

Aripiprazole Augmentation in Treatment-Resistant Depression

JAMES G. BARBEE, M.D., ERICH J. CONRAD, M.D., and
NOWAL J. JAMHOUR, M.A.

Department of Psychiatry, Louisiana State University Health Sciences Center, New Orleans, Louisiana

Background. Evidence is accumulating to support the use of atypical neuroleptics as adjunctive treatment for refractory mood disorders, although there are currently no published data on the efficacy of an atypical neuroleptic in treatment-resistant depression when a previous trial of drug from the same class has failed. The authors hypothesized that aripiprazole would be efficacious in augmenting antidepressant treatment in resistant patients with non-psychotic unipolar depression who had previously failed a trial of another atypical neuroleptic.

Methods. This study was a retrospective chart review of the efficacy of aripiprazole augmentation in 30 treatment-resistant unipolar depression patients who had failed multiple previous antidepressant trials and had also failed augmentation with at least one other atypical neuroleptic. Prospective Global Assessment of Functioning and Clinical Global Impressions—Improvement scores were completed on each patient throughout treatment.

Results. Utilizing an intent-to-treat analysis (including 9 patients who dropped out prior to completion of 6 weeks), 46.7% (14/30) patients were rated much improved or very much improved with treatment. This improvement negatively correlated with Thase-Rush staging of treatment resistance. GAF scores also showed a significant improvement. Six of the 14 patients who initially improved subsequently relapsed (yielding a long-term net response rate of 26.7%).

Conclusion. Aripiprazole may be effective as an antidepressant augmentation agent in highly treatment resistant patients who had failed a prior trial of another atypical neuroleptic.

Keywords Aripiprazole; Major depression; Treatment-resistant depression; Atypical neuroleptics; Augmentation; Dopamine receptors.

INTRODUCTION

Up to 34% of depressed patients who enter double blind, placebo controlled antidepressant trials exhibit either partial or no response to drug treatment (1). Estimates of the magnitude of this problem in clinical practice have ranged from 20% to 40% (2). Research shows that individuals who exhibit a partial response to antidepressant therapy continue

to demonstrate significant levels of functional impairment, are at increased risk of relapse, and are possibly at an increased risk of suicide as well (3,4). Thus, the development of novel treatment strategies for this patient population is a high priority.

Atypical neuroleptics are reported to be efficacious in the treatment of non-psychotic unipolar depression when used as augmentation agents. To date, their efficacy is demonstrated

Dr. Barbee is affiliated with Bristol Myers Squibb as a researcher, consultant, lecturer; Eli Lilly and Company as a researcher, consultant, lecturer; Forest Laboratories as a researcher, lecturer; GlaxoSmithKline as a researcher, consultant, lecturer; Merck as a researcher; Organon as a lecturer; Parke-Davis as a researcher; Pfizer, Inc. as a researcher, consultant, lecturer; Wyeth-Ayerst as a researcher, consultant, lecturer.

Dr. Conrad had been a speaker for Pfizer and has served as a sub-investigator in clinical research trials for GlaxoSmithKline, Lilly, Shire, Bristol-Myers Squibb and Johnson and Johnson.

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Address correspondence to James G. Barbee M.D., Louisiana State University Health Sciences Center, Department of Psychiatry, 1542 Tulane Avenue, Box T4-6, New Orleans, Louisiana, 70112. E-mail: jbarbe@lsuhsc.edu

in two double blind studies (5,6) and several open-label studies (7–10), as well as in case reports (11–14). There have not been any studies published to date regarding the effectiveness of switching from one atypical neuroleptic to another agent in this same class when one or more prior trials of similar agents have failed.

Aripiprazole is marketed in the United States for the treatment of schizophrenia. In addition to its properties as a partial agonist at the 5HT_{1A} receptor (15), aripiprazole is unique among the atypical neuroleptics in that it functions as a partial agonist at the dopamine receptor, endowing it with a mixture of both antagonist and agonist properties (16).

Drugs which function as partial agonists at the 5HT_{1A} receptor, such as buspirone and gepirone, have shown efficacy in major depression (17,18). Dopaminergic agents, such as the psychostimulants (19) and pramipexole (20,21) have also been shown to be effective as antidepressants either alone or in combination with other agents. We report here on the use of aripiprazole as an augmentation agent in a group of patients with treatment resistant depression, most of whom had failed trials of a number of antidepressants and/or augmentation agents. All of the patients in this study had previously failed augmentation trials with other atypical neuroleptics.

METHODS

Each of the patients included in this study was treated by the first author (JGB) in the setting of a fee-for-service psychiatric outpatient clinic. A systematic chart review was performed on all patients placed on aripiprazole augmentation during the course of their management for treatment resistant unipolar depression. IRB permission was obtained before the data collection was begun. All of the patients were previously evaluated utilizing a semi-structured diagnostic interview in which all of the major DSM-IV Axis I disorders were screened at the initial evaluation. Each patient qualified for a primary diagnosis of non-psychotic unipolar depression based on this interview. In order to be included in the study, patients must have failed at least one prior adequate trial of an antidepressant as defined by the Sackheim criteria (2), and at least one trial of an atypical neuroleptic other than aripiprazole as well, either due to lack of improvement or inability to tolerate the prior agent(s). Individuals with any lifetime history of hypomania or mania were excluded, as well as any patients with active alcohol or substance abuse within the past 12 months. None of these patients were psychotic or had a diagnosis of dementia.

Detailed information regarding the status of individual symptoms was collected at every visit. All concomitant medications and dosages were recorded at each visit, and adverse events were elicited and recorded at each visit as well. All of the patients who took even a single dose of aripiprazole and met the inclusion/exclusion criteria listed

previously were included in the analysis. Return visits were scheduled as necessary according to the judgment of the treating clinician (JGB). The response to aripiprazole was based upon the Clinical Global Impressions—Improvement Scale (CGI-I) (22) and the Global Assessment of Function (GAF) (23) score, recorded prospectively at each visit. These ratings were done by the treating clinician (JGB), who has extensive experience with these scales and their use in clinical trials.

In order to explore potential individual predictors of response to aripiprazole, descriptive and 2-tailed correlational analyses were performed on the following variables: age, sex, recurrence/chronicity of depression, duration of current episode, age at onset of depressive symptoms, number of prior depressive episodes, concomitant anxiety disorders, number of prior antidepressants, starting/maximum, and maintenance doses of aripiprazole, concomitant psychotherapy, GAF change scores, and CGI response scores. CGI response scores were measured on a 7-point scale, with -3 corresponding to a rating of “very much worse,” 0 corresponding to “no change,” and 3 corresponding to “very much improved.” GAF difference scores were computed by subtracting GAF ratings at visits immediately prior to augmentation from last observed GAF scores.

To determine whether response was related to dosage, the mean maintenance dose for responders (i.e., CGI \geq 2) was compared with that of non-responders using an independent-means t-test. To provide further explanation of response rates and patterns, descriptive statistics were obtained for time to reach improvement status, occurrence of loss of response to aripiprazole, and time to lose response.

In addition, the influence of degree of treatment resistance (as measured by Thase-Rush classification criteria) (24) on response was estimated by correlating response measures with Thase-Rush staging for the current depressive episode.

The hypothesis of interest for the current study was that aripiprazole augmentation would result in improvement among treatment-resistant depressed patients. Improvement was operationally defined as (1) CGI-Change rating of Much Improved or Very Much Improved, and (2) increase in GAF rating from baseline. The null hypothesis of no improvement was tested with a Chi-squared goodness-of-fit test, in which observed response rates were compared with zero-response rates. The null hypothesis of no mean change in GAF scores following augmentation was tested using a dependent-means t-test comparing pre-augmentation and last-observed GAF ratings.

RESULTS

Of the 30 individuals who met criteria for inclusion in the analysis, 24 (80%) were women and 6 (20%) were men. The mean age of the patients was 51.23 years (SD=8.98,

range: 33–69). All of the patients had current primary diagnoses of Major Depressive Disorder by DSM-IV criteria, with chronic courses specified for 9 patients and recurrent courses specified for 21 patients. Secondary comorbid anxiety disorders included Generalized Anxiety Disorder ($n=16$), Panic Disorder ($n=4$), Social Phobia ($n=2$), Obsessive-Compulsive Disorder ($n=2$), Post-Traumatic Stress Disorder ($n=2$), Specific Phobia ($n=1$) and Dysthymia ($n=3$). No patients had any other Axis I diagnoses. Three patients had comorbid chronic pain syndromes due to various medical conditions.

The patients included in this report had been on an average of 10.40 (range: 1–23) antidepressant trials prior to the initiation of aripiprazole (this figure includes trials of antidepressants conducted by other clinicians as reported by the patient at initial interview).

During treatment with aripiprazole, patients were on an average of 4 additional psychotropic medications (range: 1–8). In terms of antidepressant use, 13 patients were taking serotonin-specific reuptake inhibitors (SSRIs), 5 were taking tricyclic antidepressants (TCAs), and 17 were using other second-generation antidepressants, including venlafaxine ($n=6$), bupropion ($n=5$), mirtazapine ($n=3$), and trazodone ($n=3$). Five patients were using lithium, and 10 were on psychostimulants as well. Antidepressant augmentation strategies had been previously attempted for all patients. Many patients were taking concomitant anxiolytic medications, including 18 patients taking benzodiazepines, and 1 taking buspirone. Other concomitant psychotropic medications included anticonvulsants ($n=12$), neuroleptics ($n=12$), and zolpidem ($n=3$).

The mean duration of treatment observed on aripiprazole was 6.01 weeks (range 0.14–16 weeks). Of the 30 patients who began aripiprazole, 9 patients discontinued the drug prior to 6 weeks due to adverse events ($n=6$) or lack of efficacy ($n=3$). The most commonly reported adverse events during treatment were insomnia ($n=9$), restlessness/agitation ($n=4$), headache ($n=4$), tremor ($n=3$), nausea ($n=2$), and sedation ($n=2$). Other side effects included fatigue, word-finding difficulty, increased appetite, confusion, blurred vision, flushing, irritability, arthralgia, hypotension, rash and “flu-like symptoms” ($n=1$ for each adverse event).

Utilizing an intent-to-treat analysis, which included dropouts (i.e., those individuals who did not complete 6 weeks on the drug), 14 patients (46.7%) were rated as Much Improved or Very Much Improved, 7 (23.3%) as Mildly Improved, 7 (23.3%) as Unchanged, and 2 (6.7%) as Minimally Worse at the time of maximum improvement. Compared with a zero response rate, as would be expected in patients who are treatment resistant, the observed response rates differed significantly, $\chi^2(1)=370.68$, $p<0.001$. In the completer analysis, which excluded dropouts, the response rates were 52.6% (10/19), 26.3% (5/19), 15.8% (3/19), and 5.3% (1/19), respectively. Among those patients taking aripiprazole for at least 6 weeks, no significant difference in the maintenance doses taken by responders ($x=13.00$, $SD=3.79$) or non-responders ($x=16.67$, $SD=8.20$) was observed, $t(17)=1.31$, $p=0.21$. Responders were on aripiprazole for an average of 3.10 weeks ($SD=1.87$, range: 1–10) before obtaining CGI ratings of Much Improved. Six patients initially responded to aripiprazole augmentation according to the study criteria, but lost that response within periods of 5–16 weeks ($x=10.5$, $SD=3.94$).

Response rates for patients in each stage of the Thase-Rush classification system for treatment resistance are reported in Table I. For the intent-to-treat sample, stage of treatment resistance and CGI were significantly negatively correlated, $r(28)=-0.37$, $p<0.05$. For the completer sample, however, this relationship was non-significant, $r(17)=-0.25$, $p=0.30$.

Every patient in this study had previously failed at least one augmentation trial with an atypical neuroleptic. Numbers and percentages of aripiprazole responders who failed previous augmentation trials with each of four other agents are listed in Table II.

We grouped failure reasons into lack of efficacy (LOE) or an adverse event (AE) that led to the failure (Table II). The mean maximum dose and total duration of treatment for each previously attempted atypical neuroleptic that subsequently failed due to lack of efficacy or adverse event are reflected in Table III. Response rates to aripiprazole among patients who had failed prior trials of atypical neuroleptics due to lack of efficacy ranged from 30 to 50%, and 42 to 75% for those who had failed to tolerate the prior atypical agent. There also appeared to be no relationship between the

Table I Response Rates as a Function of Thase-Rush Classifications for Current Episodes

Stage	Description	Much or Very Much Improved	Mildly Improved	No Change or Worse
I	Failure of one adequate trial of an antidepressant	0% (0/3)	100% (3/3)	0% (0/3)
II	Failure of Stage I and one adequate trial of an alternative antidepressant from a different class	50% (4/8)	37.5% (3/8)	12.5% (1/8)
III	Failure of Stage II and an adequate trial of a tricyclic	70% (7/10)	10% (1/10)	20% (2/10)
IV	Failure of Stage III and an adequate trial of an MAOI	60% (3/5)	0% (0/5)	40% (2/5)
V	Failure of Stage IV and a trial of ECT	0% (0/4)	0% (0/4)	100% (4/4)

Table II Response Rates as a Function of Previous Neuroleptic Augmentation Failures Due to Lack of Efficacy (LOE) and Adverse Events (AE)

Previous Neuroleptic Augmentation Agent	Number (and %) Previous Failures Due to LOE Responding (CGI \geq 2) to Aripiprazole	Number (and %) Previous Failures Due to AE Responding (CGI \geq 2) to Aripiprazole
	Risperidone	7/14 (50%)
Olanzapine	3/6 (50%)	8/19 (42%)
Quetiapine	3/10 (30%)	3/4 (75%)
Ziprasidone	1/3 (33%)	4/9 (44%)

likelihood of response to aripiprazole and the number of failed prior atypical trials ($n=1$, 57%; $n=2$, 46%; $n=3$, 20%; $n=4$, 60%). There were no demographic or concomitant medication variables that allowed us to predict a subset of patient more likely to respond to aripiprazole.

The average GAF rating of the 30 patients who started the drug was 46.83 (SD=7.53, range: 38–80) at the beginning of the study, and the average GAF rating at the time of the last visit while on the drug (including those patients who discontinued treatment due to adverse events or lack of efficacy) was 51.61 (SD=7.09, range: 40–70). Results of the secondary analysis revealed a statistically significant improvement in GAF scores following treatment with aripiprazole, $t(27)=4.98$, $p<0.001$, with a mean GAF difference of 5.89 (SD=6.27, range: -5.00–20.00). No significant correlations were found between GAF difference scores and any demographic/disease-related variable.

DISCUSSION

To our knowledge this is the first report on the use of aripiprazole as an antidepressant augmentation agent in a population of patients with severe treatment-resistant, non-psychotic, unipolar depression. What is particularly intriguing about these findings is that all of the patients had previously failed at least one prior trial of another atypical antipsychotic, either due to lack of response or inability to tolerate the prior agent(s). In fact, three of the five patients

who had failed prior trials of all four of the other currently available atypical neuroleptics other than clozapine responded to aripiprazole. Thus, to our knowledge, this is also the first prospectively-based report to document the success of using an alternative atypical antipsychotic following the failure of another agent in this class.

Given that the patients in this trial were so treatment refractory, the initial response rate of 46.7% is quite encouraging. However, the eventual loss of response in six of the fourteen patients who initially improved deserves comment (this actually lowers the overall long-term response rate to 26.7%). It appeared to us that the most likely explanation of this loss of response was due to the adverse event profile that we encountered with the use of aripiprazole in this patient population. Persistent adverse events characteristic of increased central nervous system arousal (e.g., insomnia, restlessness/agitation) were reported by all six of the individuals who eventually lost their initial response to aripiprazole. The causal relationship between anxiety and increased arousal (particularly when they are chronic) and depression has been well documented (25). We began using aripiprazole in the dosages recommended for schizophrenia (10 to 15 mg). In retrospect, such dosages are likely not well tolerated in many depressive outpatients—we have subsequently learned that starting dosages of 2.5 to 7.5mg are much better tolerated. We have also learned that the aggressive use of medications with anxiolytic or hypnotic effects, such as the benzodiazepines, sedating anticonvulsants (e.g., tiagabine) and even, when necessary, sedating atypical neuroleptics (e.g., olanzapine, quetiapine) can help to maintain the initial response seen with aripiprazole.

This delay in the emergence of adverse events associated with aripiprazole may be due to either (1) the extremely long half-life of the drug or (2) the phenomenon of sensitization, which has been reported under conditions of repeated dosing with stimulant drugs such as cocaine and amphetamine. The half-life of aripiprazole is 75 hours, and that of its active metabolite, dehydro-aripiprazole, 94 hours (26). Although information in the package insert states that steady state levels are reached within 14 days for both active agents, it seems likely that this process could be prolonged in some individuals.

Table III Maximum Doses (in mg) and Duration of Treatment (in Weeks) of Each Agent for Patients Discontinuing Due to Lack of Efficacy (LOE) and Adverse Events (AE)

Agent	LOE					AE				
	N	Max Dose		Duration		N	Max Dose		Duration	
		Mean	SD	Mean	SD		Mean	SD	Mean	SD
Risperidone	12	1.29	0.96	22.5	21.79	3	0.50	0.00	17.67	20.11
Olanzapine	6	12.50	5.24	82.00	103.10	17	8.24	6.04	29.65	54.80
Quetiapine	9	288.89	312.78	34.33	44.58	4	137.5	75.00	12.50	13.30
Ziprasidone	3	93.33	61.10	14.00	12.49	8	20.00	18.52	7.88	6.24

In regard to the issue of sensitization, it is believed that this phenomenon may account for the progressive increases in anxiety and even paranoia associated with chronic stimulant use (27–29), as well as stimulant drug craving during abstinence (30,31). The biological basis of sensitization is quite complex, but it has been shown that the increases in extracellular levels of dopamine in the nucleus accumbens initially produced by psychostimulants are further augmented with repetitive exposure to these agents (32). These neurons project to the medial prefrontal cortex, where it is known that agonist activity at D₂ receptors reduces inhibitory activity of GABA-ergic interneurons that in turn connect with glutaminergic neurons in this structure (33). Glutamate is a major excitatory neurotransmitter in the brain, and has been implicated with angiogenesis in rats (34).

There are, of course, other possible explanations for the loss of improvement in a percentage of our patients. The first is the loss of a placebo effect, which seems unlikely, as the patients included in this sample had all been on multiple prior agents with little or no response at any time. However, the possibility of a placebo effect cannot be excluded, as improvements due to placebo are often transient. It may also be that aripiprazole, with partial agonist properties at the dopamine receptors, demonstrates the emergence of tolerance to the initial antidepressant effects of the drug, much like that seen at times with other dopaminergic agents, such as the psychostimulants. Given the 5HT_{1A} agonist properties of aripiprazole, it is also perhaps of note that such agents have been shown to cause an initial decrease in firing by serotonergic neurons (17), which may have exacerbated these patients' underlying symptoms of depression. This occurs by virtue of the fact that the 5HT_{1A} receptor is predominantly an inhibitory autoreceptor in structures such as the raphe nuclei, though it occurs only post-synaptically in serotonergic projections such as those in the hippocampus and cortex (35). It has been previously shown that with repeated administration of the 5HT_{1A} partial agonist buspirone, firing in the serotonergic cells of the raphe nuclei is inhibited, but that over time, the autoreceptor becomes desensitized, and the drug's effects at the postsynaptic receptor predominate (36). However, this explanation may not fit the time course of the phenomenon that we observed, in that the effects of such autoreceptor inhibition should be immediate in terms of blunting an antidepressant response, rather than delayed after a period of weeks.

In conclusion, we have shown aripiprazole to be a potentially useful augmentation agent in treatment resistant depression that improved symptoms with relative rapidity. Aripiprazole provided significant improvement in a group of patients who had previously failed one or more prior augmentation attempts with other atypical antipsychotic agents. The drug appeared to be well tolerated in a combination with a wide variety of other psychotropic agents, including

psychostimulants and lithium. Our findings must be considered tentative, as there are a number of important limitations in this study that must be considered. We cannot rule out the possibility of a placebo response due to the open-label design, and the lack of a control group. Also, there were no rating scale-based measures of the severity of the patients' depressive symptoms, either at baseline or follow-up. Visits were not scheduled at consistent intervals. Also, no measures were performed to document current or past medication compliance (such as blood levels or reports by family members). Finally, patients were not subtyped into categories of depression (atypical, melancholic), which would be of interest in further studies. However, further research is clearly indicated to evaluate aripiprazole's role in treating this refractory clinical population.

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