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

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**Key Words**

Antidepressant · Augmentation therapy · Major depressive disorder · Placebo

**Abstract**

***Background:*** We assessed the efficacy of low-dose aripiprazole added to antidepressant therapy (ADT) in major depressive disorder (MDD) patients with inadequate response to prior ADT. ***Methods:*** As per the sequential parallel comparison design, 225 MDD subjects were randomized to adjunctive treatment with aripiprazole 2 mg/day or placebo across two 30-day phases, with a 2:3:3 randomization ratio to drug/drug (aripiprazole 2 mg/day in phase 1; 5 mg/day in phase 2), placebo/placebo (placebo in both phases), and placebo/drug (placebo in phase 1; aripiprazole 2 mg/day in phase 2). Eligible subjects were patients whose MDD was independently deemed 'valid' with SAFER criteria. Subjects had been receiving ADT for ≥8 weeks, and had inadequate response to ≥1 and <4 adequate ADTs in the current episode, as defined by the Antidepressant Treatment Response Questionnaire. ***Results:*** The pooled, weighted response difference between aripiprazole 2 mg/day and placebo in the two phases was 5.6% ($p = 0.18$; NS). The aripiprazole 2 mg/day-placebo difference on the Montgomery-Asberg Depression Rating Scale pooled across the two phases was –1.51 ($p = 0.065$; NS). Other secondary endpoint analyses showed nonsignificant pooled differences favoring aripiprazole over placebo. Of the 225 randomized subjects in phase 1, 2 dropped out in both arms, while in phase 2, of 138 phase 1 placebo nonresponders, 9 dropped out on aripiprazole and 5 on placebo. There were only minimal differences in adverse event rates between treatments, except for constipation, weight gain, and dry mouth, more common on aripiprazole. ***Conclusions:*** This study provides clear support for the tolerability of low-dose aripiprazole as an ADT-augmenting agent, with marginal efficacy.

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In the meantime, M. Levy sadly died.

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## Introduction

Despite numerous treatment options, major depressive disorder (MDD) remains a challenging and debilitating illness. Following antidepressant treatment, up to 50–60% of MDD patients do not achieve adequate response [1] and two thirds of patients do not experience a timely remission [2]. The use of atypical antipsychotics as adjunctive agents in clinical practice to enhance the efficacy of antidepressant therapy (ADT) is supported by a recent meta-analysis [3], although the odds ratios decreased from 2.43 (for trials of 4-week duration) to 1.50 (for trials of 8-week duration), suggesting the possibility of a weakening of signal detection in longer trials of these compounds. Most of the augmentation studies in this meta-analysis were carried out as two-arm trials comparing the atypical antipsychotic drug to placebo when either treatment is added to the ongoing ADT. The limitation of this methodological approach is that, in the absence of a 2 × 2 factorial design, one cannot rule out the possibility that these compounds may have intrinsic antidepressant effects. Aripiprazole (within a dose range of 2–15 mg/day) was the first drug approved by the FDA for adjunctive treatment of MDD among patients who have not responded adequately to ADT, based on three double-blind studies, which involved 1,085 patients [4–6] and showed significantly higher response rates, defined as a 50% or greater reduction in the Montgomery-Asberg Depression Rating Scale (MADRS) [7] score, with aripiprazole ADT augmentation (34, 32 and 47%, respectively) compared to placebo ADT augmentation (24, 17, and 19%, respectively) [4–6]. 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 [4, 5]. When the safety data from these three trials are pooled [4–6], four central nervous system side effects have been consistently reported to be more common with aripiprazole than with placebo in the three trials: akathisia (22 vs. 4%), restlessness (12 vs. 2%), insomnia (8 vs. 3%) and fatigue (8 vs. 4%). These studies, however, did not investigate the lower dose ranges (2–5 mg/day) commonly used in practice for MDD patients. 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 using the sequential parallel comparison design (SPCD) [8], a design that is aimed at maximizing the likelihood of disclosing differences between treatments. This is the first completed study that utilizes the SPCD, a design that examines treatment differences twice within the same study, with the second assessment occurring only in prospectively defined placebo nonresponders [8].

## Methods

This was a 60-day, multicenter, double-blind, placebo-controlled study on the efficacy and tolerability of low-dose aripiprazole (2 mg/day) ADT augmentation in MDD patients with inadequate ADT response. The primary outcome was the difference in response rate (decrease in MADRS total score of at least 50%) using the SPCD [8]. Key secondary endpoints were differences in remission rates (MADRS score <11) and in absolute changes from baseline in MADRS scores, the Massachusetts General Hospital (MGH) Cognitive and Physical Functioning Questionnaire (CPFQ) [9], the Clinical Global Impression of Improvement (CGI-I) and Severity (CGI-S) [10], the Symptom Questionnaire (SQ) [11] and the 9-item Patient Health Questionnaire (PHQ-9) [12].

In accordance with the SPCD (fig. 1), the 60-day double-blind treatment was divided into two 30-day phases, with assessments performed every 10 days. Following the 14- to 28-day screening period, eligible patients were randomized to 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 stable dose of ADT for 30 days; at visit 3, day 30, the aripiprazole dose was increased to 5 mg/day adjunctive to continued ADT up to visit 6, day 60), placebo/placebo (PP, double-blind adjunctive placebo plus stable dose of ADT up to visit 6, day 60) and placebo/drug (double-blind adjunctive placebo plus the stable dose of ADT for 30 days; at visit 3 on day 30, patients were given 2 mg/day aripiprazole adjunctive to their ADT up to visit 6, day 60). All patients must have failed to respond to one, two, or three ADT trials (not relapsed) and must have continued on their stable ADT doses documented during the screening phase. No dose adjustments were allowed during the randomization phase. Patients unable to tolerate the lowest dose of any of the assigned therapies were discontinued.

Inclusion criteria were: (a) men and women, aged 18–65 years, able to give informed consent; (b) patients with a Structured Clinical Interview for DSM Disorders major depressive episode (MDE) diagnosis deemed 'valid' using the SAFER criteria interview [13] administered by remote, independent raters; (c) a score of >15 on the Quick Inventory of Depressive Symptomatology-Self-Rated [14, 15] at both screen and baseline visits; (d) patients treated with an adequate dose of selective serotonin reuptake inhibitors (SSRIs)/serotonin and norepinephrine reuptake inhibitors (SNRIs) during the current episode for at least 8 weeks, with the same, adequate dose over the last 4 weeks and throughout the study; (e) patients with a history during the current MDE of inadequate response (but not relapse) to one, two or three adequate antidepressant trials, including the current trial; an inadequate response was defined as less than a 50% reduction in depressive symptom severity both currently and at any point during the current episode, as assessed by the MGH Antidepressant Treatment Response Questionnaire (ATRQ) [1, 16] administered by remote, independent raters; (f) patients with a 17-item Hamilton Depression Rating Scale [17] score ≥18 at the end of the screening phase

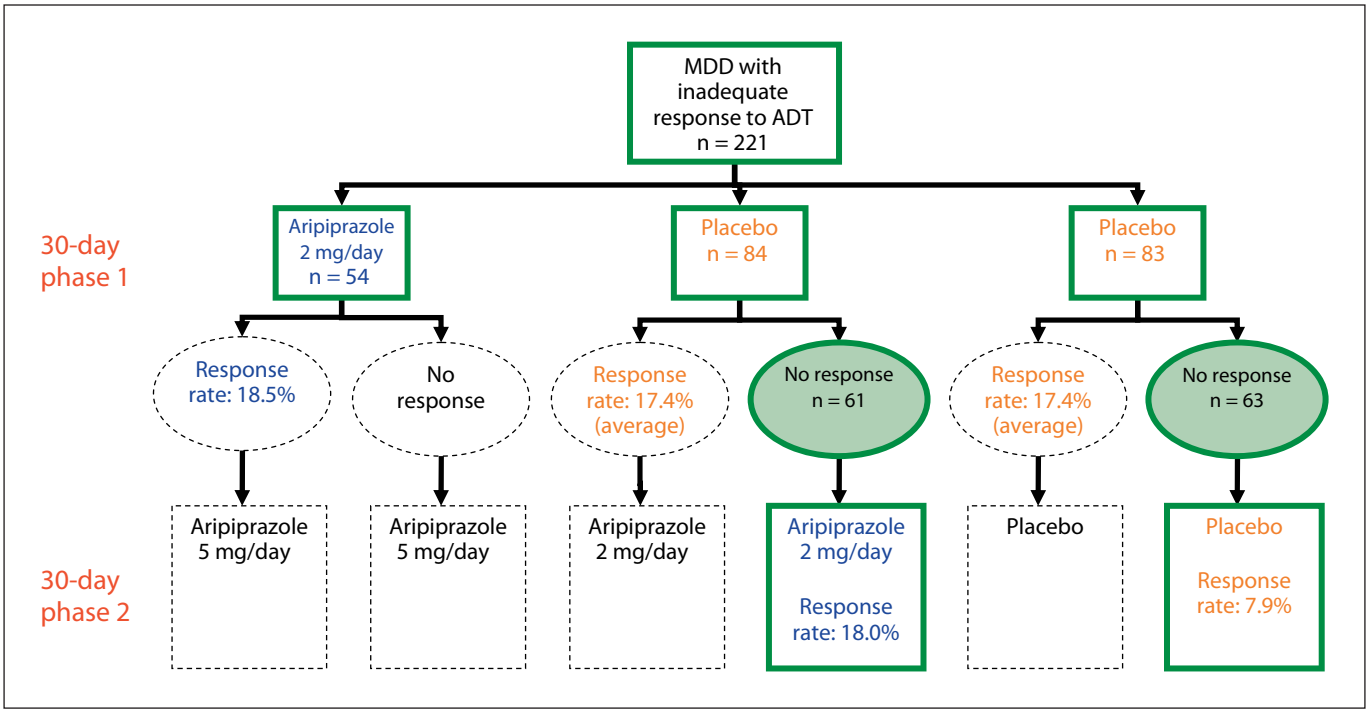


**Fig. 1.** Primary outcome: response rates in the SPCD samples (pooled, weighted drug-placebo difference: 5.6%; p = 0.18; NS).

qualified for inclusion, administered by the study clinicians at screening and baseline visits, and by remote, independent raters during the screening phase.

Among patients prerandomized to receive placebo in both phases or to receive placebo in phase 1 and aripiprazole in phase 2, only those meeting nonresponse criteria at the end of phase 1 were added to the primary efficacy sample for phase 2: (a) placebo nonresponders were defined as those patients who failed to achieve a 50% decrease in their MADRS score at visit 3; (b) they had an MADRS score of >16 at visit 3.

Exclusion criteria were: (a) patients with a >25% decrease in depressive symptoms from screen to baseline visit; (b) women pregnant or breastfeeding; (c) patients who reported an inadequate response during the current MDE to 4 or more (including the current trial) adequate ADT trials; (d) patients who reported treatment with adjunctive antipsychotic medication with an antidepressant for >2 weeks during the current MDE or lifetime with aripiprazole; (e) patients who had been hospitalized for MDE within 4 weeks of the screening visit; (f) patients who had received electroconvulsive therapy, vagal nerve stimulation or transcranial magnetic stimulation during the current episode; (g) patients who had a current diagnosis of dementia, psychosis, or bipolar disorder; (h) patients with clinically significant diagnoses of personality disorders (e.g. patients with severely pathological behavior) or with any significant substance use disorder within the past 6 months, based on the Structured Clinical Interview for DSM Disorders or a positive urine drug screen; (i) patients receiving new-onset psychotherapy within 6 weeks of screening, or at any time during the trial; (j) patients actively suicidal or with unstable medical illness; (k) patients with thyroid pathology (unless stabilized for >3 months); (l) patients with a lifetime history of a seizure disorder or of neuroleptic malignant syndrome/serotonin syndrome; (m) patients who would likely require prohibited concomitant medication during the trial (including all psychotropic agents and lithium), except for stable (for at least 2 weeks) lorazepam up to 2.0 mg/day and zolpidem up to 10 mg q.h.s. (or their equivalents).

*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 [18].

The 10-item MADRS, which measures depression severity over the past week, was completed by clinicians by using an MGH-structured interview. The CGI-S and CGI-I scales were administered by clinicians to measure depressive severity (CGI-S) and clinical improvement (CGI-I). Patient-rated versions of both scales were also utilized. The MGH-CPFQ, a brief (7-item) self-report inventory to assess rates of significant cognitive symptoms, sleepiness, and fatigue, was filled out by patients. Patients also filled out the SQ, a 92-item (yes/no), self-rating questionnaire that includes 4 distress subscales (anxiety, depression, somatic symptoms, and anger/hostility) and 4 well-being subscales, the Sexual Functioning Inventory, a self-rating questionnaire that assesses sexual functioning, and the PHQ-9, a self-administered depression measure.

Vital signs 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 and days 30, 60, 90, 120, and 150 (or endpoint). Adverse events and concomitant medications were collected at every visit.

*Statistical Analyses*

The analysis populations were defined as follows: (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, with a focus on the comparison between the aripiprazole 2 mg/day and placebo groups, and (3) the primary efficacy sample included those patients in the safety sample who had at least one efficacy evaluation after randomization. This included all phase 1 data as well as phase 2 data collected on phase 1 nonresponders in the placebo/drug or PP arms (defined as patients who had less than a 50% decrease in their MADRS total score and an MADRS score >16 at the end of phase 1 treatment visit, and who had at least one phase 2 efficacy evaluation). Statistical significance was declared only when the p value was found to be less than or equal to 0.05. Computations for all results were performed using SAS version 8.2. The last observation carried forward (LOCF) technique was employed to handle missing data for primary analysis, and observed case (OC) analysis, which included only subjects with nonmissing observations, was also conducted.

The primary analysis compared pooled MADRS response rates (defined as a 50% or greater reduction in MADRS scores; attributing equal weight to both phases in pooling the results) between placebo and aripiprazole in phase 1 and placebo nonresponders (from phase 1, defined as those patients with less than a 50% decrease in MADRS total score from baseline and a MADRS score >16) assigned to either aripiprazole 2 mg/day or placebo in phase 2. Differences in response rates were compared using binomial repeated-measures regression, accounting for correlation between subject data in phases 1 and 2. The model was analyzed using SAS Proc Genmod (with identity link, binomial repeated measures) and included study phase, treatment and their interaction and control for categorical study center variable. If study center was not significant, it was removed from the model and analyses were conducted using the statistic proposed by Fava et al. [8]. If study center was significant, it was retained in the binomial regression model and appropriate contrast corresponding to the weighted average of phase 1 and phase 2 effects was tested as the main analysis.

A generalized estimating equations model (SAS Proc Genmod) was implemented to analyze the change of MADRS scores with phase-specific baseline MADRS scores, treatment and phase indicator and their interaction as covariates on the primary efficacy sample. Treatment effect was based on appropriate contrasts, with equal weights given to each phase and adjustment for study center only if it was retained in the final model of the primary analysis.

Remission rates (MADRS score <11) in the primary analysis group (aripiprazole 2 mg vs. placebo) were compared using binomial repeated-measures regression, with the method as per the primary analysis.

A generalized estimating equations model (SAS Proc Genmod) was implemented to analyze the OC changes of the SQ, PHQ-9, CPFQ and CGI-S scores with baseline scores, treatment, and phase 1 baseline symptom severity as covariates, using an approach analogous to that applied for the change of MADRS scores.

One-way ANCOVA was used to analyze the change of MADRS scores at study endpoint from baseline between the DD group (aripiprazole 2–5 mg/day for up to 8 weeks) and the PP group (placebo for up to 8 weeks), adjusting for baseline score.

Differences in the incidence of treatment-emergent adverse events (AEs) between the treatment groups were examined and evaluated using descriptive statistics. Three different presentations of the AE data were implemented. First, AEs were summarized according to person-phase of occurrence. Each AE was attributed to the person and then to phase 1 or phase 2, depending on the initial date of onset. If the severity or other characteristics of the AE changed between phases, it could have been counted in both phases. The second AE listing focused on placebo nonresponders in phase 1 and presented them by their treatment assignment in phase 2. Third, we compared AEs between the arms that received exclusively drug or placebo throughout the study.

## Results

Two hundred and twenty-five subjects were randomized across 21 sites in the US.

*Baseline and Treatment Characteristics*

The baseline characteristics of this population are summarized in table 1 (mean age: 45 ± 11 years; 68% women). Table 2 summarizes the distribution of the concomitant SSRI or SNRI treatments. Of those initially assigned to drug (n = 56), 48 (85.7%) completed the study, with no subjects dropping out for clinically significant AEs and 5 (8.9%) lost to follow-up. Of those assigned to placebo (n = 169), 152 (89.9%) completed the study, with no subjects dropping out for clinically significant AEs and 5 (3.0%) lost to follow-up.

*Efficacy Data*

Of these 225 subjects, 221 subjects satisfied the definition of primary efficacy sample. As summarized in table 3, the LOCF primary analysis MADRS response rates for aripiprazole 2 mg/day were 18.5% in phase 1 and 18.0% in phase 2, whereas the placebo response rates were 17.4% in phase 1 and 7.9% in phase 2 (pooled, weighted drug-placebo difference: 5.6%; p = 0.18; NS); the OC-weighted difference in MADRS response rates was 4.2% (p = 0.32; NS) and the LOCF-weighted difference in MADRS remission rates was 2.3% (p = 0.50; NS).

With respect to the secondary analyses, as shown in table 4, the LOCF 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 for placebo were –8.1 in

**Table 1.** Baseline patient demographics, vital signs and substance usage – randomized population

| Measure | Drug (n = 56 patients) | Placebo (n = 169 patients) |
|---|---|---|
| *Demographics* | | |
| Age, years | | |
| Mean ± SD (n) | 45.36 ± 10.35 (56) | 45.06 ± 11.34 (169) |
| Range | 22.00 – 63.00 | 18.00 – 65.00 |
| Median | 47.00 | 46.00 |
| Male | 33.93% (19/56) | 36.09% (61/169) |
| Ethnicity | | |
| Hispanic or Latino | 8.93% (5/56) | 11.24% (19/169) |
| Not Hispanic or Latino | 82.14% (46/56) | 81.66% (138/169) |
| Unknown | 8.93% (5/56) | 7.10% (12/169) |
| Race | | |
| White (includes Hispanic or Latino) | 83.93% (47/56) | 79.88% (135/169) |
| African American/Black | 16.07% (9/56) | 18.93% (32/169) |
| Asian/Asian American | 1.79% (1/56) | 1.18% (2/169) |
| Native American/ American Indian | 0.00% (0/56) | 0.00% (0/169) |
| Native Hawaiian/ Pacific Islander | 0.00% (0/56) | 0.00% (0/169) |
| Other | 0.00% (0/56) | 0.59% (1/169) |
| Marital status | | |
| Single/never married | 35.71% (20/56) | 36.69% (62/169) |
| Divorced or separated | 26.79% (15/56) | 28.99% (49/169) |
| Married or living as married | 35.71% (20/56) | 31.95% (54/169) |
| Widowed | 1.79% (1/56) | 2.37% (4/169) |
| Number of children | | |
| Mean ± SD (n) | 1.57 ± 1.33 (56) | 1.40 ± 1.36 (169) |
| Range | 0.00 – 5.00 | 0.00 – 6.00 |
| Median | 2.00 | 1.00 |
| Educational background (highest level achieved) | | |
| Less than high school | 7.14% (4/56) | 8.28% (14/169) |
| High school diploma or GED | 25.00% (14/56) | 19.53% (33/169) |
| Some college (at least 1 year) | 16.07% (9/56) | 20.71% (35/169) |
| Technical school or associates degree | 14.29% (8/56) | 10.06% (17/169) |
| College diploma (Bachelor's degree) | 19.64% (11/56) | 32.54% (55/169) |
| Graduate or professional degree | 17.86% (10/56) | 8.88% (15/169) |
| Employment status | | |
| Employed | 51.79% (29/56) | 57.40% (97/169) |
| Unemployed | 35.71% (20/56) | 31.36% (53/169) |
| Disability recipient | 7.14% (4/56) | 4.73% (8/169) |
| Student | 0.00% (0/56) | 5.33% (9/169) |
| Retired | 0.00% (0/56) | 0.59% (1/169) |
| Other | 5.36% (3/56) | 0.59% (1/169) |
| Household income, USD | | |
| 24,999 or less | 32.14% (18/56) | 25.15% (42/167) |
| 25,000–49,999 | 25.00% (14/56) | 23.35% (39/167) |
| 50,000–74,999 | 5.36% (3/56) | 14.97% (25/167) |
| 75,000 or greater | 10.71% (6/56) | 8.38% (14/167) |
| Refuse to answer | 26.79% (15/56) | 28.14% (47/167) |
| Weight, lbs | | |
| Mean ± SD (n) | 190.83 ± 54.54 (56) | 196.43 ± 49.97 (167) |
| Range | 114.60 – 350.00 | 108.00 – 380.00 |
| Median | 182.10 | 192.00 |
| *Standing blood pressure, mm Hg* | | |
| Systolic | | |
| Mean ± SD (n) | 120.34 ± 11.82 (56) | 121.64 ± 13.40 (167) |
| Range | 92.00 – 145.00 | 92.00 – 164.00 |
| Median | 120.00 | 121.00 |
| Diastolic | | |
| Mean ± SD (n) | 79.09 ± 7.39 (56) | 78.98 ± 8.83 (167) |
| Range | 60.00 – 94.00 | 56.00 – 105.00 |
| Median | 80.00 | 78.00 |
| *Supine blood pressure, mm Hg* | | |
| Systolic | | |
| Mean ± SD (n) | 120.29 ± 11.25 (56) | 121.24 ± 13.39 (167) |
| Range | 100.00 – 147.00 | 90.00 – 160.00 |
| Median | 120.00 | 120.00 |
| Diastolic | | |
| Mean ± SD (n) | 77.84 ± 8.38 (56) | 77.71 ± 8.48 (167) |
| Range | 59.00 – 96.00 | 52.00 – 105.00 |
| Median | 79.00 | 78.00 |
| *Pulse, beats per minute* | | |
| Mean ± SD (n) | 74.29 ± 8.58 (56) | 73.28 ± 10.47 (167) |
| Range | 60.00 – 93.00 | 56.00 – 120.00 |
| Median | 72.00 | 72.00 |
| *Substance use* | | |
| Tobacco use | | |
| Never | 57.14% (32/56) | 57.40% (97/169) |
| Current | 25.00% (14/56) | 26.04% (44/169) |
| Former | 17.86% (10/56) | 16.57% (28/169) |
| Alcohol use | | |
| Never | 23.21% (13/56) | 27.22% (46/169) |
| Current | 51.79% (29/56) | 50.30% (85/169) |
| Former | 25.00% (14/56) | 22.49% (38/169) |
| Caffeine use | | |
| Never | 3.57% (2/56) | 8.88% (15/169) |
| Current | 96.43% (54/56) | 86.98% (147/169) |
| Former | 0.00% (0/56) | 4.14% (7/169) |
| Medications | | |
| Lorazepam | 5.36% (3/56) | 5.33% (9/169) |
| Zolpidem | 3.57% (2/56) | 4.14% (7/169) |

GED = General equivalency degree.

phase 1 and –3.3 in phase 2 (weighted difference, attributing equal weight: –1.51; p = 0.065; NS). The drug-placebo difference in phase 1 was –0.45 (effect size: 0.06), whereas the drug-placebo difference in phase 2 was –2.48 (effect size: 0.38). We also observed a significant difference in the LOCF change in MADRS scores in phase 2 adjusting for baseline score (p = 0.04). As summarized in table 4, the CGI-S OC mean changes for aripiprazole 2 mg/day were –0.8 in phase 1 and –0.6 in phase 2, whereas the CGI-S mean changes were –0.8 in phase 1 and –0.4 in phase 2 (weighted difference, attributing equal weight: –0.11; p = 0.31; NS).

**Table 2.** Summary of concomitant antidepressant treatments – randomized sample

| Antidepressant | Drug (n = 56 patients) | Placebo (n = 169 patients) |
|---|---|---|
| Escitalopram | 17.86% (10/56) | 12.43% (21/169) |
| Sertraline | 14.29% (8/56) | 10.65% (18/169) |
| Venlafaxine XR | 1.79% (1/56) | 7.10% (12/169) |
| Fluoxetine | 17.86% (10/56) | 20.12% (34/169) |
| Paroxetine CR | 0.00% (0/56) | 0.59% (1/169) |
| Paroxetine tablets | 7.14% (4/56) | 5.33% (9/169) |
| Citalopram | 7.14% (4/56) | 17.16% (29/169) |
| Desvenlafaxine | 3.57% (2/56) | 6.51% (11/169) |
| Duloxetine | 19.64% (11/56) | 14.20% (24/169) |
| Other[1] | 10.71% (6/56) | 5.92% (10/169) |

[1] Nonstandard doses of SSRIs (n = 3 for fluoxetine; n = 4 for sertraline; n = 2 for escitalopram; n = 1 for citalopram) and SNRIs (n = 4 for venlafaxine; n = 2 for duloxetine).

The SQ psychological distress OC 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 = 0.36; NS). The SQ well-being OC 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).

The secondary analysis PHQ-9 OC 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 OC 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 versus PP comparison, the MADRS response rate to aripiprazole 2–5 mg/day over 60 days (phases 1 and 2) was 37.3%, while it was 32.9% for placebo (difference: 4.34%; p = 0.6).

*Tolerability and Safety*

Of the 225 randomized subjects in phase 1, 2 dropped out in the aripiprazole 2 mg/day arm and 2 in the placebo arm. Furthermore, of the 138 phase 1 placebo nonresponders, 14 dropped out in phase 2: 9 in the aripiprazole 2 mg/day arm and 5 in the placebo arm. Table 5 reports AEs occurring at frequencies greater than 5% in either treatment arm, showing minimal differences in rates of

**Table 3.** Primary analyses: comparison of weighted MADRS response and remission rates between treatment groups – primary efficacy sample

| Measure | Drug (n = 54 patients) | | Placebo (n = 167 patients) | | Weighted difference (95% CI) | p value |
|---|---|---|---|---|---|---|
| | phase 1 | phase 2 | phase 1 | phase 2 | | |
| *LOCF analysis* MADRS response rate (50% or greater score reduction) | 18.52% (10/54) | 18.03% (11/61) | 17.37% (29/167) | 7.94% (5/63) | 5.62% (–2.69 to 13.94) | 0.1848 |
| *OC analysis* MADRS response rate (50% or greater score reduction) | 17.31% (9/52) | 17.24% (10/58) | 17.90% (29/162) | 8.20% (5/61) | 4.23% (–4.15 to 12.60) | 0.3229 |
| *LOCF analysis* MADRS remission rate (MADRS score <11) | 7.41% (4/54) | 13.11% (8/61) | 9.58% (16/167) | 6.35% (4/63) | 2.30% (–4.35 to 8.94) | 0.4984 |

AEs between aripiprazole and placebo, with the exception of constipation and dry mouth, which were more common on aripiprazole. No significant differences in rates of AEs such as restlessness, akathisia, fatigue, and insomnia were noted. The comparable rates of concomitant p.r.n. use of hypnotics during the study, reported at the bottom of table 1 (less than 6% for either lorazepam or zolpidem in both treatment arms), is consistent with the lack of significant differences in rates of spontaneously reported insomnia. While the changes in blood pressure and pulse were similar between the aripiprazole (n = 52; standing systolic blood pressure change: –0.67; SD: 11.46; standing diastolic blood pressure change: –0.40; SD: 7.54; pulse change: 1.88; SD: 9.20) and the placebo (n = 157; standing systolic blood pressure change: –0.62; SD: 11.22; standing diastolic blood pressure change: –0.33; SD: 7.52; pulse change: 1.14; SD: 8.41) groups, the mean increase of weight on aripiprazole 2 mg/day was 1.5 lbs (SD: 4.62), while it was 0.01 lbs (SD: 3.97) on placebo at the end of phase 1.

## Discussion

This multicenter placebo-controlled study, which is the first to utilize the SPCD [8], shows minimal benefits of low-dose aripiprazole (2 mg/day) when added to ADT in phase 1 and more robust benefits in phase 2. When the data are pooled from both phases, as per the SPCD analytical plan, there is a 5.6% difference in response rates (statistically nonsignificant) and a 1.51 MADRS unit difference in favor of aripiprazole (p = 0.0649). We observed a significant difference in the LOCF change in MADRS scores in phase 2 adjusting for baseline score (p = 0.04), and the drug-placebo difference in phase 1 was –0.45 (effect size: 0.06), whereas the drug-placebo difference in phase 2 was –2.48 (effect size: 0.38). The MADRS effect size detected in phase 2 of this SPCD study (0.38) is therefore similar to the reported effect sizes of 0.39 and 0.35 in the first two positive studies of aripiprazole at the higher doses in MDD [4, 5]. Yet, the MADRS effect size in phase 1 is 0.06, suggesting minimal if no effects. The interpretation of these results is therefore complex, in that, although the study did not show statistically significant differences in any of the efficacy outcome measures between low-dose aripiprazole and placebo, the medium effect size detected in phase 2 of the SPCD would be consistent with the effect of an active treatment, and the drug-placebo difference in MADRS change scores is statistically significant in phase 2. Since the placebo response rate reported in phase 1 (17.4%) is consistent with the placebo response rates reported in the three positive trials of aripiprazole in MDD (24, 17, and 19%, respectively) [4–6], the fact that the other trials showed robust effects for ari-

**Table 4.** Comparison of change of scores from baseline to the end of follow-up between treatment groups – primary efficacy sample

| Measure | Drug[1] (n = 54 patients) | | Placebo[1] (n = 167 patients) | | Weighted difference (95% CI) | p value |
|---|---|---|---|---|---|---|
| | phase 1 | phase 2 | phase 1 | phase 2 | | |
| *LOCF analysis* | | | | | | |
| Baseline MADRS score | 30.69 ± 4.02 (54) | 26.80 ± 5.85 (61) | 31.20 ± 4.75 (167) | 26.29 ± 5.48 (63) | 0.31 (–0.72 to 1.34) | |
| Follow-up MADRS score | 22.15 ± 7.68 (54) | 21.00 ± 8.83 (58) | 23.11 ± 9.08 (167) | 22.97 ± 7.79 (63) | –1.59 (–3.31 to 0.13) | |
| Mean change of MADRS scores from baseline | –8.54 ± 7.21 (54) | –5.80 ± 7.08 (61) | –8.09 ± 8.13 (167) | –3.32 ± 5.97 (63) | –1.51 (–3.11 to 0.09) | 0.0649 |
| *OC analysis* | | | | | | |
| Baseline CGI-S score | 4.50 ± 0.64 (54) | 4.07 ± 0.63 (61) | 4.53 ± 0.65 (167) | 4.14 ± 0.76 (63) | –0.05 (–0.19 to 0.10) | |
| Follow-up CGI-S score | 3.69 ± 0.96 (52) | 3.41 ± 1.14 (58) | 3.68 ± 1.11 (162) | 3.72 ± 0.97 (61) | –0.13 (–0.35 to 0.10) | |
| Mean change of CGI-S scores from baseline | –0.81 ± 1.03 (52) | –0.64 ± 0.95 (58) | –0.84 ± 1.15 (162) | –0.43 ± 0.78 (61) | –0.11 (–0.33 to 0.11) | 0.3125 |
| *OC analysis* | | | | | | |
| Four subscaled distress scores | | | | | | |
| Baseline SQ score | 34.89 ± 13.87 (54) | 31.77 ± 13.46 (61) | 38.43 ± 11.95 (167) | 31.17 ± 12.42 (63) | –1.04 (–3.71 to 1.63) | |
| Follow-up SQ score | 25.31 ± 14.20 (52) | 25.22 ± 15.26 (59) | 28.49 ± 14.73 (162) | 26.48 ± 14.82 (61) | –2.53 (–5.64 to 0.58) | |
| Mean change of SQ scores from baseline | –9.44 ± 11.19 (52) | –6.78 ± 13.78 (59) | –9.70 ± 12.51 (162) | –4.52 ± 9.52 (61) | –1.27 (–3.96 to 1.43) | 0.3574 |
| Four subscaled well-being scores | | | | | | |
| Baseline SQ score | 5.89 ± 5.11 (54) | 6.62 ± 5.53 (61) | 5.46 ± 4.99 (167) | 6.32 ± 5.49 (63) | 0.16 (–0.89 to 1.22) | |
| Follow-up SQ score | 9.50 ± 6.22 (52) | 10.05 ± 6.79 (59) | 8.14 ± 6.68 (162) | 8.49 ± 6.77 (61) | 1.40 (0.02 to 2.79) | |
| Mean change of SQ scores from baseline | 3.71 ± 5.12 (52) | 3.34 ± 5.79 (59) | 2.75 ± 5.88 (162) | 1.98 ± 4.97 (61) | 1.21 (–0.02 to 2.44) | 0.0548 |

[1] Figures are means ± SD with number in parentheses.

**Table 5.** Treatment-emergent AEs (frequency >5%)

| Measure | Safety sample (frequency >5%) | | | Phase 2 on drug (aripiprazole 2 mg/day) or placebo among phase 1 placebo nonresponders | | | Patients exclusively on drug (aripiprazole 2–5 mg/day) or placebo in phases 1 and 2 | | |
|---|---|---|---|---|---|---|---|---|---|
| | drug (n = 115 patients-phases) | placebo (n = 231 patients-phases) | difference | drug (n = 61 patients) | placebo (n = 63 patients) | difference | drug (n = 54 patients) | placebo (n = 83 patients) | difference |
| Any AE | 50.43% (58/115) | 47.62% (110/231) | 2.8% | 65.6% (40/61) | 69.8% (44/63) | –4.3% | 72.2% (39/54) | 72.3% (60/83) | –0.1% |
| Gastrointestinal disorders | 16.52% (19/115) | 16.88% (39/231) | –0.4% | 24.6% (15/61) | 27.0% (17/63) | –2.4% | 29.6% (16/54) | 30.1% (25/83) | –0.5% |
| Constipation | 6.96% (8/115) | 1.30% (3/231) | 5.7% | 13.1% (8/61) | 11.1% (7/63) | 2.0% | 11.1% (6/54) | 2.4% (2/83) | 10.6% |
| Diarrhea | 6.09% (7/115) | 5.19% (12/231) | 0.9% | – | – | – | 13.0% (7/54) | 8.4% (7/83) | 2.7% |
| Dry mouth | – | – | – | – | – | – | 7.4% (4/54) | 3.6% (3/83) | 3.8% |
| Nausea | 3.48% (4/115) | 5.63% (13/231) | –2.1% | 6.6% (4/61) | 9.5% (6/63) | –3.0% | 9.3% (5/54) | 10.8% (9/83) | –1.6% |
| General disorders and administration site conditions | – | – | – | 8.2% (5/61) | 12.7% (8/63) | –4.5% | 16.7% (9/54) | 13.3% (11/83) | 3.4% |
| Fatigue | – | – | – | 6.6% (4/61) | 6.3% (4/63) | 0.2% | 5.6% (3/54) | 1.2% (1/83) | 4.4% |
| Peripheral edema | – | – | – | – | – | – | 25.9% (14/54) | 13.3% (11/83) | 12.7% |
| Infections and infestations | – | – | – | – | – | – | 5.6% (3/54) | 1.2% (1/83) | 4.4% |
| Nasopharyngitis | – | – | – | – | – | – | 13.0% (7/54) | 1.2% (1/83) | 11.8% |
| Upper respiratory tract infection | – | – | – | – | – | – | 7.4% (4/54) | 8.4% (7/83) | –1.0% |
| Investigations | – | – | – | 9.8% (6/61) | 7.9% (5/63) | 1.9% | 5.6% (3/54) | 7.2% (6/83) | –1.7% |
| Weight increased | – | – | – | 6.6% (4/61) | 6.3% (4/63) | 0.2% | 24.1% (13/54) | 27.7% (23/83) | –3.6% |
| Nervous system disorders | | | | | | | | | |
| Akathisia | 14.78% (17/115) | 13.42% (31/231) | 1.4% | 23.0% (14/61) | 23.8% (15/63) | –0.9% | – | – | – |
| Headache | 1.74% (2/115) | 1.73% (4/231) | 0.0% | – | – | – | 7.4% (4/54) | 10.8% (9/83) | –3.4% |
| Somnolence | 5.22% (6/115) | 6.06% (14/231) | –0.8% | 11.5% (7/61) | 9.5% (6/63) | 2.0% | 7.4% (4/54) | 3.6% (3/83) | 3.8% |
| Psychiatric disorders | 10.43% (12/115) | 10.82% (25/231) | –0.4% | 16.4% (10/61) | 19.0% (12/63) | –2.7% | 20.4% (11/54) | 21.7% (18/83) | –1.3% |
| Insomnia | 6.09% (7/115) | 4.33% (10/231) | 1.8% | 8.2% (5/61) | 7.9% (5/63) | 0.3% | 9.3% (5/54) | 8.4% (7/83) | 0.8% |

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 characteristics of the AE change between phases, it can be counted in both phases.

piprazole 2–15 mg/day in contrast to the results of the present study in phase 1 suggests that the efficacy of low-dose aripiprazole 2 mg/day is minimal. Even when the dose is raised to 5 mg/day in the second phase of the study (as in the DD group), the difference from placebo (PP group) at 8 weeks, using a standard parallel comparison, is only 4.3% (vs. 1.1% at the end of the first phase), suggesting a relative lack of effectiveness of low-dose aripiprazole and only minimal benefits from raising the dose from 2 to 5 mg/day. The separation of aripiprazole 2–5 mg/day from placebo therefore remains rather small and relatively flat for a population of SSRI and SNRI nonresponders that includes a nontrivial degree of placebo responders. The failure to achieve statistical significance in the pooled analyses of both phases in a study using the SPCD [8], a design aimed at maximizing the likelihood of disclosing differences between treatments, is certainly consistent with a reduced efficacy of low-dose aripiprazole compared to the doses used in the three positive previously completed trials. Aripiprazole is a partial agonist at dopamine $D_2$, $D_3$, and serotonin 5-HT1A receptors and an antagonist at 5-HT2A receptors [5], and it is possible that the augmentation effects in MDD may require higher doses, similar to the 5–20 mg/day range of the three positive previously completed trials, so that its neurobiological effects are primarily of antagonism rather than partial agonism. On the other hand, the tolerability data suggest a relative absence of significant difference in rates of AEs such as restlessness, akathisia, insomnia, and fatigue, in contrast to the safety data pooled from the three trials with aripiprazole 2–15 mg/day [4–6], with significant differences from placebo in AE rates for akathisia (22 vs. 4%), restlessness (12 vs. 2%), insomnia (8 vs. 3%) and fatigue (8 vs. 4%). The very low dropout rate with aripiprazole augmentation of this study seems to confirm the impression of enhanced tolerability of the ADT augmentation with low-dose aripiprazole.

The study does provide strong support to the concept that the SPCD may enhance the chances of detecting a signal in placebo-controlled trials. The placebo response rate was reduced by more than 50% from phase 1 (17.4%) to phase 2 (7.9%), and this is consistent with the examination via simulation of the efficiency of the SPCD in psychiatric clinical trials by Tamura and Huang [19]. In addition, the drug-placebo effect size detected in phase 2 is markedly greater than the minimal effect size evidenced in phase 1, again supporting the utility of the design. One could argue that despite the mixed results of the present study, an initial therapeutic approach targeting patients with inadequate response to ADT may involve trying first a low-dose (2 mg/day) augmentation of aripiprazole, given how well tolerated this strategy was in our study. However, in the face of continued nonresponse, a dose increase of aripiprazole to 5 mg/day and, if necessary, to 10 or 15 mg/day is certainly supported by the robust evidence of three consecutive positive studies [4–6]. On the other hand, one could view our results as unsupportive of the efficacy of 2 mg/day of aripiprazole and therefore draw the conclusion that targeting a dose range of up to 15 mg/day from the outset would be preferable.

The main limitation of this study is related to the fact that these are all patients with historical failures to ADT, whereas the three previous positive studies of aripiprazole augmentation in patients with inadequate response to ADT all had at least one prospective failure. On the other hand, the degree of placebo response rate in phase 1 of this study was consistent with the placebo response observed following prospective antidepressant failures [4–6], and the remote SAFER interview, together with the ATRQ assessment, provided independent verification of the resistance to ADT among patients in this study. In addition, the remote administration of the ATRQ by independent raters ensured that no patients with a history of relapse (e.g. with a greater than 50% reduction of symptoms at some point during the ADT) entered the study, contrary to the methodology used in some of the other atypical antipsychotic augmentation studies [3]. Furthermore, as both Kellner [11] and Bech [20] have noted, responsiveness to change during treatment is probably the most important issue in clinical trials of antidepressants, and the instruments used in this study have shown the ability to be responsive to change, and therefore a lack of effect cannot be attributed to poor or insensitive measurements. Finally, we cannot rule out the possibility that the benefit of aripiprazole 2 mg/day noted in phase 2 may have diminished, had both SPCD phases been longer than 4 weeks. As shown in the recent meta-analysis [3], the odds ratios decreased from 2.43 (for trials of 4-week duration) to 1.50 (for trials of 8-week duration), suggesting the possibility of a weakening of signal detection in longer trials of these compounds or of phenomena of tolerance [21] or supersensitivity [22]. On the other hand, for those patients who stayed on drug or placebo in both phases, there was a marginal increase in drug-placebo separation. A recent study that extended the aripiprazole antidepressant augmentation treatment for about 28 weeks showed no relapses in a small cohort of depressed patients [23]. It is also possible, given the evidence of dif-

ferential responsiveness to antidepressant therapies of specific subtypes of MDD [24, 25], that our findings may not be generalizable to all depressive subtypes, as the population enrolled in the study had an average MADRS score above 30, thereby consistent with more melancholic/endogenous forms of depression.

In conclusion, this study provides clear support for the tolerability of low-dose aripiprazole (2 mg/day) as an augmenting agent for patients with inadequate response to ADT. In terms of efficacy, it appears that the efficacy of this strategy may be marginal, with the nonsignificant, pooled weighted difference from placebo in response rates of 5.6%.


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