ORIGINAL RESEARCH

Efficacy of adjunctive aripiprazole in patients with major depressive disorder whose symptoms worsened with antidepressant monotherapy

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Introduction. Efficacy of depression treatments, including adjunctive antipsychotic treatment, has not been explored for patients with worsening symptoms after antidepressant therapy (ADT).

Methods. This *post-hoc* analysis utilized pooled data from 3 similarly designed, randomized, double-blind, placebo-controlled trials that assessed the efficacy, safety, and tolerability of adjunctive aripiprazole in patients with major depressive disorder with inadequate response to ADT. The studies had 2 phases: an 8-week prospective ADT phase and 6-week adjunctive (aripiprazole or placebo) treatment phase. This analysis focused on patients whose symptoms worsened during the prospective 8-week ADT phase (worsening defined as >0% increase in Montgomery–Åsberg Depressive Rating Scale [MADRS] Total score). During the 6-week, double-blind, adjunctive phase, response was defined as ≥50% reduction in MADRS Total score and remission as ≥50% reduction in MADRS Total score and MADRS score ≤10.

Results. Of 1065 patients who failed to achieve a response during the prospective phase, 160 exhibited worsening of symptoms (ADT-Worseners), and 905 exhibited no change/reduction in MADRS scores (ADT-Non-worseners). Response rates for ADT-Worseners at endpoint were 36.6% (adjunctive aripiprazole) and 22.5% (placebo). Similarly, response rates at endpoint for ADT-Non-worseners were 37.5% (adjunctive aripiprazole) and 22.5% (placebo). Remission rates at endpoint for ADT-Worseners were 25.4% (adjunctive aripiprazole) and 12.4% (placebo). For ADT-Non-worseners, remission rates were 29.9% (adjunctive aripiprazole) and 17.4% (placebo).

Conclusion. These results suggest that adjunctive aripiprazole is an effective intervention for patients whose symptoms worsen during antidepressant monotherapy. The results challenge the view that benefits of adjunctive therapy with aripiprazole are limited to partial responders to ADT.

Introduction

Key treatment goals in major depressive disorder (MDD) are symptom remission and a return to pre-episode levels of functioning. However, incomplete or nonresponse to treatment is common in patients with MDD. Using data from clinical trials, Fava and Davidson[1] estimated that up to 46% of patients have treatment-resistant depression; this estimate is deemed to be conservative, given that most clinical trials exclude patients not likely to respond. Data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial indicate that 64% of patients do not achieve an adequate response or remission to adequate antidepressant therapy (ADT)[2]; reports from clinical practice suggest rates of 65%–85%.[3]

Available strategies to address incomplete response to antidepressant monotherapy include maximizing initial therapy, neuromodulation, switching treatments, and augmentation.[4] Current treatment guidelines for MDD from the American Psychiatric Association recommend antidepressant augmentation as one option for patients with MDD after 4–8 weeks of inadequate response to initial ADT.[4] Augmentation with atypical antipsychotic agents is now supported by a sizeable body of evidence: results from 16 trials including 3480 patients demonstrated the efficacy of adjunctive treatment strategy.[5-7] However, clinical practice guidelines do not provide much direction for selecting among the various treatment strategies based on the level of improvement with initial ADT. Clinicians have traditionally favored switching antidepressants over augmentation for patients who do not achieve at least a partial response.[8] However, it was shown recently that adjunctive aripiprazole was an effective treatment in patients with minimal[9] or inadequate response to ADT.[10-12] Preclinical research has shown that the addition of atypical antipsychotics such as aripiprazole can reverse the suppression of firing of norepinephrine neurons produced by selective serotonin re-uptake inhibitors through their antagonism of serotonin 2A (5-HT$_{2A}$) receptors.[13] Inhibition of the 5-HT$_2$ receptor has also been shown to enhance the effects of serotonin in the prefrontal cortex.[14] Both mechanisms may help to explain the adjunctive effects of atypical antipsychotics in MDD. The efficacy of atypical antipsychotic agents in monotherapy is not well established. For example, evidence shows that olanzapine monotherapy is not as effective as olanzapine/fluoxetine combination therapy.[15] Quetiapine ER has been shown to be efficacious as monotherapy for nonpsychotic MDD.[16] Similar evidence for aripiprazole is not available. However, aripiprazole has other mechanisms of action that potentially could improve depressive symptoms but are not related to its pharmacodynamic interaction with an antidepressant. As a dopamine D$_2$ partial agonist, aripiprazole may increase dopamine levels in hypo-dopaminergic states; as a 5-HT$_{1A}$ partial agonist, it may enhance serotonergic transmission; and as a 5-HT$_{2C}$ partial agonist, it may increase extracellular dopamine and norepinephrine concentrations.[17] The combination of 5-HT$_{1A}$ agonism, 5-HT$_{2A}$ antagonism, and D$_2$/D$_3$ partial agonism activity is unique among atypical antipsychotics and appears to be a desirable profile for augmentation of antidepressants that are monoamine re-uptake inhibitors. However, it has not been established how this pharmacologic profile translates into efficacy during adjunctive treatment.

Clinicians may encounter patients in clinical practice whose symptoms worsen following antidepressant treatment, and a small body of literature has called attention to this possibility.[18,19] Clinicians should consider reassessment of the diagnosis in these patients, specifically if there are features present, such as psychotic symptoms or undiagnosed bipolar depression, that require other treatment. If these features are not present, to our knowledge, no systematic investigation of treatments for patients whose symptoms worsen has been reported. The objective of the current *post-hoc* analysis was to determine the efficacy of adjunctive aripiprazole in patients whose symptoms, as assessed using the Montgomery–Åsberg Depressive Rating Scale (MADRS), worsened during 8 weeks of antidepressant monotherapy. This was a retrospective analysis of data pooled from 3 similarly designed, randomized, double-blind, placebo-controlled trials of adjunctive aripiprazole in patients with MDD.[10-12]

Methods

Study design

This study was a *post-hoc* analysis using pooled data from 3 similarly designed, randomized, double-blind, placebo-controlled trials of aripiprazole adjunctive to ADT in patients with MDD.[10-12] Full details of the study design and methods have been reported previously. In brief, eligible patients were aged 18–65 years, with a diagnosis of major depressive episode (according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision [DSM-IV-TR]) lasting ≥8 weeks and a 17-item Hamilton Rating Scale for Depression (HAM-D17) Total score ≥18. All patients reported an inadequate response to 1–3 prior ADTs. An inadequate response was defined as less than a 50% reduction in severity of depressive symptoms, as assessed by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire. Patients were enrolled in an 8-week, prospective antidepressant monotherapy phase (Phase B), and

received 1 of 5 antidepressants (fluoxetine, paroxetine [either immediate- or controlled-release [CR] formulation], sertraline escitalopram, or venlafaxine extended release [ER]), flexibly dosed, along with co-administration of a single-blind placebo. Patients with an inadequate response to the prospective antidepressant monotherapy at the end of Phase B then entered a 6-week, randomized, double-blind, placebo-controlled phase (Phase C). An inadequate response to treatment in Phase B was defined as a <50% reduction in HAM-D17 Total score, a HAM-D17 Total score of ≥14, and a Clinical Global Impression–Improvement score of ≥3. Patients were randomized to receive either adjunctive aripiprazole or placebo, while continuing on the same open-label ADT at an unchanged dose. This *post-hoc* analysis focused on the subset of patients randomized in Phase C whose MADRS score increased during initial treatment in Phase B.

Medication doses

In the prospective phase, the following ADT doses were targeted: escitalopram (10 or 20 mg/day), fluoxetine (20 or 40 mg/day), paroxetine CR (37.5 or 50 mg/day; paroxetine 30 or 40 mg/day if paroxetine CR unavailable), sertraline (100 or 150 mg/day), or venlafaxine ER (150 or 225 mg/day). No ADT dose increases were permitted after Week 4.

In the randomized phase, aripiprazole dosing was started at 5 mg/day and was increased to 10 mg/day after the first week of treatment (Week 9) if tolerated, with a maximum dose of 15–20 mg/day. Patients unable to tolerate 5 mg/day of aripiprazole could have their dose decreased to 2 mg/day.

Assessments

The current analysis examined the subset of patients who showed an increase in MADRS Total score (worsening of symptoms) during Phase B from Week 1 to the end of Week 8 and who were later randomized to adjunctive aripiprazole or adjunctive placebo. This subset of patients was considered "ADT-Worseners." "ADT-Non-worseners" were defined as patients who showed a ≥0% decrease (no change or an improvement of symptoms) in MADRS Total score during the prospective phase (Phase B, Week 0–8). Response in Phase C was defined as a ≥50% reduction in MADRS Total score, whereas remission in Phase C was defined as a ≥50% reduction in MADRS Total score and a MADRS Total score of ≤10 at endpoint.

Phase B ADT-Worseners and ADT-Non-worseners were also assessed using the Sheehan Disability Scale (SDS) to measure functional disability in work, social, and family life.[20]

Statistical methods

Mean MADRS Total score analysis was performed using an analysis of covariance, with treatment and protocol as the main effects, end of Phase B score as the covariate, and last observation carried forward (LOCF). Response and remission rates were evaluated using Fisher exact test.

Findings

Patients

Of the 1065 patients who failed to achieve a response in Phase B and were randomized to Phase C, 160 patients (15.0%) exhibited a worsening of symptoms with ADT, and 905 (85.0%) exhibited no change or a reduction in objective scale scores (ADT-Non-worseners). Completion rates during the adjunctive treatment phase were similar in ADT-Worseners (aripiprazole, 80/89 [89.9%]; placebo, 63/71 [88.7%]) and ADT-Non-worseners (aripiprazole, 391/436 [89.7%]; placebo, 406/469 [86.6%]). Among the ADT-Worseners, 48.1% showed a <10% increase in MADRS Total score, 33.8% showed an increase of 10–20%, and 18.1% an increase >20%. At Phase C endpoint, ADT-Worseners and ADT-Non-worseners received similar doses of aripiprazole (10.7 vs 10.8 mg/day, respectively).

Most demographic and psychiatric characteristics (ie, mean age [46.8 y vs 45.1 y], mean weight [89.3 kg vs 86.0 kg], sex [70.0% women vs 67.4% women], race [88.8% white vs 88.8% white], ethnicity [96.9% not Hispanic vs 94.1% not Hispanic], type of depressive episode [ie, single (22.5% vs 17.9%) or recurrent (77.5% vs 82.1%)], mean age at first depressive episode [25.9 y vs 27.5 y], and number of prior adequate ADTs [1.5 vs 1.3]) did not differ between ADT-Worseners and ADT-Non-worseners, respectively. However, the median duration of the current depressive episode was significantly longer for ADT-Worseners compared with ADT-Non-worseners (24.2 vs 18.4 months, respectively; $P = .022$). In ADT-Worseners and ADT-Non-worseners, respectively, mean (SD) MADRS Total scores were 28.2 (4.6) and 31.6 (4.8) at the beginning of antidepressant monotherapy and 31.8 (4.7) and 25.3 (5.7) at the end of Phase B; mean (SD) HAM-D17 scores were 22.2 (3.1) and 23.4 (3.3) at the beginning of antidepressant monotherapy and 22.6 (3.8) and 19.3 (3.7) at the end of Phase B. Mean (SD) SDS score at the end of Phase B was significantly higher in ADT-Worseners (6.4 [2.1]) versus ADT-Non-worseners (5.3 [2.3]; $P < .0001$).

Efficacy

During Phase B (Weeks 0–8), ADT-Worseners exhibited a mean change in MADRS Total score of 3.6, while ADT-Non-worseners experienced a mean change of –6.3.
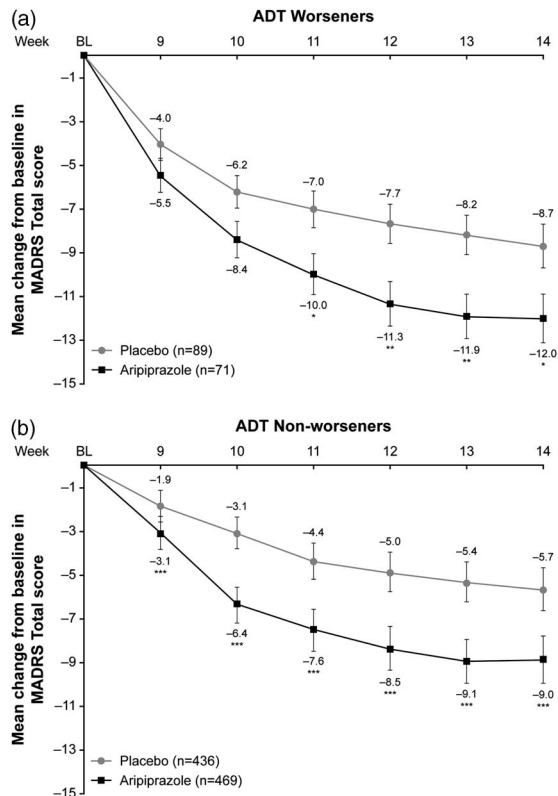
FIGURE 1. Mean change in MADRS Total score from baseline of Phase C (BL, Week 8) to endpoint (Week 14) by treatment for (a) ADT-Worseners and (b) ADT-Non-worseners (LOCF). *$P<.05$; **$P<.01$; ***$P\leq.001$ vs placebo. ADT-Worsener was defined as having a >0% increase in MADRS Total score during the prospective Phase B (Week 0–14). Baseline scores: ADT-Worseners placebo = 31.5; ADT-Worseners aripiprazole = 32.1; ADT-Non-worseners placebo = 25.7; ADT-Non-worseners aripiprazole = 24.9. MADRS = Montgomery–Åsberg Depression Rating Scale; BL = baseline; ADT = antidepressant therapy; LOCF = last observation carried forward.

Changes in MADRS Total score for ADT-Worseners during the adjunctive treatment phase (Weeks 9–14) are shown in Figure 1. ADT-Worseners exhibited significant improvements in symptoms every week after the third week of adjunctive aripiprazole treatment (Week 11) compared with patients receiving adjunctive placebo. MADRS Total scores improved from 32.1 to 20.1 in the adjunctive aripiprazole group, compared with 31.5 to 22.8 in the adjunctive placebo group (Figure 1a). ADT-Non-worseners exhibited significant improvements in symptoms, as assessed by mean changes in MADRS Total score, every week starting the first week of adjunctive aripiprazole treatment (Week 9) compared with adjunctive placebo. MADRS Total scores improved from 25.7 to 15.9 in the adjunctive aripiprazole group compared with 25.7 to 20.0 in the adjunctive placebo group (Figure 1b). The difference in mean change of MADRS Total score was identical (−3.3) between adjunctive aripiprazole and placebo at endpoint of Phase C in ADT-Worseners and ADT-Non-worseners.

At endpoint, 36.6% of ADT-Worseners in the aripiprazole group and 22.5% of ADT-Worseners in the placebo group exhibited a response to treatment (≥50% reduction in MADRS Total score), but the difference between treatment groups was not significant. In comparison, 37.5% of ADT-Non-worseners (176/469) receiving adjunctive aripiprazole showed a response to treatment at endpoint (Week 14) compared with 22.5% of those receiving adjunctive placebo (98/436). The magnitude of the difference in response to adjunctive aripiprazole and placebo was similar in the ADT-Worseners and ADT-Non-Worseners, with a number needed to treat (NNT) of 7 for aripiprazole in both groups.

During the adjunctive treatment phase, a higher proportion of ADT-Worseners who received adjunctive aripiprazole compared with ADT-Worseners who received adjunctive placebo achieved remission (≥50% reduction in MADRS Total score and MADRS Total score of ≤10) at the fifth and sixth week of aripiprazole treatment (Weeks 13 and 14; $P<.05$), with an NNT of 8 for remission. At endpoint, 25.4% of ADT-Worseners receiving adjunctive aripiprazole achieved remission compared with 12.4% of ADT-Worseners receiving adjunctive placebo (Fisher exact test; $P=.04$), whereas 29.9% of ADT-Non-worseners who received adjunctive aripiprazole achieved remission at endpoint compared with 17.4% of ADT-Non-worseners receiving adjunctive placebo.

On the SDS, ADT-Worseners receiving adjunctive aripiprazole and placebo showed a mean change from baseline to endpoint of −1.5 and −1.2, respectively. This difference was not statistically significant. The difference in mean change from baseline to endpoint on the SDS was statistically significant for ADT-Non-worseners receiving adjunctive aripiprazole (−1.2, baseline = 5.2) compared with those receiving adjunctive placebo (−0.6, baseline = 5.3; $P<.0001$).

Safety and tolerability

Treatment-emergent adverse events (AEs) reported at an incidence of ≥5% and at least at twice the rate of placebo are shown in Figure 2. The types of AEs reported by ADT-Worseners did not appear to be qualitatively different from the AEs reported by the entire patient population in the 3 parent MDD trials.[10-12]

During the adjunctive treatment phase, clinically significant weight gain (≥7% gain from baseline) was reported by 7.4% of ADT-Worseners (n = 5/68) receiving adjunctive aripiprazole compared with no patients in the adjunctive placebo group. The mean change in weight from baseline to endpoint was 1.8 kg and 0.7 kg for ADT-Worseners receiving adjunctive aripiprazole or placebo, respectively.
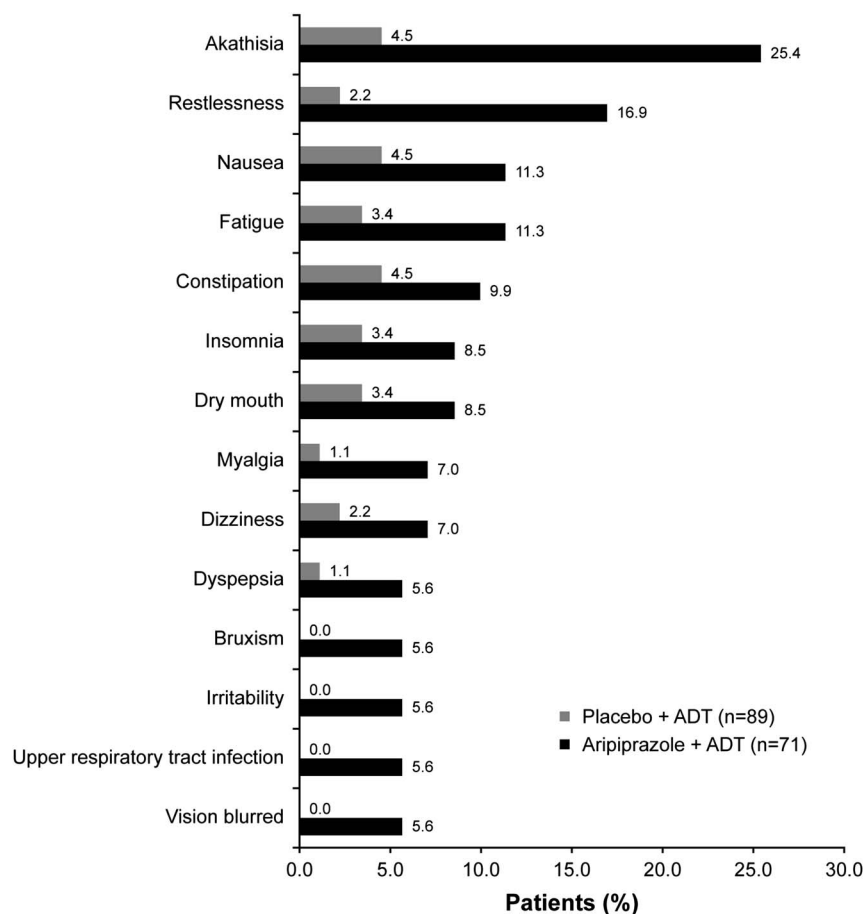
FIGURE 2. Adverse events (≥5% incidence for ADT-Worseners and at least twice the rate of the placebo group), safety sample. ADT = antidepressant therapy.

Discussion

This is the first study to assess whether adjunctive aripiprazole is beneficial in patients with MDD whose symptoms have worsened during treatment with antidepressant monotherapy. On average, symptoms of these patients worsened by a clinically relevant 3–4 points on the MADRS scale during ADT monotherapy. Furthermore, to our knowledge, this is the first *post-hoc* analysis to analyze the impact of any atypical antipsychotic or adjunctive agent for the treatment of a patient population experiencing a worsening of depressive symptoms. Interestingly, the response and remission rates for ADT-Worseners receiving adjunctive aripiprazole treatment were similar (36.6% and 25.4%, respectively) to the response (36.0%) and remission rates (24.0%) of ADT-Minimal Responders,[9] suggesting that adjunctive aripiprazole may be an effective intervention across the spectrum of patients with an inadequate response to ADT.

In the current analysis, fewer of the weekly change scores and the weekly response and remission rates were significant in the ADT-Worseners subgroup than in the ADT-Non-worseners. Mean change from baseline on the SDS at endpoint was not significantly different between ADT-Worseners receiving adjunctive aripiprazole and placebo, whereas there was a significantly greater mean reduction from baseline at endpoint in ADT-Non-worseners receiving adjunctive aripiprazole versus adjunctive placebo. The sample size of ADT-Worseners, however, was considerably smaller than the subset of ADT-Non-worseners (n = 160 vs n = 905, respectively), and this may have limited the number of significant differences in the ADT-Worsener group. The magnitude of differences appeared to be relatively similar in the two groups. For example, change in MADRS Total score for patients receiving adjunctive aripiprazole compared with those receiving placebo (Figure 1) was similar in ADT-Worseners and ADT-Non-worseners. In addition, the NNTs to achieve response and remission were also similar for both ADT-Worseners and ADT-Non-worseners.

Clinical practice and certain guidelines have favored augmentation therapy in patients with a partial response to ADT, but with a preference for switching to alternative antidepressants in patients with minimal response. The Canadian Network for Mood and Anxiety Treatment guidelines recommend increasing dose or

switching to an alternative ADT when patient improvement on a depression rating scale is <20% and augmentation for patients with a response to ADT >20%.[21] However, in the past, such guidelines have been based on rational or practical grounds rather than evidence of efficacy, or lack thereof. The argument for switching medication is strengthened in patients whose symptoms worsen during ADT. However, the findings of the current analysis challenge this consideration and suggest that adjunctive aripiprazole is effective in ADT-Worseners.

Every change in treatment requires additional practical considerations, including safety and tolerability considerations and patient preference. A practical advantage of using adjunctive aripiprazole in the treatment of MDD is the fact that changes occur quickly and are highly predictive of final effectiveness.[22,23] In the current study, 70% of the overall change in MADRS Total scores from baseline to endpoint occurred within the first 2 weeks of treatment. The results presented here are not informative regarding the comparison of adjunctive aripiprazole and a switch in ADT. This would require a different study design.

Although augmentation with atypical antipsychotics is the most well studied treatment approach for non-responders to ADT,[24] as a class, atypical antipsychotics are associated with long-term safety issues including metabolic syndrome, weight gain, extrapyramidal symptoms, and tardive dyskinesia.[4,24] A meta-analysis of randomized, placebo-controlled trials of augmentation with atypical antipsychotics showed comparable odds ratios for discontinuations due to AEs across agents, though rates of specific AEs may differ.[25] In placebo-controlled trials in patients with MDD, adjunctive aripiprazole was commonly associated with akathisia[26–29] and, in some trials, significant weight gain.[27,28] Thus, it is important to evaluate the overall risk–benefit profile of a strategy of augmentation with aripiprazole. Pharmacokinetic drug interactions also need to be considered; compared with therapy switching, adjunctive therapy presents a greater risk of drug interactions.[24] Because aripiprazole is a substrate of cytochrome P450 (CYP) 3A4 and CYP2D6, dose adjustments of aripiprazole are necessary when used with strong CYP3A4 and CYP2D6 (eg, fluoxetine, paroxetine) inhibitors; however, aripiprazole does not affect the steady-state pharmacokinetics of escitalopram, venlafaxine, fluoxetine, paroxetine, or sertraline.[30] Cost may also be higher compared with a switching approach.[24]

The current analysis has interesting neuropharmacologic implications relative to mechanism of action for adjunctive aripiprazole in MDD. In this study, the addition of aripiprazole resulted in symptomatic improvement in patients who exhibited no improvement on the initial antidepressant and, in fact, experienced some worsening of symptoms. This suggests that either the initial antidepressant monotherapy may have had neuropharmacologic effects that acted synergistically with the addition of aripiprazole, or that aripiprazole has independent antidepressant properties. There is no definitive evidence to support either hypothesis, and it is conceivable that both mechanisms could play a role.

Limitations

The current analysis has limitations, including its *post-hoc* nature and small sample sizes; the power for some analyses may be insufficient to detect statistical significance. None of the analyses presented here were pre-specified, and all *P*-values reported represent nominal *P*-values without adjustment for multiplicity. This is a retrospective analysis, and, although the 3 trials included in this retrospective analysis were not designed to assess the outcomes in patients who showed worsening of symptoms with an initial ADT, the similar design of the 3 studies allowed the pooling of data. Although an objective threshold of any worsening was elected as >0% change in the MADRS score, 48% of patients had a <10% increase in MADRS score, and this increase may reflect fluctuations in MADRS score rather than meaningful deterioration; future studies might incorporate additional outcome measures assessing symptoms such as anxiety or compare degree of worsening using larger sample sizes. The adjunctive treatment phase in the 3 trials was relatively brief (6 weeks), perhaps underestimating the full effect of augmentation during a longer trial. In addition, these short-term trials do not address whether response and remission rates in the short term will be sustained in the long term. The strict inclusion/exclusion criteria used in patient selection for these trials may limit the generalizability of the findings to clinical practice.

Conclusions

The results presented here suggest that adjunctive aripiprazole is an effective intervention across the spectrum of patients who show an inadequate response to antidepressant monotherapy, including patients whose symptoms worsen during antidepressant monotherapy. This finding challenges the view that the benefits of adjunctive treatment are limited to patients with MDD who have had a partial response to ADT, and suggests that augmentation may constitute a viable treatment strategy among ADT-Worseners.

Disclosures

During the past 3 years, J. Craig Nelson has received international lecture honoraria from Otsuka (Asia).

REFERENCES:

1. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. *Psychiatr Clin North Am*. 1996; **19**(2): 179–200.

2. Rush AJ, Trivedi MH, Wisniewski SR, *et al*. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006; **163**(11): 1905–1917.

3. Nemeroff CB. Prevalence and management of treatment-resistant depression. *J Clin Psychiatry*. 2007; **68**(Suppl 8): 17–25.

4. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder. *Am J Psychiatry*. 2010; **167**(10): A34.

5. Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. *Am J Psychiatry*. 2009; **166**(9): 980–991.

6. Nutt DJ, Davidson JR, Gelenberg AJ, *et al*. International consensus statement on major depressive disorder. *J Clin Psychiatry*. 2010; **71**(Suppl E1): e08.

7. Baghai TC, Blier P, Baldwin DS, *et al*. General and comparative efficacy and effectiveness of antidepressants in the acute treatment of depressive disorders: a report by the WPA section of pharmacopsychiatry. *Eur Arch Psychiatry Clin Neurosci*. 2011; **261**(Suppl 3): 207–245.

8. Nelson JC. Augmentation strategies in the treatment of major depressive disorder: recent findings and current status of augmentation strategies. *CNS Spectr*. 2007; **12**(Suppl 22): 6–9.

9. Nelson J, Thase M, Bellocchio E, *et al*. Efficacy of adjunctive aripiprazole in patients with major depressive disorder who showed minimal response to initial antidepressant therapy. *Int Clin Psychopharmacol*. 2012; **27**(3): 125–133.

10. Marcus RN, McQuade RD, Carson WH, *et al*. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2008; **28**(2): 156–165.

11. Berman R, Fava M, Thase M, *et al*. Aripiprazole augmentation in major depression: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. *CNS Spectr*. 2009; **14**(4): 197–206.

12. Berman RM, Marcus RN, Swanink R, *et al*. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007; **68**(6): 843–853.

13. Chernoloz O, El Mansari M, Blier P. Electrophysiological studies in the rat brain on the basis for aripiprazole augmentation of antidepressants in major depressive disorder. *Psychopharmacology (Berl)*. 2009; **206**(2): 335–344.

14. Lakoski JM, Aghajanian GK. Effects of ketanserin on neuronal responses to serotonin in the prefrontal cortex, lateral geniculate and dorsal raphe nucleus. *Neuropharmacology*. 1985; **24**(4): 265–273.

15. Thase ME, Corya SA, Osuntokun O, *et al*. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. *J Clin Psychiatry*. 2007; **68**(2): 224–236.

16. McElroy SL, Guerdjikova A, Mori N, Keck PE Jr. Therapeutic potential of new second generation antipsychotics for major depressive disorder. *Expert Opin Investig Drugs*. 2010; **19**(12): 1527–1544.

17. Blier P, Blondeau C. Neurobiological bases and clinical aspects of the use of aripiprazole in treatment-resistant major depressive disorder. *J Affect Disord*. 2011; **128**(Suppl 1): S3–S10.

18. Fava GA. Do antidepressant and antianxiety drugs increase chronicity in affective disorders? *Psychother Psychosom*. 1994; **61**(3–4): 125–131.

19. Fava GA. Can long-term treatment with antidepressant drugs worsen the course of depression? *J Clin Psychiatry*. 2003; **64**(2): 123–133.

20. Sheehan KH, Sheehan DV. Assessing treatment effects in clinical trials with the Discan metric of the Sheehan Disability Scale. *Int Clin Psychopharmacol*. 2008; **23**(2): 70–83.

21. Lam RW, Kennedy SH, Grigoriadis S, *et al*. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. III. Pharmacotherapy. *J Affect Disord*. 2009; **117**(Suppl 1): S26–S43.

22. Muzina DJ, Chambers J, Camacho T, *et al*. Adjunctive aripiprazole for depression: predictive value of early assessment. *Am J Manag Care*. 2011; **17**(12): 793–801.

23. Casey D, Laubmeier K, Marler S, Forbes R, Baker R. Efficacy of adjunctive aripiprazole in major depressive disorder: a pooled response quartile analysis and the predictive value of week 2 early response. *Prim Care Comp for CNS Disorders*. 2012; **14**(3):pii: PCC.11m01251. doi: 10.4088/PCC.4011m01251.

24. Papakostas GI. Managing partial response or nonresponse: switching, augmentation, and combination strategies for major depressive disorder. *J Clin Psychiatry*. 2009; **70**(Suppl 6): 16–25.

25. Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. *Am J Psychiatry*. 2009; **166**(9): 980–991.

26. Berman RM, Fava M, Thase ME, *et al*. Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. *CNS Spectr*. 2009; **14**(4): 197–206.

27. Berman RM, Marcus RN, Swanink R, *et al*. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007; **68**(6): 843–853.

28. Marcus RN, McQuade RD, Carson WH, *et al*. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2008; **28**(2): 156–165.

29. Nelson JC, Thase ME, Bellocchio EE, *et al*. Efficacy of adjunctive aripiprazole in patients with major depressive disorder who showed minimal response to initial antidepressant therapy. *Int Clin Psychopharmacol*. 2012; **27**(3): 125–133.

30. Abilify® (aripiprazole). Full prescribing information. Tokyo, Japan: Otsuka Pharmaceutical Co., Ltd.; 2013.