonsignificant, however. Aripiprazole and placebo were well tolerated.

Conclusions: Augmentation with aripiprazole 5 mg/d may provide only a modest additional benefit in patients who do not benefit from lower doses.

Trial Registration: clinicaltrials.gov Identifier: NCT00683852

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Despite various treatment strategies for major depressive disorder (MDD), up to 50%–60% of MDD patients will not achieve adequate response, based on a minimal 50% reduction in symptom severity,[1] and two-thirds of patients who are prescribed antidepressant medications will not experience a timely remission, as conventionally defined by a minimal 50% reduction in symptom severity and an absolute score below a specified cutoff level.[2]

The addition of atypical antipsychotics in cases of inadequate response to antidepressant therapy is an increasingly popular strategy that is well supported in the literature,[3] though these medications may result in greater discontinuation due to adverse events. Aripiprazole was the first drug approved by the US Food and Drug Administration for adjunctive treatment of MDD in adults with inadequate response to antidepressant therapy in the current episode. Recommended doses of aripiprazole range from 2 mg/d to 15 mg/d based on 2 large, multicenter randomized, double-blind, placebo-controlled studies,[4,5] which were later supported by a third large trial.[6]

Two of these double-blind studies are limited in that their prescribed dose of aripiprazole is similar to that used in other psychiatric conditions and do not reflect the relatively lower doses of 2–5 mg/d often used in clinical practice for patients with MDD. Since higher doses of 10–15 mg aripiprazole as adjunctive treatment have been associated with various central nervous system side effects, we recently examined the safety, tolerability, and efficacy of low doses of aripiprazole (2 mg/d) adjunctive to antidepressant therapy in patients with an inadequate antidepressant response (eFigure1).[7] This study demonstrated tolerability of low-dose aripiprazole 2 mg/d as an augmenting agent for patients with inadequate response to antidepressant therapy. However, the efficacy of this strategy was marginal. The study contained a second phase in which a dose increase of aripiprazole to 5 mg/d was provided to subjects who did not respond after 4 weeks of 2 mg/d, with the expectation that nonresponders to 2 mg/d would have a greater response rate to 5 mg/d. The results of that investigation are reported here.

METHOD

The methods of the parent study are detailed in Fava et al[7] (clinicaltrials.gov identifier NCT00683852). Briefly, this was a multicenter, double-blind, placebo-controlled efficacy

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Clinical Points

- Atypical antipsychotics are being used more frequently as augmentation therapy in cases of inadequate response to standard antidepressants. Several studies have supported the efficacy and safety of aripiprazole augmentation at doses of up to 15 mg/d. Given the concern over side effects, it is worth investigating whether lower doses are also effective as augmentation.
- We examined 2 low-dose regimens of aripiprazole (2 mg/d for 30 days, followed by 5 mg/d for 30 days) as augmentation therapy in partial and nonresponders to selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor antidepressants.
- Both regimens were well tolerated but provided only marginal benefit. However, the 5-mg/d dose alleviated depressive symptoms in a modest number of patients who did not respond adequately to 2 mg/d. Starting aripiprazole at lower doses in antidepressant partial responders could be considered if patients are worried about side effects and rapid response is not urgent.

trial examining low-dose aripiprazole (2 mg/d) augmentation of selective serotonin reuptake inhibitors (SSRIs) or selective serotonin-norepinephrine reuptake inhibitors (SNRIs) in 221 subjects aged 18–65 years with MDD (mean ± SD age, 45 ± 11; 64% women) with inadequate response to antidepressants. Patients were recruited from September 2008 through July 2009. Prior to admission, subjects underwent a screening period between 14–28 days. During this time, subjects were diagnosed with *DSM-IV-TR* MDD, based on the Structured Clinical Interview for *DSM-IV* Axis I Disorders-Patient Edition; their major depressive episode had to be deemed "valid" using the SAFER criteria interview[8] administered by remote, independent raters. These raters were Massachusetts General Hospital psychiatrists and psychologists trained in the use of the SAFER interview. Raters administered the SAFER by telephone to verify eligibility of patients already screened at their respective sites and provisionally admitted into the study.

Inclusion criteria were as follows:

1. The participants had the ability to give informed consent, and understand the nature of the study, agree to comply with the prescribed dosage regimens, report for regularly scheduled office visits and communicate to study personnel about adverse events and concomitant medication use. All participants signed an informed consent approved by the Massachusetts General Hospital (MGH) Institutional Review Board.
2. The participants had been treated with an adequate dose of SSRIs/SNRIs during the current episode for at least 8 weeks and had received the same, adequate dose (defined as a total daily dose of at least 10 mg of escitalopram; 20 mg of fluoxetine, citalopram, or paroxetine; 25 mg of paroxetine controlled release; 50 mg of sertraline; 150 mg of venlafaxine; 60 mg of duloxetine; 50 mg of fluvoxamine; and 50 mg of desvenlafaxine) over the last 4 weeks.
3. The participants had a history of an inadequate response to 1, 2, or 3 adequate antidepressant treatments for the current depressive episode, including the current trial. Inadequate response was defined as less than a 50% reduction in depressive symptom severity, as assessed by the MGH Antidepressant Treatment Response Questionnaire[9] administered by remote, independent raters during the SAFER telephone interview. An adequate trial was defined as an antidepressant treatment for at least 6 weeks' duration with at least a minimum dose as specified in the MGH Antidepressant Treatment Response Questionnaire.
4. The participants had a 17-item Hamilton Depression Rating Scale (HDRS-17)[10] score ≥ 18 at the end of the screening phase. The HDRS-17 was administered by the study clinicians at the screening and baseline visits and by remote, independent raters during the screening phase at the time of the SAFER interview.

Eligible patients were randomized to double-blind augmentation treatment with either aripiprazole or placebo for 60 days, divided into 2 phases of 30 days each. Using the sequential parallel comparison design,[1] we randomly assigned patients to either aripiprazole 2 mg/d (n = 56) or placebo (n = 169) with the following treatment sequences in a 2:3:3 ratio: drug/drug (aripiprazole 2 mg/d in phase 1 and aripiprazole 5 mg/d in phase 2); placebo/placebo (placebo in both phases); and placebo/drug (placebo in phase 1 and aripiprazole 2 mg/d in phase 2). Patients continued on their stable antidepressant doses, with no dose adjustments allowed during the randomization phase. Safety and efficacy assessments were performed approximately every 10 days throughout the study.

Clinical improvement was measured as change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS)[11] score. Remission was defined as a final MADRS score of 10 or less, and response was defined as a decrease in MADRS total score of at least 50%. Nonresponse in phase 1 was determined by patients failing to achieve a 50% decrease in their MADRS score at visit 3 and/or having MADRS score of > 16 at visit 3. Patients who were unable to tolerate the lowest dose of any of the assigned therapies were discontinued from the study.

The analysis population for this report was drawn from all patients who were randomized to aripiprazole 2 mg/d in phase 1 and who entered phase 2 (5 mg/d). The analysis focused on subjects who failed to respond to low-dose aripiprazole in phase 1. The last-observation-carried-forward (LOCF) technique was employed to handle missing data. The data recorded at a given visit after randomization were used; if no observation was recorded at that visit, data were carried forward from the previous postrandomization visit. The

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LOCF was employed for efficacy analysis, and observed case analysis, which included only subjects with nonmissing observations, was also conducted.

Response to dose increase was assessed based on response rates and changes in various instruments. Response rates were calculated based on the number of subjects with a decrease of 50% or more in 10-item MADRS[11] score. Other outcome measures included the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR)[12]; the Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales[13]; patient-rated versions of the CGI-I and CGI-S scales; and, to further assess depressive status, the 9-item Patient Health Questionnaire (PHQ-9).[14]

Generalized estimating equations model (SAS PROC GENMOD; SAS Institute Inc, Cary, North Carolina) was implemented to analyze the change of Symptoms Questionnaire,[15] PHQ-9, Cognitive and Physical Functioning Questionnaire, and CGI-S scores, with baseline scores, treatment, and phase 1 baseline symptom severity as covariates, by using an approach analogous to that applied for the change of MADRS scores.

Adverse events were compared between patients who were assigned to the drug group in phase 1 (2 mg) and phase 2 (5 mg). Adverse events were assigned to a dose based on the date of their appearance. Patients who received aripiprazole (2 mg) in phase 2 were not included in order to maintain a strict "within patient" comparison of 2 mg vs 5 mg. Also, any residual effects of first dose of aripiprazole 2 mg were not accounted for. An additional comparison of adverse events between the complete aripiprazole 5-mg phase-2 group (safety sample of responders and nonresponders to 2 mg who increased dose) versus placebo was also carried out. Significance was assessed by the exact form of McNemar test.

For all analyses, significance was set at $P < .05$. Computations for all results were performed using SAS Version 8.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS

The response rate for low-dose (2 mg/d) aripiprazole in phase 1 in the LOCF sample was 18.5% (n/n = 10/54),[7] as compared to a placebo response rate of 17.4% (n/n = 29/167)[7] ($P > .05$, not significant). Thirty-nine aripiprazole nonresponders who increased their dose to 5 mg/d were eligible for intent-to-treat analysis. The response rate in phase 2 for these subjects was 12.8% (5/39) (95% CI, 4.30%–27.43%), which was not significantly different from that of the placebo group (7.9%; n/n = 5/63) in phase 2 ($P = .50$).

In the LOCF sample of low-dose aripiprazole augmentation nonresponders (n = 39), there was a significant overall reduction from the baseline visit of phase 1 to the end of phase 2 in mean ± SD MADRS scores (−9.46 ± 7.83 [95% CI, −12.00 to −6.92]; $P < .0001$), Symptoms Questionnaire Distress scores (19.51 ± 17.73 [95% CI, 13.60 to 25.43]; $P < .0001$), PHQ-9 scores (−7.92 ± 5.92 [95% CI, −9.89 to −5.94]; $P < .0001$), and CGI-S scores (−0.86 ± 0.86 [95% CI, −1.15 to −0.58]; $P < .0001$). Regarding improvement specific to phase 2 (dose increase), changes in these outcome measures were more modest, and we found no significant differences between the 5-mg/d group and the placebo group ($P > .05$ for all comparisons) (Table 1).

Table 1. Changes in Depression Outcome Measures in Subjects Who Increased Aripiprazole From 2 mg/d to 5 mg/d Compared to Placebo Group in Phase 2 of the Study

	Aripiprazole 5 mg/d		Placebo		Aripiprazole 5 mg/d vs Placebo, *P* Value
Instrument	Change in Phase 2, Mean ± SD	n	Change in Phase 2, Mean ± SD	n	
MADRS (LOCF)	−3.74 ± 6.82	39	−3.32 ± 5.97	63	.741
SQ (observed case)	−8.22 ± 12.78	37	−6.51 ± 13.19	61	.531
PHQ-9 (observed case)	−2.68 ± 4.30	37	−2.39 ± 4.83	61	.771
CGI-S (observed case)	−0.51 ± 0.80	37	−0.43 ± 0.78	61	.598

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, PHQ-9 = 9-item Patient Health Questionnaire, SQ = Symptoms Questionaire.

Fifty-four patients in the 2-mg and 5-mg dosing phases and 83 placebo patients met criteria for adverse events comparison. Adverse events did not vary significantly between the 2 dosing groups ($P > .05$ for all comparisons) or between the 5-mg group versus the placebo group ($P > .05$ for all comparisons) (Table 2). A few modest and perhaps clinically significant differences were observed with dose increase, however. Gastrointestinal side effects were lower by 13% in the 5-mg phase than in the 2-mg phase ($P = .118$; Table 2); this difference was driven largely by a decrease in constipation (n/n = 7/54 in the 2-mg phase vs n/n = 0/54 in the 5-mg phase), dry mouth (n/n = 4/54 in the 2-mg phase vs n/n = 0/54 in the 5-mg phase), and nausea (n/n = 4/54 in the 2-mg phase vs n/n = 1/54 in the 5-mg phase). There was a greater rate of infections and infestations in the 5-mg phase (n/n = 9/54; 16.67%) compared to the 2-mg phase (n/n = 2/54; 3.70%) ($P = .065$). Reported infections in the 2-mg phase included genital herpes (n = 1) and an upper respiratory tract infection (n = 1); the 5-mg phase included bronchitis (n = 1), herpes zoster (n = 1), nasopharyngitis (n = 2), upper respiratory tract infection (n = 4), and a urinary tract infection (n = 1). Nervous system symptoms were lower in the 5-mg phase (n/n = 5/54; 9.26%) compared to the 2-mg phase (n/n = 10/54; 18.52%) ($P = .227$); this difference was driven largely by a lower rate of headaches (n/n = 4/54 in the 2-mg phase vs n/n = 0/54 in the 5-mg phase) and somnolence (n/n = 3/54 in the 2-mg phase and n/n = 1/54 in the 5-mg phase). Insomnia was also less common in the 5-mg group (n/n = 1/54; 1.85%) compared to the 2-mg group (n/n = 4/54; 7.41%). No tardive dyskinesia or extrapyramidal symptoms were reported in any active treatment group or in the placebo group.

DISCUSSION

Augmentation of antidepressant treatment with atypical antipsychotics has been well supported by a recent

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Table 2. Treatment-Emergent Adverse Events for Aripiprazole (2 mg and 5 mg) and Placebo (safety sample)[a]

Measure	Aripiprazole		Placebo
	2 mg in Phase 1 (n = 54), % (n)	5 mg in Phase 2 (n = 54), % (n)[b]	in Phase 2 (n = 83), % (n)
Any adverse event	51.85 (28)	50.00 (27)	51.8 (43)
Blood and lymphatic	0.00 (0)	1.85 (1)	0.0 (0)
Cardiac	0.00 (0)	1.85 (1)	1.2 (1)
Eye	1.85 (1)	1.85 (1)	0.0 (0)
Gastrointestinal	22.22 (12)	9.26 (5)	18.1 (15)
General disorders and administration site conditions	9.26 (5)	9.26 (5)	4.8 (4)
Immune system	1.85 (1)	1.85 (1)	1.2 (1)
Infections and infestations	3.70 (2)	16.67 (9)	9.6 (8)
Injury, poisoning, and procedural complications	0.00 (0)	1.85 (1)	3.6 (3)
Weight gain	1.85 (1)	3.70 (2)	6.0 (5)
Increased appetite	1.85 (1)	0.00 (0)	1.2 (1)
Musculoskeletal/connective tissue	1.85 (1)	7.41 (4)	2.4 (2)
Nervous system	18.52 (10)	9.26 (5)	14.5 (12)
Akathisia	1.85 (1)	0.00 (0)	1.2 (1)
Amnesia	0.00 (0)	1.85 (1)	1.2 (1)
Dizziness	1.85 (1)	1.85 (1)	4.8 (4)
Headache	7.41 (4)	0.00 (0)	3.6 (3)
Mental impairment	0.00 (0)	1.85 (1)	0.0 (0)
Somnolence	5.56 (3)	1.85 (1)	2.4 (2)
Tremor	1.85 (1)	1.85 (1)	1.2 (1)
Psychiatric	9.26 (5)	11.11 (6)	9.6 (8)
Abnormal dreams	0.00 (0)	3.70 (2)	0.0 (0)
Depression	0.00 (0)	1.85 (1)	0.0 (0)
Hypomania	1.85 (1)	0.00 (0)	0.0 (0)
Anxiety	0.00 (0)	0.00 (0)	1.2 (1)
Insomnia	7.41 (4)	1.85 (1)	3.6 (3)
Libido decreased	0.00 (0)	1.85 (1)	0.0 (0)
Restlessness	0.00 (0)	1.85 (1)	3.6 (3)
Sleep disorder	0.00 (0)	0.00 (0)	1.2 (1)
Reproductive/breast	1.85 (1)	0.00 (0)	1.2 (1)
Ejaculation delayed	1.85 (1)	0.00 (0)	0.0 (0)
Erectile dysfunction	1.85 (1)	0.00 (0)	1.2 (1)
Skin/subcutaneous tissue	3.70 (2)	1.85 (1)	0.0 (0)
Vascular	0.00 (0)	3.70 (2)	2.4 (2)

[a]All comparisons between dosing groups and between drug and placebo groups were nonsignificant ($P > .05$ for all, based on exact McNemar test).
[b]Includes all subjects from phase 1 who increased dose to 5 mg/d in phase 2.

meta-analysis by Nelson and Papakostas.[3] However, there are concerns about a greater risk of adverse effects leading to early discontinuation, as well as safety concerns about this strategy. There is yet no consensus as to the optimal dose of atypical antipsychotics in MDD, and further investigation into this question is important.

The parent study[7] demonstrated good tolerability and low discontinuation rates with low-dose aripiprazole in depressed adults with inadequate response to antidepressant therapy in the current episode, but the observed response was limited. It therefore made sense to investigate the efficacy and tolerability of higher doses of aripiprazole. In the secondary investigation reported here, a modest percentage of nonresponders to a low dose of aripiprazole 2 mg/d responded to an increase to a higher dose of 5 mg/d. In addition, we observed significant overall improvement in various outcome measures throughout the entire treatment period. This finding suggests that augmentation with a higher dose of aripiprazole may provide some additional benefit in patients who do not benefit from lower doses. However, it must be observed that aripiprazole's modest advantage over placebo in response rates and in the other outcome measures did not reach statistical significance.

There was little change in adverse effects overall following the aripiprazole dose increase to 5 mg/d, and, in cases where relatively robust differences were observed, tolerability tended to favor the higher dose group. This may reflect spontaneous resolution of adverse events after a greater period of time on the drug, which often occurs with psychotropics. None of the reported infections have previously been associated with aripiprazole treatment, and it is therefore unlikely that the study drug would have been responsible for their occurrence. More likely they were due to environmental exposures (eg, respiratory infections) or the natural course of chronic infections (eg, herpes). Overall, tolerability of the higher aripiprazole dose was comparable to the lower dose and to placebo, suggesting that aripiprazole may be safely increased if needed in cases of limited efficacy at 2 mg daily.

The parent study was limited by the fact that all subjects had a history of failures to antidepressants, whereas the 3 previous positive studies[4–6] of aripiprazole augmentation in patients with inadequate response to antidepressants had all at least 1 prospective failure. The adverse event analysis was based on the safety sample, so it is possible that subjects may or may not have taken either of their assigned doses as prescribed.

While augmentation with low-dose aripiprazole followed by an increase to 5 mg/d was safe and well-tolerated, the response rates were modest, particularly in light of other studies, such as those of lithium augmentation, which have reported response rates of about 40%,[16] and the Sequenced Treatment Alternatives to Relieve Depression study,[2] in which response rates to buspirone and bupropion augmentation were about 30%. Practitioners who are contemplating augmentation in antidepressant partial responders should therefore consider these data carefully when selecting an agent to add to their patient's regimen.

In cases where rapid results are especially desirable, it may be worth trying an aripiprazole dose of at least 5 mg/d from the outset, in the hopes of obtaining a satisfactory improvement in depressive symptoms. If 5 mg/d proves ineffective, higher doses could be tried with careful watching for emergence of side effects, as suggested by the robust evidence from 3 positive studies.[4–6] Clinicians who are considering adding atypical antipsychotics to patients with inadequate response to antidepressant therapy need to weigh the pros and cons of this strategy. While the tolerability of aripiprazole appears good, the optimal dose remains to be clarified.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin, Aplenzin, and others), buspirone (BuSpar and others), citalopram (Celexa and others), desvenlafaxine (Pristiq), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine

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(Luvox and others), lithium (Lithobid and others), norepinephrine (Levophed and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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Supplementary material: The poster from the parent study is available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Efficacy of Dose Increase Among Nonresponders to Low-Dose Aripiprazole Augmentation in Patients With Inadequate Response to Antidepressant Treatment

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List of Supplementary Material for the article

1. eFigure 1 — A Double-Blind, Placebo-Controlled Study of Aripiprazole Adjunctive to Antidepressant Therapy (ADT) Among Depressed Outpatients with Inadequate Response to Prior ADT (ADAPT-A Study)

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A Double-Blind, Placebo-Controlled Study of Aripiprazole Adjunctive to Antidepressant Therapy (ADT) Among Depressed Outpatients with Inadequate Response to Prior ADT (ADAPT-A Study)

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ABSTRACT

This multicenter, placebo-controlled study was aimed at assessing the efficacy of low-dose aripiprazole (2 mg/day) adjunctive to antidepressant therapy (ADT) in the treatment of MDD patients with a history of inadequate response to prior ADT. In accordance with the sequential parallel comparison design (SPCD), 225 subjects with MDD (mean age: 45+/-11; 64% women; 19% non-white; 56% employed; 29% without college education), with inadequate response to ADT, were recruited across 22 US sites and randomized to 60 days of double-blind treatment with either aripiprazole (Abilify) 2 mg/d or placebo, divided into 2 phases of 30 days each. There was a 2:3:3 ratio for random assignment to the treatment sequences drug/drug (aripiprazole 2 mg/d in phase 1 and 5 mg/d in phase 2), placebo/placebo (placebo in both phases), and placebo/drug (placebo in phase 1 and aripiprazole 2 mg/d in phase 2). Safety and efficacy assessments, including the MADRS, CGI-S, CGI-I, SQ, CPFQ, and PHQ-9, were performed every 10 days throughout the 60 days of treatment. The pooled, weighted difference between aripiprazole 2 mg/d and placebo in percent of responders (defined as a 50% decrease in the MADRS) in the two phases was 5.6%; p=0.18; NS). With respect to the secondary analyses, the MADRS mean changes for aripiprazole 2 mg/day were -8.5 in phase 1 and -5.8 in phase 2, whereas the MADRS mean changes were -8.3 in phase 1 and -3.3 in phase 2 (weighted difference, attributing equal weight: -1.45; p=0.08; NS). Other secondary endpoints showed non-significant pooled differences between aripiprazole 2 mg/d and placebo in terms of differences in remission rates (MADRS < 11), differences in changes from baseline in CGI-S and CGI-I, as well as changes from baseline in total scores at endpoint of MGH CPFQ and PHQ-9. The SQ well-being mean changes for aripiprazole 2 mg/day were 3.7 in phase 1 and 3.3 in phase 2, whereas the SQ well-being mean changes for placebo were 2.8 in phase 1 and 2.0 in phase 2 (weighted difference, attributing equal weight: -1.21; p=0.0548; NS). From a safety perspective, of the 225 randomized subjects in phase I, 2 dropped out in the aripiprazole 2 mg/day arm and 2 in the placebo arm. Furthermore, of the 138 phase I placebo non-responders, 14 dropped out in phase II: 9 in the aripiprazole 2 mg/day arm and 5 in the placebo arm. There were only minimal differences in rates of AEs between aripiprazole and placebo, with the exception of constipation and dry mouth, which were more common on aripiprazole. In conclusion, this study provides clear support for the tolerability of low-dose aripiprazole (2 mg/day) as augmenting agent for patients with inadequate response to ADT. However, its efficacy appears to be marginal.

Study was supported by a grant from Bristol-Myers Squibb

INTRODUCTION

Three identical, large, multicenter, randomized, double-blind placebo-controlled trials in patients who had demonstrated an inadequate response to a prospective 8-week trial of the same antidepressant therapy (ADT) and at least one historical ADT trial have shown significantly higher response rates, (defined as a 50% or greater reduction in the MADRS) score, with aripiprazole augmentation of ADT (34%, 32% and 47%, respectively) compared to placebo augmentation of ADT (24%, 17%, and 19%, respectively) (Berman et al, 2007; Marcus et al, 2008; Berman et al, 2009). The mean aripiprazole-placebo difference in MADRS endpoint scores was 3.0, 2.8, and 3.7, respectively, with a reported effect size of 0.39 and 0.35 in the first two studies (Berman et al, 2007; Marcus et al, 2008). When the safety data from these three trials are pooled (Berman et al, 2007; Marcus et al, 2008; Berman et al, 2009), four central nervous system (CNS) side-effects have been consistently reported to be more common with aripiprazole than with placebo in the three trials: akathesia (22% vs 4%), restlessness (12% vs 2%), insomnia (8% vs 3%) and fatigue (8% vs 4%). This proposed study therefore assessed the effectiveness and tolerability of a low dose of aripiprazole (2 mg/day) adjunctive to ADT in treatment of MDD.

METHODS

This was a 60-day, multi-center, double-blind, placebo-controlled study on the efficacy of low-dose aripiprazole (2 mg/day) augmentation of selective serotonin reuptake inhibitors (SSRIs) or selective serotonin norepinephrine uptake inhibitors (SNRIs) in patients with MDD who had responded inadequately to ADT. The primary outcome was the difference in rate of response (decrease in MADRS total score of at least 50%) between patients treated with adjunctive aripiprazole 2 mg and adjunctive placebo using the sequential parallel comparison design (SPCD) (Fava et al, 2003). An additional aim of the study was to document the safety and tolerability of low doses of aripiprazole augmentation. Key secondary endpoints were difference in absolute change from baseline in MADRS score between aripiprazole 2 mg and placebo, difference in remission rates (MADRS < 11) between aripiprazole 2 mg and placebo, the change from baseline in total score at endpoint of the MGH Cognitive and Physical Functioning Questionnaire (CPFQ; Fava et al, 2009), difference in change scores on the clinical global impression of improvement (CGI-I) and severity (CGI-S) (Guy, 1976), change from baseline in total score at endpoint of Symptom Questionnaire, (SQ; Kellner, 1987) and the change in score of the 9-item Patient Health Questionnaire (PHQ-9; Kroenke et al, 2001).

In accordance with the sequential parallel design (see Figure 1), the 60-day, double-blind treatment was divided into two phases of 30 days each, with assessments performed every 10 days (+/- 3 days) to assess the safety and efficacy of treatment. The study consisted of a screening period and a randomization period. Patients who met eligibility during the screening period (lasting between 14 and 28 days) were randomized to double-blind treatment with either aripiprazole 2 mg/day (n=56) or placebo (n=169), with a 2:3:3 ratio for assignment to the treatment sequences drug/drug (DD, 2 mg/day aripiprazole plus the stable daily dose of ADT as documented in the screening phase for 30 days; at visit 3 on day 30, for all patients the aripiprazole dose was increased to 5 mg/day adjunctive to continued ADT, regardless of whether or not they had responded to aripiprazole 2 mg/day during phase 1), placebo/placebo (PP, double-blind adjunctive placebo plus the stable dose of ADT as documented in the screening phase up to visit 6, day 60) and placebo/drug (PD, double-blind adjunctive placebo plus the stable dose of ADT as documented in the screening phase; at visit 3 on day 30, patients were given 2 mg/day aripiprazole adjunctive to their ADT instead of placebo up to visit 6, day 60). Patients continued on their stable ADT doses documented during the screening phase. No dose adjustments were allowed during the randomization phase.

Inclusion Criteria:

- Men and women, ages 18 to 65; .Patients with a diagnosis of major depressive episode (MDE) as defined by DSM-IV-TR criteria, based on the SCID-I/P; their MDE had to be deemed "valid" using the SAFER criteria interview (Targum et al, 2008) administered by remote, independent raters.
- Quick Inventory of Depressive Symptomatology – Self-Rated (QIDS-SR) (22) score of at least 16 at both screen and baseline visits.
- Patients treated with an adequate dose of SSRIs/SNRIs during the current episode = or > 8 weeks, with the same, adequate dose over the last 4 weeks, adequate dose defined as total daily dose of at least 20mg of fluoxetine, citalopram, paroxetine, 25mg of paroxetine CR, 10 mg of escitalopram,50mg of sertraline, 150mg of venlafaxine, 60mg of duloxetine, 50mg of fluvoxamine and 50mg of desvenlafaxine.
- Between the screen and baseline visit, patients must have been documented prospectively to have received a stable dose of their SSRI or SNRI.
- Patients with a history for the current depressive episode of an inadequate response to one, two or three adequate antidepressant treatments, including the current trial. An inadequate response was defined as less than a 50% reduction in depressive symptom severity, as assessed by the MGH ATRQ(Fava, 2003; Chandler et al, epub) administered by remote, independent raters during the same SAFER interview call. An adequate trial was defined as an antidepressant treatment for at least 6 weeks duration at least at a minimum dose as specified in the MGH ATRQ.
-Patients with a HAM-D17 score ≥ 18 at the end of the screening phase qualified for inclusion. The HAM-D17 was administered by the study clinicians at the screening and baseline visits, and by remote, independent raters during the screening phase at the time of the SAFER interview.

Additional criteria for defining response and non-response for patients in Phase 2 eligible for the pooling of the data with all the patients in Phase 1: Among patients pre-randomized to receive placebo in both phases or to receive placebo in Phase 1 and aripiprazole in phase 2, only those meeting non-response criteria were added to the primary efficacy sample:

- Placebo non-responders were defined as those patients who failed to achieve a 50% decrease in their MADRS score at visit 3,
Had a MADRS score of > 16 at visit 3

Efficacy and Safety Assessments

Efficacy assessments were performed every 10 days (+/- 3 days) during the two 30-day phases of the study and included the MADRS, the CGI-S and CGI-I, the SQ, the PHQ-9, the MGH-CPFQ, and the Sexual Functioning Inventory (Fava et al, 1998). Vital signs (weight, and standing and supine pulse and blood pressure) were recorded at each visit and a physical exam was performed at screen and visit 6 (or endpoint). Consumptive habits (smoking, alcohol, and caffeinated beverages) were recorded at baseline, day 30, day 60, day 90, day 120, and day 150 (or endpoint). Adverse events and concomitant medications were collected at every visit.

Statistical Analyses

The analysis populations were defined as: 1) The randomized sample included all patients who were randomized; 2) The safety sample included those randomized patients who received at least one dose of double-blind study medication as indicated on the dosing record; 3) The primary efficacy sample included those patients in the safety sample who had at least one efficacy evaluation post-randomization. Statistical significance was declared only when the p-value was found to be less than or equal to 0.05. The Last Observation Carried Forward (LOCF) technique was employed to handle missing data. The primary analysis compared pooled MADRS response rates (attributing equal weight to both phases) between placebo and aripiprazole in phase 1 and placebo non-responders (from phase 1, defined as those patients with less than a 50% decrease in MADRS total score from baseline and a MADRS score > 16) who were given either aripiprazole 2 mg/day, or remained on placebo in phase 2. Differences in response rates were compared using binomial repeated measures regression, accounting for correlation between subject data in phase 1 and 2. Generalized Estimating Equations model (SAS proc genmod) was implemented to analyze the change of MADRS, CGI-S, CPFQ, and PHQ-9 scores with phase-specific baseline MADRS scores, treatment, and phase-1 baseline symptom severity on the primary efficacy sample.

RESULTS

Figure 1: Primary Outcome – Response Rates in the SPCD Samples (pooled, weighted drug-placebo difference: 5.6%; p=0.18; NS)

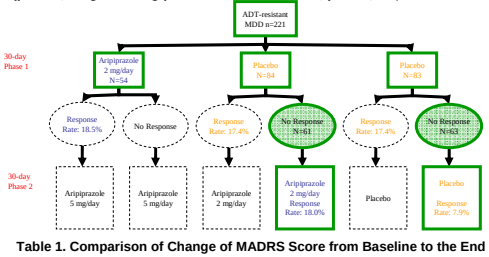

Table 1. Comparison of Change of MADRS Score from Baseline to the End of Follow-up between . Treatment Groups - Primary Efficacy Sample (PES)

	Drug (N=54 Patients)		Placebo (N=167 Patients)			
Measure	Phase I	Phase II	Phase I	Phase II	Weighted Difference (95% CI)	P-value*
Baseline MADRS Mean±SD (N)	30.69±4.02 (54)	26.80±5.85 (61)	31.20±4.75 (167)	26.29±5.48 (63)	0.31 [-0.72,1.34]	
Follow-up MADRS Mean±SD (N)	22.19±7.80 (52)	20.62±8.58 (58)	22.93±9.08 (162)	22.90±7.91 (61)	-1.57 [-3.34,0.20]	
Mean Change of MADRS from BSL Mean±SD (N)	-8.46±7.18 (52)	-5.84±6.98 (58)	-8.26±8.15 (162)	-3.30±6.00 (61)	-1.45 [-3.08,0.19]	0.0826

Drug-placebo ES in phase 1: 0.03, drug-placebo ES in phase 2: 0.39 (-2.54)

Table 2. Comparison of Remission Rates between Treatment Groups - PES

	Drug (N=54 Patients)		Placebo (N=167 Patients)			
Measure	Phase I	Phase II	Phase I	Phase II	Weighted Difference (95% CI)	P-value*
Remission Rate (MADRS<11)	7.69% (4/52)	13.79% (8/58)	9.88% (16/162)	6.56% (4/61)	2.53% [-4.38%,9.43%]	0.4736

Table 3. Comparison of Change of CGI-S Score from BSL to the End of Follow-up - PES

	Drug (N=54 Patients)		Placebo (N=167 Patients)			
Measure	Phase I	Phase II	Phase I	Phase II	Weighted Difference (95% CI)	P-value*
Baseline CGI-S Mean±SD (N)	4.50±0.64 (54)	4.07±0.63 (61)	4.53±0.65 (167)	4.14±0.76 (63)	-0.05 [-0.19,0.10]	
Follow-up CGI-S Mean±SD (N)	3.69±0.96 (52)	3.41±1.14 (58)	3.68±1.11 (162)	3.72±0.97 (61)	-0.13 [-0.35,0.10]	
Mean Change of CGI-S from BSL Mean±SD (N)	-0.81±1.03 (52)	-0.64±0.95 (58)	-0.84±1.15 (162)	-0.43±0.78 (61)	-0.11 [-0.33,0.11]	0.3125

Table 4 - Comparison of Change of SQ Score Based on Four Sub-Scaled Wellbeing Scores from BSL to the End of Follow-up - Primary Efficacy Sample

	Drug (N=54 Patients)		Placebo (N=167 Patients)			
Measure	Phase I	Phase II	Phase I	Phase II	Weighted Difference (95% CI)	P-value*
Baseline SQ Score Mean±SD (N)	5.89 ±5.11 (54)	6.62 ±5.53 (61)	5.46 ±4.99 (167)	6.32 ±5.49 (63)	0.16 [-0.89,1.22]	
Follow-up SQ Score Mean±SD (N)	9.50 ±6.22 (52)	10.05 ±6.79 (59)	8.14 ±6.68 (162)	8.49 ±6.77 (61)	1.40 [0.02,2.79]	
Mean Change of SQ Scores from Baseline Mean±SD (N)	3.71 ±5.12 (52)	3.34 ±5.79 (59)	2.75 ±5.88 (162)	1.98 ±4.97 (61)	1.21 [-0.02,2.44]	0.0548

Table 5. Treatment Emergent AEs in Two Treatment Groups - Safety Sample (Frequency >5%)

Measure	Drug (N=115 Patients-phases)	Placebo (N=231 Patients-phases)	Difference
Any AE	50.43% (58/115)	47.62% (110/231)	2.8%
Gastrointestinal disorders	16.52% (19/115)	16.88% (39/231)	-0.4%
Constipation	6.96% (8/115)	1.30% (3/231)	5.7%
Diarrhoea	6.09% (7/115)	5.19% (12/231)	0.9%
Nausea	3.48% (4/115)	5.63% (13/231)	-2.1%
Nervous system disorders	14.78% (17/115)	13.42% (31/231)	1.4%
Akathisia	1.74% (2/115)	1.73% (4/231)	0.0%
Headache	5.22% (6/115)	6.06% (14/231)	-0.8%
Psychiatric disorders	10.43% (12/115)	10.82% (25/231)	-0.4%
Insomnia	6.09% (7/115)	4.33% (10/231)	1.8%

*AEs were summarized according to person-phase of occurrence. Each AE will be attributed to the person and then to phase 1 or phase 2, depending on the initial date of onset. If the severity or other characteristic of the AE changes between phases, it can be counted in both phases.

The SQ psychological distress mean changes for aripiprazole 2 mg/day were -9.4 in phase 1 and -6.8 in phase 2, whereas the SQ psychological distress mean changes for placebo were -9.7 in phase 1 and -4.5 in phase 2 (weighted difference, attributing equal weight: -1.27; p=0.35; NS). The secondary analysis PHQ-9 mean changes for aripiprazole 2 mg/day were -5.8 in phase 1 and -2.9 in phase 2, whereas the PHQ-9 mean changes for placebo were -5.6 in phase 1 and -2.4 in phase 2 (weighted difference attributing equal weight: -0.43; p=0.45; NS). Similarly, the secondary analysis CPFQ mean changes for aripiprazole 2 mg/day were -4.7 in phase 1 and -3.7 in phase 2, whereas the CPFQ mean changes for placebo were -4.7 in phase 1 and -2.4 in phase 2 (weighted difference, attributing equal weight: -0.32; p=0.60; NS).
In the DD vs PP comparison, the MADRS response rate to aripiprazole 2-5 mg/day over 60 days (phase 1 and 2) was 37.3%, while it was 32.9% for placebo (difference: 4.34%; p=0.6). From a safety perspective, of the 225 randomized subjects in phase I, 2 dropped out in the aripiprazole 2 mg/day arm and 2 in the placebo arm. Furthermore, of the 138 phase I placebo non-responders, 14 dropped out in phase II: 9 in the aripiprazole 2 mg/day arm and 5 in the placebo arm.

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