# Aripiprazole Augmentation of Antidepressants for the Treatment of Partially Responding and Nonresponding Patients With Major Depressive Disorder

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***Objective:*** To determine the efficacy and tolerability of aripiprazole, a dopamine $D_2$ and 5-$HT_{1A}$ receptor partial agonist, as augmentation of antidepressant treatment of partially responding and nonresponding patients with major depressive disorder.

***Method:*** Fifteen patients with major depressive disorder (diagnosed with a site-generated form described in the text) and an incomplete response or no response to ≥ 8 weeks of antidepressant (selective serotonin reuptake inhibitor, venlafaxine, or bupropion) monotherapy were treated with aripiprazole augmentation in an 8-week, open-label study. Data were gathered from July 2003 to March 2004.

***Results:*** The mean duration of antidepressant monotherapy at baseline was 43.1 weeks. At baseline, mean Clinical Global Impressions-Severity of Illness scale and Hamilton Rating Scale for Depression (HAM-D) scores were 4.3 and 18.9, respectively. After initiation of aripiprazole augmentation, 6 of 15 patients achieved remission (HAM-D score ≤ 7) at week 1, and 9 of 15 patients remitted by week 2. All 8 completers achieved remission by study endpoint. Akathisia in 2 patients who withdrew prematurely prompted a reduction in the starting dose of aripiprazole from 10 mg/day to 2.5 mg/day, resulting in a 50% reduction in attrition due to akathisia (2/7 withdrew due to akathisia with the 10-mg starting dose, 1/8 withdrew due to akathisia with the 2.5-mg starting dose). Discontinuation rates after 4 weeks of treatment were lower for the 2.5-mg starting dose (1/8 patients) than for the 10-mg starting dose (3/7 patients). Overall discontinuation rates at endpoint were lower for the 2.5-mg dose (3/8 patients) than the 10-mg dose (4/7 patients). Response to aripiprazole augmentation did not appear to be related to the antidepressant used at study initiation.

***Conclusion:*** Aripiprazole is an effective augmentation strategy for improving therapeutic response in patients with treatment-resistant major depressive disorder when administered in combination with standard antidepressant therapy. Based on this clinical signal, a double-blind, placebo-controlled trial is warranted.

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Pharmacologic treatment of major depressive disorder has improved dramatically over the past 2 decades. However, despite the availability of a broad array of antidepressants and many patient-years of clinical experience, a substantial percentage of patients do not completely return to predepression levels of function. Full remission, which is defined as a Hamilton Rating Scale for Depression (HAM-D) score ≤ 7, is generally achieved by only 30% to 50% of patients in 8-week depression trials.[1,2] Residual depressive symptoms are common and are associated with many negative outcomes, including increased relapse rates, more severe future episodes, risk of comorbid medical and psychiatric illness, and psychosocial impairment.[3–5]

New treatment strategies for refractory depression are greatly needed, and a body of clinical trial data evaluating the use of novel strategies is emerging. One particularly promising new treatment approach is the augmentation of antidepressant therapy with an atypical antipsychotic. There is a relatively small body of literature on this topic, consisting primarily of small open-label studies, retrospective chart reviews, and case reports.[6–12] The findings of 1 double-blind, placebo-controlled comparison of fluoxetine, olanzapine, and the combination of olanzapine and fluoxetine in 28 patients with treatment-resistant major depressive disorder have been published and demonstrate greater efficacy for the combination than either agent alone.[13] In addition, the combination of atypical antipsychotic and fluoxetine resulted in significantly



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greater reductions in the Montgomery-Asberg Depression Rating Scale score compared with monotherapy by the first week of treatment.[13] This nascent literature suggests that augmentation of antidepressant therapy with an atypical antipsychotic is effective for treatment-resistant major depressive disorder.

Aripiprazole is an atypical antipsychotic with partial agonist activity at the dopamine $D_2$ and 5-$HT_{1A}$ receptors and antagonist activity at the 5-$HT_{2A}$ receptors.[14,15] To date, clinical experience with aripiprazole augmentation in treatment-resistant major depressive disorder has not been reported. Herein, we describe the first experience with aripiprazole as augmentation of antidepressant therapy in partially responding or nonresponding patients with major depressive disorder.

## METHOD

This trial consisted of a 4-week open-label assessment of aripiprazole augmentation of antidepressant therapy followed by a 4-week open-label extension phase. Adult outpatients 26 to 61 years of age (mean = 44.1 years) who had a diagnosis of major depressive disorder based on a site-generated assessment form that included evaluation with the Clinical Global Impressions scale[16] and HAM-D[17] and who had been treated with antidepressant monotherapy for 8 or more weeks without an adequate response were eligible for enrollment. An inadequate response to antidepressant treatment was defined as a total score of 14 or greater on the 17-item HAM-D. Exclusion criteria were previous aripiprazole treatment, more than 1 prior failed trial of antidepressant therapy, failure to respond to augmentation with another antipsychotic, presence of psychotic features, substance abuse within 6 months of study entry, or a seizure disorder. All patients provided written informed consent, and the study protocol was approved by the center's institutional review board. Data were gathered from July 2003 to March 2004.

Patients continued on treatment with their existing antidepressant monotherapy and upon enrollment were initiated on daily aripiprazole augmentation treatment. The initial starting dose of aripiprazole was 10 mg/day, but the observation of akathisia in 2 patients prompted a reduction in the starting dose to 2.5 mg/day for subsequently enrolled patients. Patients were seen weekly for the first 4 weeks of the study and at week 8 for the final visit. The primary efficacy endpoint was full remission with a HAM-D total score of 7 or less. Secondary efficacy variables were response (i.e., ≥ 50% reduction in baseline HAM-D total score) and Clinical Global Impressions-Improvement scale (CGI-I) score of 1 (very much improved) or 2 (much improved). The intent-to-treat (ITT) population was defined as patients who received 1 or more doses of aripiprazole. Results are reported as last-observation-carried-forward (LOCF) and observed-case/completer datasets of the ITT population. Efficacy and safety results are reported using descriptive statistics.

**Table 1. Demographics and Patient Disposition of 15 Patients With Major Depressive Disorder Who Received Aripiprazole Augmentation Therapy**

| Variable | Value |
|---|---|
| Sex, N | |
| Male | 6 |
| Female | 9 |
| Age, y | |
| Mean | 44.1 |
| Range | 26–61 |
| Antidepressant monotherapy, N | |
| SSRI | 11 |
| Venlafaxine | 3 |
| Bupropion | 1 |
| Antidepressant treatment duration, wk | |
| Mean ± SD | 43.1 ± 30.5 |
| Median | 30 |
| Range | 8–104 |
| Baseline 17-item HAM-D score | |
| Mean ± SD | 18.9 ± 3.4 |
| Range | 15–28 |
| Baseline CGI-S score | |
| Mean ± SD | 4.3 ± 0.6 |
| Range | 4–6 |
| Patients completing 8 weeks, N (%) | 8 (53) |
| Augmentation therapy duration, mean ± SD, d | 40.1 ± 18.0 |
| Patients discontinuing study, N (%) | |
| Adverse events | 4 (27) |
| Lost to follow-up | 3 (20) |

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor.

## RESULTS

Fifteen patients fulfilled eligibility criteria and were enrolled at the Northbrooke Research Center in Milwaukee, Wis. This population was moderately ill, with a mean baseline Clinical Global Impressions-Severity of Illness scale score of 4.3 and a mean baseline HAM-D score of 18.9. The mean duration of antidepressant treatment at baseline was 43.1 weeks (Table 1). Most patients entered the study receiving a selective serotonin reuptake inhibitor (11 patients), and fewer were being treated with venlafaxine (3 patients) or bupropion (1 patient). Eleven out of 15 patients completed the 4-week study, and 8 of 11 completed the 4-week extension phase. The mean duration of treatment was 40 days. Seven patients were treated with aripiprazole 10 mg/day. The starting dose of aripiprazole in the remaining 8 patients was 2.5 mg/day, which was increased weekly in 2.5-mg increments as tolerated. Daily doses at endpoint for these 8 patients were 2.5 mg (1 patient), 5 mg (3 patients), and 10 mg (4 patients).

The mean ± SD endpoint HAM-D total scores at week 8 were 4.3 ± 4.4 for the LOCF analysis and 2.5 ± 2.7 for the 8 patients who completed the study. The mean ± SD



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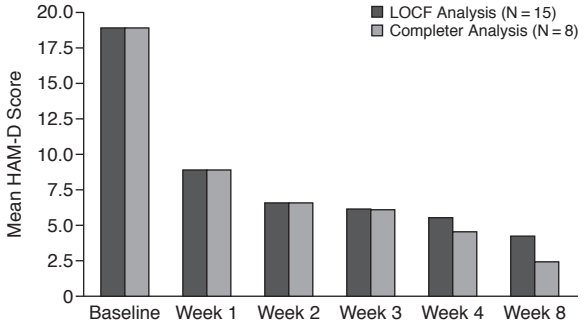
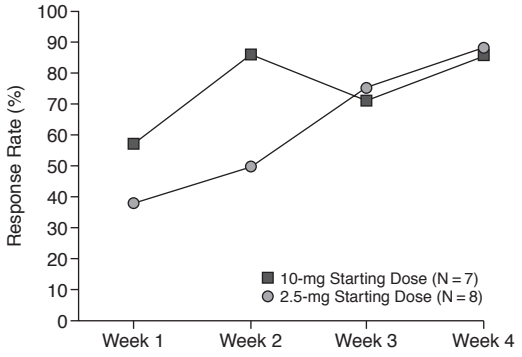
**Figure 1. Total Scores on the 17-Item HAM-D for Major Depressive Disorder Patients Receiving Augmentation Therapy With Aripiprazole (LOCF and completer datasets)**



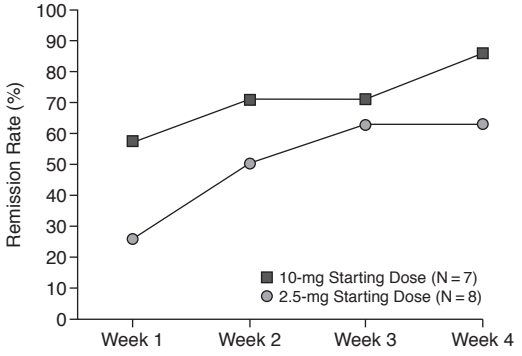

Abbreviations: HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward.

**Figure 2. LOCF Response Rates as a Function of Starting Dose in Major Depressive Disorder Patients Receiving Augmentation Therapy With Aripiprazole (response defined as ≥ 50% reduction in baseline HAM-D score)**




Abbreviations: HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward.

**Figure 3. LOCF Remission Rates as a Function of Starting Dose in Major Depressive Disorder Patients Receiving Augmentation Therapy With Aripiprazole (remission defined as HAM-D score ≤ 7)**




Abbreviations: HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward.

HAM-D total scores at weeks 1 and 2 were 8.9 ± 5.3 and 6.6 ± 5.1, respectively (Figure 1). Mean HAM-D total scores at week 2 were 5.3 ± 4.4 for the 10-mg starting dose and 7.8 ± 5.6 for the 2.5-mg starting dose.

All 8 of the patients who completed the study fulfilled criteria for both response and remission. By week 8, 14 of 15 patients in the LOCF analysis were responders, and 13 of 15 patients were remitters. Response at week 1 was achieved by 7 of 15 patients and by 10 of 15 patients at week 2. By week 1, 6 of the 15 patients achieved remission, and 9 of the 15 patients remitted by week 2. More patients who started therapy with the 10-mg dose of aripiprazole were responders at weeks 1 and 2 compared with patients in the 2.5-mg group (Figure 2). Remission rates were higher for the 10-mg group compared with the 2.5-mg group for the entire 4-week period (Figure 3). Response was not related to concomitantly administered antidepressant. A CGI-I score of 1 (very much improved) was achieved by all 8 completers. In the LOCF analysis, 14 of 15 patients achieved a CGI-I score of 1 or 2.

Aripiprazole was relatively well tolerated in this population, particularly at the lower starting dose of 2.5 mg/day. Overall, 7 patients discontinued because of akathisia (N = 3), impaired memory (N = 1), or loss to follow-up (N = 3). Discontinuation rates after 4 weeks for the 10-mg starting dose (3/7 patients) were higher than for the 2.5-mg starting dose (1/8). Overall discontinuation rates at endpoint also were higher for the 10-mg dose (4/7) than for the 2.5-mg dose (3/8). Reduction of the starting dose to 2.5 mg lowered the discontinuation rate due to akathisia by 50%. Sedation was reported by 2 patients and led to withdrawal from the study for 1 (akathisia was an additional reason for this patient's study withdrawal). Insomnia was reported by 2 patients. Mean body weight at baseline was 89.6 kg and at endpoint was 90.5 kg.

## DISCUSSION

This first study of the use of aripiprazole to augment antidepressant therapy suggests a potential role for this atypical antipsychotic in treatment-resistant major depressive disorder. Consistent with the findings from some studies of other atypical antipsychotics,[9,10,13] the addition of aripiprazole to an antidepressant regimen resulted in a rapid and clinically meaningful improvement in depression and global functioning scores.

Dose determination in this antipsychotic-naive patient population is obviously of clinical relevance in terms of maximizing efficacy and tolerability. Although this study was not powered to identify a dose-response relationship, a starting dose of 2.5 mg was efficacious and appeared to be better tolerated, but the 10-mg dose appeared to elicit a

more rapid onset of response. This study was open-label, and it is possible that the addition of a second pharmacologic agent (i.e., aripiprazole) resulted in improvement that was in part due to a placebo response. In addition, the eligibility criteria required a minimum of 8 weeks of treatment with an antidepressant. However, the mean duration of antidepressant therapy prior to entering the study was 43 weeks (median = 30 weeks), with only 1 patient entering with the required minimum 8 weeks of prior antidepressant therapy. These findings should serve as an impetus for randomized, double-blind, placebo-controlled fixed-dose and flexible-dose trials of aripiprazole that would better characterize the optimal dose, titration schedule, and duration of augmentation treatment.

The mechanisms that underlie the additive efficacy of antidepressants and atypical antipsychotics are not fully understood. There is evidence that a relationship may exist between depressive symptoms and dopamine regulation of psychomotor activity, motivation, pleasure, and appetite.[18] In fact, dopamine agonists (e.g., pramipexole, bromocriptine) and agents that positively influence dopamine transmission (e.g., stimulants) have historically been used to augment antidepressant response.[19–25] Laboratory animal data demonstrate that the combination of fluoxetine with olanzapine results in different profiles of norepinephrine, serotonin, and dopamine release from the prefrontal cortex of rats.[26] Aripiprazole is a partial agonist of the dopamine $D_2$ and serotonin 5-$HT_{1A}$ receptors and an antagonist of the serotonin 5-$HT_{2A}$ receptor.[14,15] It has been suggested that partial 5-$HT_{1A}$ receptor agonism may be associated with antidepressant and anxiolytic effects.[14,27–29] Indeed, the 5-$HT_{1A}$ receptor has been shown to be essential for the effects of antidepressants on neurogenesis in the hippocampus.[30] Further studies are warranted to better characterize the relationship between 5-$HT_{1A}$ agonists and clinically meaningful antidepressant effects.

## CONCLUSION

The findings of this small, open-label study suggest that the addition of aripiprazole to an existing antidepressant regimen in partially responsive or nonresponsive patients with major depressive disorder results in the rapid achievement of remission. Remission was achieved by 6 of 15 patients in the first week of treatment and by 9 of 15 patients at week 2. Aripiprazole augmentation, particularly at a starting dose of 2.5 mg, is well tolerated and thus may provide a reasonable treatment alternative for patients with refractory depression.

*Drug names:* aripiprazole (Abilify), bromocriptine (Parlodel and others), bupropion (Wellbutrin and others), fluoxetine (Prozac and others), olanzapine (Zyprexa), pramipexole (Mirapex), venlafaxine (Effexor and others).

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## REFERENCES

1. Thase ME. Evaluating antidepressant therapies: remission as the optimal outcome. J Clin Psychiatry 2003;64(suppl 13):18–25
2. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. Br J Psychiatry 2001;178:234–241
3. Judd LL, Schettler PJ, Akiskal HS. The prevalence, clinical relevance, and public health significance of subthreshold depressions. Psychiatr Clin North Am 2002;25:685–698
4. Menza M, Marin H, Opper RS. Residual symptoms in depression: can treatment be symptom-specific? J Clin Psychiatry 2003;64:516–523
5. Paykel ES, Ramana R, Cooper Z, et al. Residual symptoms after partial remission: an important outcome in depression. Psychol Med 1995;25: 1171–1180
6. Barbee JG, Conrad EJ, Jamhour NJ. The effectiveness of olanzapine, risperidone, quetiapine, and ziprasidone as augmentation agents in treatment-resistant major depressive disorder. J Clin Psychiatry 2004;65: 975–981
7. Marangell LB, Johnson CR, Kertz B, et al. Olanzapine in the treatment of apathy in previously depressed participants maintained with selective serotonin reuptake inhibitors: an open-label, flexible-dose study. J Clin Psychiatry 2002;63:391–395
8. O'Connor M, Silver H. Adding risperidone to selective serotonin reuptake inhibitor improves chronic depression. J Clin Psychopharmacol 1998;18:89–91
9. Ostroff RB, Nelson JC. Risperidone augmentation of selective serotonin reuptake inhibitors in major depression. J Clin Psychiatry 1999;60: 256–259
10. Papakostas GI, Petersen TJ, Nierenberg AA, et al. Ziprasidone augmentation of selective serotonin reuptake inhibitors (SSRIs) for SSRI-resistant major depressive disorder. J Clin Psychiatry 2004;65:217–221
11. Pitchot W, Ansseau M. Addition of olanzapine for treatment-resistant depression [letter]. Am J Psychiatry 2001;158:1737–1738
12. Viner MW, Chen Y, Bakshi I, et al. Low-dose risperidone augmentation of antidepressants in nonpsychotic depressive disorders with suicidal ideation. J Clin Psychopharmacol 2003;23:104–106
13. Shelton RC, Tollefson GD, Tohen M, et al. A novel augmentation strategy for treating resistant major depression. Am J Psychiatry 2001;158: 131–134
14. Jordan S, Koprivica V, Chen R, et al. The antipsychotic aripiprazole is a potent, partial agonist at the human 5-HT1A receptor. Eur J Pharmacol 2002;441:137–140
15. Lieberman JA. Dopamine partial agonists: a new class of antipsychotic. CNS Drugs 2004;18:251–267
16. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
17. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62



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18. Willner P. The mesolimbic dopamine system as a target for rapid antidepressant action. Int Clin Psychopharmacol 1997;12(suppl 3):S7–S14
19. Bader GM, Hawley JM, Short DD. Venlafaxine augmentation with methylphenidate for treatment-refractory depression: a case report [letter]. J Clin Psychopharmacol 1998;18:255–256
20. Fava M, Thase ME, DeBattista C. A multicenter, placebo-controlled study of modafinil augmentation in partial responders to selective serotonin reuptake inhibitors with persistent fatigue and sleepiness. J Clin Psychiatry 2005;66:85–93
21. Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. Am J Psychiatry 2004;161: 564–566
22. Lattanzi L, Dell'Osso L, Cassano P, et al. Pramipexole in treatment-resistant depression: a 16-week naturalistic study. Bipolar Disord 2002;4:307–314
23. Masand PS, Anand VS, Tanquary JF. Psychostimulant augmentation of second generation antidepressants: a case series. Depress Anxiety 1998;7:89–91
24. Wada T, Kanno M, Aoshima T, et al. Dose-dependent augmentation effect of bromocriptine in a case with refractory depression. Prog Neuropsychopharmacol Biol Psychiatry 2001;25:457–462
25. Zarate CA Jr, Payne JL, Singh J, et al. Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. Biol Psychiatry 2004;56:54–60
26. Zhang W, Perry KW, Wong DT, et al. Synergistic effects of olanzapine and other antipsychotic agents in combination with fluoxetine on norepinephrine and dopamine release in rat prefrontal cortex. Neuropsychopharmacology 2000;23:250–262
27. Dimitriou EC, Dimitriou CE. Buspirone augmentation of antidepressant therapy. J Clin Psychopharmacol 1998;18:465–469
28. Rausch JL, Ruegg R, Moeller FG. Gepirone as a 5-HT1A agonist in the treatment of major depression. Psychopharmacol Bull 1990;26:169–171
29. Robinson DS, Rickels K, Feighner J, et al. Clinical effects of the 5-HT1A partial agonists in depression: a composite analysis of buspirone in the treatment of depression. J Clin Psychopharmacol 1990;10(suppl 3): 67S–76S
30. Santarelli L, Saxe M, Gross C, et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 2003;301: 805–809