ORIGINAL RESEARCH

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An Open-Label Assessment of Aripiprazole in the Treatment of PTSD

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ABSTRACT ~ Background: *Recent studies suggest that atypical antipsychotics may be effective augmentation strategies for the treatment of posttraumatic stress disorder (PTSD). Limited data were available on the newest agent, aripiprazole, so we aimed to evaluate its efficacy and tolerability in the treatment of PTSD.* ***Methods:*** *A 12-week, prospective, open-label, flexible-dose, adjunctive trial of aripiprazole was conducted in military veterans meeting DSM-IV criteria for PTSD. Concomitant psychiatric medications continued unchanged, except for other neuroleptics which were not allowed. The primary outcome variable was change from baseline in the Clinician Administered PTSD scale (CAPS).* ***Results:*** *All 17 subjects were male, with an average age of 57 years. Total CAPS scores decreased from 78.2 (SD = 17.8) at baseline to 60.0 (23.5) at study end (p = 0.002). Re-experiencing (CAPS-B) and avoidance/numbing symptoms (CAPS-C) were significantly improved, and trend level reductions were observed in hyperarousal symptoms (CAPS-D). Fifty-three percent (9/17) were considered responders, as defined by a decrease in total CAPS scores of at least 20%. Reductions in the Positive and Negative Symptom Scale (PANSS) total score and positive and general psychopathology subscale scores were statistically significant. The final average dose of aripiprazole was 13.06 (SD = 6.45) mg daily. Nine patients discontinued because of side effects. The most common adverse events consisted of gastro-intestinal disturbances, sedation, and psychomotor activation. Tolerability was improved with lower starting doses (e.g., 5 mg daily) and slow titration.* ***Conclusions:*** *Addition of aripiprazole to ongoing treatment further reduced PTSD symptoms in military veterans with severe PTSD. These preliminary findings await confirmation in randomized, controlled trials.* Psychopharmacology Bulletin. *2009;42(1):69–80.*

INTRODUCTION

Post-traumatic stress disorder, or PTSD, is an anxiety disorder that can develop after severe psychological trauma. The general population lifetime prevalence of PTSD is approximately 8%, while the lifetime prevalence among Vietnam combat veterans is 30%.[1,2] PTSD is an anxiety disorder characterized by three symptom clusters: re-experiencing of the traumatic event; avoidance of stimuli

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associated with the trauma and numbing of general responsiveness; and hyperarousal symptoms.[3] Beyond these symptoms, PTSD is often associated with other psychiatric disorders, namely substance use disorders, depression, and anxiety disorders.[1,4,5] Work by our group and others has demonstrated that combat veterans with chronic PTSD may also have a high prevalence of associated psychotic features including auditory and visual hallucinations and other positive symptoms.[6–9] These symptoms may reflect greater PTSD illness burden and conceivably contribute to more refractory illness.[10,11]

Several controlled trials have demonstrated the efficacy of different antidepressants in the treatment of PTSD.[12–16] Two selective serotonin reuptake inhibitor (SSRI) antidepressants, sertraline and paroxetine, are currently FDA-approved for this indication. However, many patients, especially male veterans, have partial or minimal benefits from antidepressants.[17–19] Other treatment alternatives are often needed to provide relief from various PTSD symptoms. Recent practice guidelines suggest that the combination of anxiolytics, antidepressants, mood stabilizers and antipsychotics may be useful.[20]

Preliminary data have suggested a role for atypical antipsychotics in the treatment of PTSD symptoms and associated psychotic features.[21–36] Our open trial of adjunctive quetiapine demonstrated significant improvement in PTSD and depressive symptoms in veterans who had had at best a partial response to prior treatments.[25] Controlled studies with risperidone and olanzapine have confirmed these preliminary results although there have been two negative controlled studies in civilian PTSD.[26,37–43] Published reports on the efficacy of aripiprazole in the treatment of PTSD consist of a case report,[44] a small case series,[45] and an open trial.[46]

Dopamine and serotonin are likely critical neurotransmitters in the psychobiology of PTSD.[47] Aripriprazole is a novel agent that, unlike other classes of antipsychotics, shows partial agonist activity at D2 receptors and 5HT1A receptors, and antagonist activity at 5-HT2A receptors.[48] It is efficacious against both positive and negative symptoms of schizophrenia with less risk for extrapyramidal side effects than traditional antipsychotics.[49,50] Its efficacy has also been demonstrated in the treatment of acute mania and in the prevention of manic relapse.[51]

Based on its pharmacology, and on positive findings with other atypical antipsychotics, we hypothesized that aripiprazole would be efficacious for core PTSD symptoms, and for psychotic symptoms (if present), and would be well tolerated in this patient population. In view of the preliminary nature of this investigation, and to reflect clinical practice, we conducted a 12-week, open-label adjunctive trial of aripiprazole in patients meeting DSM-IV criteria for PTSD who had been minimally or partially responsive to their existing medications.

METHODS

Subject Inclusion/Exclusion Criteria

Subjects were recruited predominantly through the PTSD clinic but also through other outpatient clinics at the Ralph H. Johnson VA Medical Center. The protocol was approved by the Institutional Review Board, and all study-related procedures were performed after patients signed informed consent.

Patients had to meet the following inclusion criteria: 1) outpatients 18 years of age or older; 2) competence to give written informed consent; 3) meeting DSM-IV criteria for PTSD; 4) negative pregnancy test and using a medically approved contraceptive method for females of child-bearing age. A minimum Clinician Administered PTSD Symptom Scale (CAPS) score was not required for entry into the study.[52]

Patients were excluded from the study if they had any of the following: 1) history of sensitivity to aripiprazole; 2) medical disorders that may cause or exacerbate anxiety symptoms; 3) unstable medical conditions; 4) alcohol or drug abuse or dependence within one month of study entry; 5) DSM-IV diagnoses of schizophrenia, schizoaffective disorder, or bipolar disorder; 6) active suicidality or homicidality or other clinically significant dangerousness.

Study Procedures

During the screening visit, subjects received a comprehensive psychiatric evaluation, physical examination, electrocardiogram, and laboratory tests (complete blood count with white count differential, serum electrolytes, glucose, creatinine, blood urea nitrogen, liver function tests, urinalysis and urine drug screen). Efficacy and safety assessments, including vital sign measurements and recording of adverse events, were performed bi-weekly until week 8 and then at week 12. Movement disorder side effects were evaluated at the first and last visits by using the Abnormal Involuntary Movement Scale (AIMS),[53] Simpson-Angus Scale (SAS),[54] and Barnes Akathisia Scale (BAS).[55]

The initial dose of aripiprazole was 15 mg daily in the original protocol, based on data in schizophrenia and bipolar disorder populations as no information was available at the time in PTSD. After evidence of poor tolerability within the first 6 months of the study, the starting dose was subsequently reduced to 5 mg daily, with further dose titrations based on tolerability and clinical response, up to a maximum of 30 mg daily. The lower starting dose was chosen to enhance tolerability and retention of subjects. When clinically significant improvement was not observed, we were aggressive in increasing to a maximum tolerated dose (no greater than 30 mg daily) so that we would not miss a signal for response.

Antidepressants, anxiolytics, and thymoleptics were allowed but had to be kept at a constant dose for one month prior to study entry and during the treatment phase of the study. Other antipsychotics were not allowed during the study, and were discontinued at least one week prior to study initiation.

Outcome Variables

The primary efficacy variable was the global score on the CAPS-SX.[52] A priori response to aripiprazole was defined as a 20% or greater reduction in the CAPS from baseline. Secondary efficacy measures included the Clinical Global Impression Severity and Improvement (CGI-I and CGI-S) scales,[56] the Positive and Negative Syndrome scale (PANSS),[57] the Hamilton Depression rating scale (HAM-D),[58] the Davidson Trauma scale (DTS),[59] the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[60] the Pittsburgh Sleep Quality Index (PSQI)[61] and Addendum for PTSD (PSQI-A).[62] PTSD and comorbid diagnoses were assessed with the Structured Clinical Interview for DSM-IV (SCID).[63]

All efficacy measures were administered at baseline and week 12 (or end of study for early terminations). The CAPS-SX, CGI-S, CGI-I, PANSS, HAM-D and DTS were also administered at weeks 2,4,6,8, and 12. The Q-LES-Q and PSQI were administered on a monthly basis throughout the study period.

Statistics

Published literature with the CAPS as an efficacy variable in assessing treatment of PTSD with novel psychotropic agents suggests an average baseline CAPS score of 83 ± 17, which is similar to what is found in our patient population.[11,25,33,64] Assuming that at least a 20 percent decrease from baseline to final clinic visit in the CAPS would be clinically significant, an N of 20 patients would yield an 83% power to detect significant differences at the $p < 0.05$ level using a 2-tailed test (assuming a standard deviation of differences to be 24.5). Although response to treatment has been defined as a 30% reduction in CAPS score in large clinical trials with sertraline and paroxetine, we chose a more conservative 20% reduction for our veteran population since their PTSD, predominantly combat-related, is often less responsive to treatment.

For the primary outcome, the Wilcoxon signed rank test was used to determine the statistical significance of the change from baseline in CAPS scores. The last-observation-carried-forward (LOCF) method was used to assign missing Week 12 CAPS score the most recent non-missing observation for that subject. To evaluate sensitivity of the conclusions to the presence of missing data, the CAPS total score was analyzed using only the data from subjects that adhere to the study protocol. Secondary

assessments included the use of the Wilcoxon signed rank test to determine the statistical significance of the change in secondary assessment scale scores from baseline to final visit. Responders were defined as subjects that had at least a 20% decrease from baseline in CAPS total score. Descriptive statistics and baseline values for demographics, clinical and outcome variables are provided for the enrolled population.

RESULTS

Demographics and Clinical Characteristics

All subjects were male, with an average age of 57 years. Demographics of the study population are presented in Table 1. All patients had combat-related PTSD. Twelve patients (60%) had comorbid major depressive disorder.

Treatment Efficacy

Seventeen of 20 patients had at least one post-baseline efficacy evaluation thus were included in the efficacy analysis. Total CAPS scores decreased from 78.2 (SD = 17.8) at baseline to 60.0 (23.5) at study end ($p = 0.002$). Re-experiencing (CAPS-B) and avoidance/numbing symptoms (CAPS-C) were significantly improved, and trend level reductions were observed in hyperarousal symptoms (CAPS-D) (Table 2). Reductions in PANSS total score and positive and general psychopathology subscale scores were statistically significant, with a trend level decrease noted in the negative subscale score (Table 2). Seven patients (41%) had a score of 4 or greater on at least one of the critical PANSS positive items and were categorized as having psychotic symptoms. Although their baseline CAPS and PANSS global ratings were numerically higher, they exhibited the same pattern of improvement on the CAPS and PANSS as the other 10 patients who were not classified as having psychotic symptoms.

Fifty-three percent (9/17) were considered responders, based on our a priori definition of 20% or greater decrease in total CAPS scores, or 41% (7/17) if defined as a 30% or greater reduction in CAPS scores. The CGI-S decreased significantly from baseline to endpoint (Table 2). Seventy-six percent (5/13) of patients improved based on the CGI-I, of which 38.5% (5/13) were much or very much improved. Changes in other secondary outcomes were not statistically significant (Table 2).

Withdrawals

Eleven subjects discontinued early: one due to unsatisfactory response, and one because of disorientation unrelated to study medication. The other nine patients discontinued because of side effects: two

TABLE 1

BASELINE CHARACTERISTICS OF STUDY POPULATION

	N = 20
Age (SD)	56.6 (6.5)
Gender, N (%)	
Male	20 (100)
Female	0
Marital Status, N (%)	
Married	18 (90)
Single	1 (5)
Divorced	1 (5)
Race, N (%)	
Caucasian	11 (55)
African-American	9 (45)
Employment, N (%)	
Disabled	11 (55)
Full-Time	5 (25)
Retired	2 (10)
Unemployed	2 (10)
Education, years (SD)	13.25 (2.65)
Type of trauma, N (%)	
Combat	20 (100)
Comorbid Psychiatric Disorders, N (%)	
Current Major Depressive Disorder	12 (60)
Lifetime Major Depressive Disorder	11 (55)
Lifetime Alcohol Abuse/Dependence	7 (35)
Lifetime Drug Abuse/Dependence	1 (5)

due to sedation; one each due to psychomotor activation, irritability, diarrhea, rash, non-cardiac chest pains, hyperglycemia; and one due to weakness, stomach upset, and headaches.

Dose and Tolerability

The final average dose of aripiprazole was 13.06 (SD = 6.45) mg daily. Mean weight decreased by 4 lbs (SD 4.7) from a baseline mean of 215.7 lbs. There were no significant changes in abnormal movement scales between baseline and endpoint. The most common adverse events consisted of gastro-intestinal disturbances (n = 10), sedation (n = 6), restlessness (n = 5), insomnia (n = 4), irritability (n = 4), nervousness (n = 2), dizziness (n = 2), headaches (n = 2), and difficulty concentrating (n = 2). Tolerability was improved with lower starting doses (e.g., 5 mg daily) and slow titration in the last 7 patients enrolled.

Concomitant Psychiatric Medications

Fourteen subjects (82%) were taking an antidepressant, most commonly an SSRI (10/17, 59%). Seven patients (41%) were taking a hypnotic.

TABLE 2

EFFECT OF ARIPIPRAZOLE TREAMENT ON PRIMARY AND SECONDARY EFFICACY MEASURES (LOCF)

OUTCOME MEASURE	BASELINE SCORE (SD) (N = 17)	FINAL SCORE (SD) (N = 17)	P VALUE
CAPS Total	78.2 (17.8)	60.0 (23.5)	0.002
CAPS-B	20.1 (7.8)	13.5 (8.9)	0.005
CAPS-C	31.3 (9.3)	24.2 (11.9)	0.002
CAPS-D	26.9 (4.8)	22.3 (7.4)	0.061
HAM-D	20.4 (6.6)	17.3 (8.9)	0.104
PANSS	60.8 (10.8)	50.9 (11.6)	0.0002
Positive	12.9 (4.2)	10.0 (2.7)	0.0002
Negative	14.3 (4.4)	12.6 (4.3)	0.0537
General	33.6 (10.8)	28.2 (6.7)	0.0002
CGI-S	4.9 (0.8)	4.1 (0.8)	0.002
DTS	94.3 (25.6)	86.6 (29.0)	0.179
Q-LES-Q	37.8 (7.2)	37.1 (8.4)	0.659
PSQI	14.8 (2.9)	13.8 (3.3)	0.346
PSQI-A	10.8 (4.2)	10.2 (5.6)	0.603

Only one patient was on no other psychotropic medication (6%). Seventeen patients (85%) had been previously treated, with an average of 1.5 therapeutic antidepressant trials.

DISCUSSION

In this open-label study, the addition of aripiprazole to ongoing treatment lead to improvement in PTSD symptomatology. These results are encouraging given the chronicity and severity of illness of the study population, and their minimal or partial response to current or prior therapeutic agents. The majority of subjects (17/20, 85%) had been previously treated, with an average of 1.5 therapeutic antidepressant trials. Most patients were already taking an antidepressant at baseline (14/17, 85%); however, despite treatment, all continued to experience clinically significant PTSD symptoms. Although no minimum CAPS score was specified for entry into the study, all subjects had scores greater than 60, reflecting severe PTSD symptomatology (mean baseline CAPS 78.2), except for two subjects who had moderate PTSD symptoms (CAPS of 53 and 57 each).

Aripiprazole treatment lead to a significant reduction in PTSD symptoms overall, with specific improvement noted in re-experiencing and avoidance/numbing symptom clusters. Psychomotor activation, experienced by a majority of patients (n = 10, 59%), may have mitigated the effect on hyperarousal symptoms, potentially explaining the trend level improvement but lack of statistical significance observed. Fifty-three percent (9/17) met criteria for response on the CAPS

(decrease in total CAPS scores of at least 20%). These findings are consistent with results from a small case series in OIF veterans with PTSD[45] and an open-label trial of aripiprazole monotherapy in veterans with PTSD,[46] although the latter showed a significant improvement in hyperarousal symptoms despite a high incidence of restlessness, insomnia and anxiety (50%, 36.4% and 27.3%, respectively).

Emerging data suggest that several atypical antipsychotics may be effective in the treatment of refractory depression. Response rates between 60 and 70% and remission rates of 30 to 50% have been observed in open-label augmentation studies of aripiprazole in partially responsive and treatment-resistant depression,[66–72] while placebo-controlled studies have yielded lower response and remission rates (approximately 33% and 25%, respectively).[73,74] Aripiprazole is now FDA-indicated as augmentation therapy in the treatment of major depressive disorder. Positive effects on depressive symptoms in PTSD populations have also been observed in an open-label trial[33,34] and a controlled study with olanzapine,[41] two open-label trials with quetiapine[21,25] and an open-label study of aripiprazole.[46] Villarreal et al evaluated aripiprazole monotherapy in 22 veterans with PTSD. In addition to significant reductions observed on the CAPS, PANSS, and HAM-A, average HAM-D scores decreased from 20.68 at baseline to 14.50 at week 12 ($p < 0.01$ with Bonferroni correction). Our study was very similar in terms of trauma population and baseline severity of illness. The reduction in depressive symptomatology measured by the HAM-D, although numerically lower at the end of the study, did not reach statistical significance, however. Differences in study design (ours was adjunctive to other psychotropics, mainly antidepressants) and ethnicities (Caucasian/African-American in our study versus Caucasian/Hispanic in Villarreal et al's study) may have accounted for the different results observed. Additional studies are needed to delineate the effects of aripiprazole on depressive symptoms that are comorbid with PTSD.

The reduction in PANSS ratings observed in this study is consistent with our risperidone[26] and quetiapine[25] studies, as well as with work by other investigators with risperidone,[22,27,37] quetiapine,[28] olanzapine,[35] and aripiprazole.[46] Among combat veterans with PTSD, 30 to 40% have psychotic symptoms that are distinct from PTSD-specific perceptual disturbances in the absence of psychotic disorders such as schizophrenia or bipolar disorder.[7,8,75] These psychotic symptoms may or may not be trauma-related, and have been associated with higher levels of general psychopathology, paranoia, violent thoughts, feelings and behavior, and greater overall burden of illness.[10,76] The improvement in PANSS Positive subscale observed in this study suggest that aripiprazole

improves psychotic symptoms in this population, while reduction in the PANSS General Psychopathology subscale indicate improvement in a broader range of symptoms.

It is notable that sleep difficulties as measured by the PSQI did not change significantly from baseline to endpoint. This is important since sleep disturbances are often the more refractory symptoms in PTSD. Future studies should carefully explore the effects of aripiprazole on specific sleep parameters as well as global PTSD symptoms.

Cautious interpretation of our findings is warranted given the limitations of this study. This was a preliminary, open-label study, with a small sample size further reduced by a high drop-out rate. An initial starting dose of 15 mg daily was selected in the original protocol based on data from schizophrenia and bipolar disorder trials, which were the only data available at the time. The starting dose was eventually reduced to 5 mg daily after evidence of poor tolerability and ensuing early terminations from the study. The lower starting dose resulted in a better retention rate (5/7 versus 6/13 drop-outs, before and after change in starting dose, respectively). Bipolar depression,[77] treatment-resistant depression[66,70] and PTSD[46] studies have also noted high attrition rates due to poor tolerability, namely due to restlessness or akathisia. Lower starting doses appear to be associated with lower discontinuation rates.[70] The beneficial effects of aripiprazole observed in this study are noteworthy, given the overall high drop-out rates, conservative LOCF data analysis, and our chronic, relatively resistant PTSD population. Most subjects (76.9%, 10/13) improved with the addition of aripiprazole, with 38.5% (5/13) rated as much or very much improved. Double-blind, placebo-controlled studies using lower starting doses and possibly lower target doses are needed to confirm our findings and further delineate the usefulness of aripiprazole in the treatment of PTSD.✤

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