THE JOURNAL OF CLINICAL PSYCHIATRY

Supplementary Material

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

Author(s): David Mischoulon, MD, PhD; Janet Witte, MD; Michael Levy, MD†; George I. Papakostas, MD; L. Russell Pet, MD; Wen-hua Hsieh, PhD; Michael J. Pencina, PhD; Sean Ward, MBA; Mark H. Pollack, MD; and Maurizio Fava, MD

DOI Number: 10.4088/JCP.10m06541

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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)

Maurizio Fava*, David Mischoulon, Dan Iosifescu, Janet Witte, Michael Pencina, Martina Flynn, Linda Harper, Michael Levy, Karl Rickels, Mark Pollack

***MGH Psychiatry Clinical Trials Network and Institute, Massachusetts General Hospital, Boston, Massachusetts**

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)

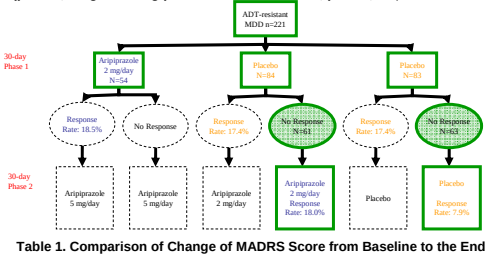

Table 1. Comparison of Change of MADRS Score from Baseline to the End of Follow-up between . Treatment Groups - Primary Efficacy Sample (PES)

	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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