ORIGINAL RESEARCH
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Prospective Study to Evaluate the Efficacy of Aripiprazole as a Monotherapy in Patients with Severe Chronic Posttraumatic Stress Disorder: An Open Trial

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ABSTRACT *~ The objective of the study was to assess the efficacy and safety of aripiprazole in outpatients with posttraumatic stress disorder (PTSD) on a 12-week, open-label trial. Twenty-two subjects with DSM-IV diagnosis of PTSD participated; 16 were combat veterans. The primary outcome measure was PTSD symptom severity assessed with the Clinician Administered PTSD Scale (CAPS). Secondary outcome measures included the Positive and Negative Symptoms Scale and the Hamilton Depression and Anxiety Scales. All subjects had a CAPS score of ≥ 60 at baseline. Lifetime history of psychotic disorders or bipolar illness was exclusionary. The overall analysis across time was Repeated Measures ANOVA, using Bonferroni corrections. Fourteen subjects completed 12 weeks of treatment. Eight subjects dropped-out due to side effects. For patients who discontinued, missing values were estimated using "the last observation carried forward" method. Significant improvements were seen on: CAPS total, all its subscales, positive symptoms, anxiety and depression scores. Fourteen participants were classified as responders, defined by 20% or greater improvement on CAPS total score. Of the 13 subjects who completed final ratings, CAPS total scores improved significantly (P = .011). Two subjects attained remission of PTSD (CAPS < 20), and three had a final CAPS ≤ 26. The mean daily dose of aripiprazole was 12.95 mg. The most common side effects were somnolence (54.5%), restlessness (50%), insomnia (36.4%), and asthenia (31.8%). These*

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results indicate that aripiprazole was effective in about two thirds of subjects that tolerated this medication. The initially high dropout rate may be related to intolerability due to a high starting dose (10 mg), suggesting beginning treatment at lower doses. These preliminary results are encouraging; a double blind study seems warranted. Psychopharmacology Bulletin. *2007;40(2):6-18.*

INTRODUCTION

Posttraumatic Stress Disorder (PTSD) is a common anxiety condition that affects individuals who have been exposed to psychological trauma, such as combat or rape. Characteristic symptoms encompass reexperiencing memories of traumatic events, persistent avoidance of stimuli associated with the trauma, numbing of general responsiveness, and persistent hyperarousal.[1] The general population lifetime prevalence of PTSD is ~8% or up to 25 million individuals in the United States,[2] while the lifetime prevalence of PTSD among Vietnam combat veterans is about 30%.[3] A recent reanalysis of the National Vietnam Veterans Readjustment Study (NVVRS) adjusted the lifetime prevalence of PTSD among Vietnam veterans at 18.7% with 9.1% who are currently suffering from PTSD.[4] PTSD has a significant impact on a person's well being and is often associated with increased health service utilization, poor social and occupational functioning, and substantial cost to society, especially among people who experience combat trauma or sexual assault.[5–7] Hoge and et al.[8] in their recent survey reported that 12.2–12.9% of active-duty veterans returning from Iraq met screening criteria for PTSD as compared with their Afghanistan counterparts (6.2%) that correlated directly with rates of combat exposure. Treatment guidelines for PTSD cite a group of selective serotonin reuptake inhibitor (SSRI) antidepressants as the first line of treatment.[9,10] Currently, there are two SSRI (sertraline and paroxetine) that are U.S. FDA-approved for PTSD.[10] However, many chronic PTSD patients, especially male combat veterans, have a partial or minimal response to antidepressants.[11–14] These studies underscore that PTSD among combat veterans is difficult to treat and often requires additional psychotropic medications.[11,15] In addition, there is an evidence that 36–46% of patients with PTSD also suffer from psychotic symptoms.[16–19]

There is an increasing interest in the use of atypical antipsychotics (AAP) to treat PTSD. A series of double-blind, placebo-controlled studies of AAP as adjunct treatment in PTSD report benefit from risperidone.[20–23] Only one of these studies focused on PTSD patients with psychotic symptoms.[21] An 8-week, double-blind, placebo-controlled study demonstrated that adjunctive olanzapine was effective in reducing PTSD symptoms and depression in combat veterans with

PTSD without psychotic symptoms who had minimal response to an SSRI.[24] Open-label trials of risperidone,[25] olanzapine,[26] and quetiapine[27] also reported beneficial effects. In another study, olanzapine was not superior to placebo.[28]

PTSD is probably associated with abnormalities in serotonin, norepinephine, and dopamine systems, among others.[29] Aripiprazole is a novel and efficacious antipsychotic with 5-HT_{2A} antagonist effect and partial agonist activity at the 5-HT_{1A} and D_2 receptors, which may confer a favorable effect on anxiety along with less extrapyramidal symptoms.[30,31] Aripiprazole has been proven effective in schizophrenia and was not associated with extrapyramidal side effects, prolactin elevation, weight gain, or QT_c interval prolongation as compared with placebo.[32,33] A recent report indicated that four out of five PTSD cases benefited from open-label aripiprazole treatment,[34] indicating the potential usefulness of this medication in PTSD. The pharmacological profile of aripiprazole, the insufficient evidence about its efficacy in PTSD and the hopes that it may be an effective compound among veterans who appear not to respond to FDA-approved agents led us to study its efficacy in PTSD in the hopes of eventually conducting a double-blind study. To our knowledge, this is the first monotherapy design clinical trial of aripiprazole using standardized rating scales in the treatment of PTSD. We report the results of a twelve-week, open-label, flexible dose trial of aripiprazole monotherapy conducted to assess its efficacy in core PTSD symptoms and associated psychiatric symptoms, including anxiety, depressive and positive psychotic symptoms.

METHOD

Patient Selection

Subjects were recruited from the New Mexico VA Health Care System. All participants signed an Institutional Review Board-approved consent. The Protocol including the Informed Consent was approved by the New Mexico VA Health Care System Research and Development Committee and by the University of New Mexico Human Research Review Committee. The inclusion criteria were: 1) male or female patients ages 18–65 of any ethnic background meeting DSM-IV criteria for PTSD; 2) score of at least 60 on the Clinician Administered PTSD Scale (CAPS-SX[35]) at baseline; 3) competent to give informed consent; 4) female, patients using a medically approved contraceptive, or not otherwise be of childbearing potential; and 5) patients who have not taken psychotropic medications (medications for a psychiatric indication) within 1 week prior to the baseline visit (treatment phase), or 2 weeks prior in the case of fluoxetine.

Patients were excluded from the study if they met any of the following: 1) history of sensitivity to aripiprazole; 2) medical conditions that could prevent safe administration of aripiprazole including clinically significant hepatic, cardiac, or pulmonary disease; 3) medical disorders that could cause or exacerbate anxiety symptoms; 4) alcohol or drug abuse or dependence within 1 month of study entry as defined by DSM-IV criteria; 5) schizophrenia, schizoaffective disorder, or bipolar disorder; or 6) suicidal or homicidal ideation or other clinically significant dangerousness.

None of the subjects had an initiation or change in psychotherapy and were not involved in exposure based psychotherapy within the last 3 months prior to the baseline visit or throughout the study. No subjects were seeking compensation for the effects of trauma during the study.

Study Flow

During visit 1, the screening visit, patients received a comprehensive psychiatric evaluation as well as a physical and neurological examination, and laboratories (see below) if indicated by the medical history. Eligible patients then started a 1-week washout phase (2 weeks if the patient was taking fluoxetine). Visit 2 involved baseline efficacy and safety assessments. Patients with CAPS score less than 60 were excluded.

Patients who continued to meet study criteria were started on aripiprazole 10 mg Q.D. and were seen for follow-up visits at weeks 1, 2, 4, 8, and 12, with weekly contact (either by phone or office visit) for monitoring if needed. At each visit the dose of aripiprazole could be lowered due to side effects or increased due to lack of efficacy, within a range of 5–30 mg daily in increments of 5–10 mg. Concomitant use of lorazepam up to 3 mg daily was allowed for agitation, anxiety, or insomnia during washout and the first 2 weeks of treatment. Patients requiring continued use of lorazepam after 2 weeks of active study participation were discontinued from the protocol. Adherence to treatment was evaluated at each study visit by patient interview and pill count of medication returned.

Efficacy Measures and Safety Assessments

The primary efficacy variables were the CAPS total score, the Clinical Global Impressions Scale-Severity of Illness (CGI-S), and the Clinical Global Impressions Scale for Improvement (CGI-I). Additional secondary assessments included the CAPS re-experiencing (CAPS-RXP), avoidance/numbing (CAPS-AVD), and hyperarousal (CAPS-HYP) symptom cluster scores. The Positive and Negative Symptoms Scale (PANSS)[36] was a secondary outcome measure to assess psychosis, including PANSS-total score, PANSS Positive symptoms subscale

(PANSS-P), PANSS Negative symptoms subscale (PANSS-N), and PANSS General Psychopathology subscale (PANSS-G). Other secondary measures were: the 17-Item Hamilton Rating Scale for Depression (HAM-D), Hamilton Rating Scale for Anxiety (HAM-A), the patient self-rated Davidson Trauma Scale (DTS),[37] the Pittsburgh Sleep Quality Inventory (PSQI),[38] and the Arizona Sexual Experiences Scale (ASEX).[39] Response to aripiprazole was defined as a 20% or greater reduction in the CAPS total score. PTSD diagnosis and comorbidity were established using the CAPS-DX and the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-CV).[40] Movement disorder rating scales were performed at baseline and weeks 4, 8, and 12 and included the Abnormal Involuntary Movement Scale (AIMS),[41] Simpson-Angus Scale (SAS),[42] and Barnes Akathisia Scale (BAS).[43]

Adverse events and vital signs were evaluated at each visit. Prior to beginning the study a physical exam, electrocardiogram, and clinical laboratories were obtained if indicated by the medical history. Clinical laboratories included serum electrolytes, creatinine, blood urea nitrogen, glucose, liver function tests, complete blood cell count and differential white cell count, urinalysis, and urine drug screen.

Data Analysis

The overall analysis across the six time-measures was a Repeated Measures (RM) ANOVA. If there was a significant change over time, then post hoc paired *t*-tests were used to determine the time course. This analysis was generalized to handle occasional missing values by using SAS's PROC MIXED. In addition, missing values due to dropouts were estimated using the last observation carried forward (LOCF) method. Each of the secondary outcome measures were analyzed in a similar manner. Bonferroni corrections were made to protect against type I errors caused by multiple comparisons.

RESULTS

Patients

Twenty-two subjects met study criteria and were enrolled in the study. Demographic characteristics of the sample are presented in Table 1.

Efficacy

Fourteen subjects completed 12 weeks of treatment, however one of these subject missed his 12th week evaluation due to a relapse of alcohol caused by marital stress and threat of divorce and was subsequently hospitalized, the subject recovered and was discharged. Therefore, only

TABLE 1

DEMOGRAPHIC CHARACTERISTICS TOTAL SAMPLE ($n = 22$)

CHARACTERISTIC	MEAN	SD
Age	51.32	9.94
Gender	N	%
Male	18	81.8
Female	4	18.2
Race		
Caucasian	13	59
Hispanic/Native American	9	41
Type of Trauma		
Combat-Related	16	73
Military Sexual Trauma (MST)	4	18
Other	2	9
Comorbid Psychiatric Diagnoses		
Major Depressive Disorder	14	64
Depression NOS	1	5
Panic Disorder	6	27
Alcohol Abuse/Dependence in Remission	15	68
Substance Abuse/Dependence in Remission	5	23

13 subjects were included in the separate analysis of completers. There were no statistically significant differences in baseline scores between completers and noncompleters across all rating scales (*t*-test, all *P*-values > .27). For patients who completed the study, baseline values were compared to week 12 values. For patients who discontinued the study, missing values were estimated using the last observation carried forward (LOCF) method. RM ANOVAs showed a significant improvement between baseline and final visit for the following measures: CAPS total and all CAPS subscales, PANSS total, PANSS positive and PANSS general psychopathology subscales, HAM-D, HAM-A, and patient self administered DTS scale scores (see Table 2). Also, there was an increase in sleep duration and an improvement in the PTSD component of the Pittsburgh Sleep Quality Index (PSQI). These results held when a "conservative" Bonferroni correction was made [0.05/13 = 0.004; 0.01/13 = 0.0008] except for the improvement of sleep duration and the PTSD component of the PSQI (see Table 2). The CAPS-total scores showed significant improvement between every study visit, except between week 4 and 8 (see Figure 1). A separate analysis was conducted for the 13 subjects that completed evaluations through week 12. As shown in Table 3, most of the clinical variables also showed significant improvement by the end of the trial.

TABLE 2

CHANGES IN CLINICAL VARIABLES FOR ENTIRE SAMPLE FROM BASELINE TO FINAL VISIT INCLUDING LAST OBSERVATION CARRIED FORWARD (LOCF) *N* = 22

VARIABLE	BASELINE MEAN (SE)	WEEK 12 MEAN (SE)	SIGNIFICANCE
CAPS-RXP	17.41 (1.62)	10.59 (2.02)	.001**[a]
CAPS-AVD	32.73 (1.59)	23.68 (2.60)	.000**[b]
CAPS-HYP	24.77 (0.77)	17.73 (1.62)	.000**[b]
CAPS-Total	74.91 (2.68)	52.00 (5.41)	.000**[b]
PANSS-P	14.09 (0.72)	11.73 (0.54)	.002**[a]
PANSS-N	14.23 (0.98)	13.54 (0.92)	.266
PANSS-G	36.73 (0.93)	30.32 (1.27)	.000**[b]
PANSS-Total	64.81 (1.89)	56.05 (2.37)	.000**[b]
HAM-D	20.68 (1.16)	14.50 (1.29)	.000**[b]
HAM-A	22.59 (1.03)	16.73 (1.45)	.002**[a]
DTS	82.82 (5.48)	61.59 (7.65)	.001**[b]
Sleep Duration (PSQI)	2.11 (.212)	1.61 (.231)	.008**
PTSD Component (PSQI)	13.68 (1.48)	9.74 (1.82)	.019*

CAPS-RXP, CAPS reexperiencing subscale; CAPS-AVD, CAPS avoidance/numbness subscale; CAPS-HYP, CAPS hyperarousal subscale; PANSS-P, PANSS positive subscale; PANSS-N, PANSS negative subscale; PANSS-G, PANSS general subscale; HAM-D, Hamilton Depression Rating Scale; HAM-A, Hamilton Anxiety Scale; DTS, Davidson Trauma Scale; PSQI, Pittsburg Sleep Quality Index (note: this is a composite score, lower numbers indicate more hours of sleep).
RM ANOVA $^{**}P < .01$, $^{*}P < .05$.
[a]Retains significance at $P < .05$ level with Bonferroni correction.
[b]Retains significance at $P < .01$ level with Bonferroni correction.

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The total daily dose of aripiprazole ranged from 5 to 30 mg with a mean dose of 12.95 mg (SD 4.27).

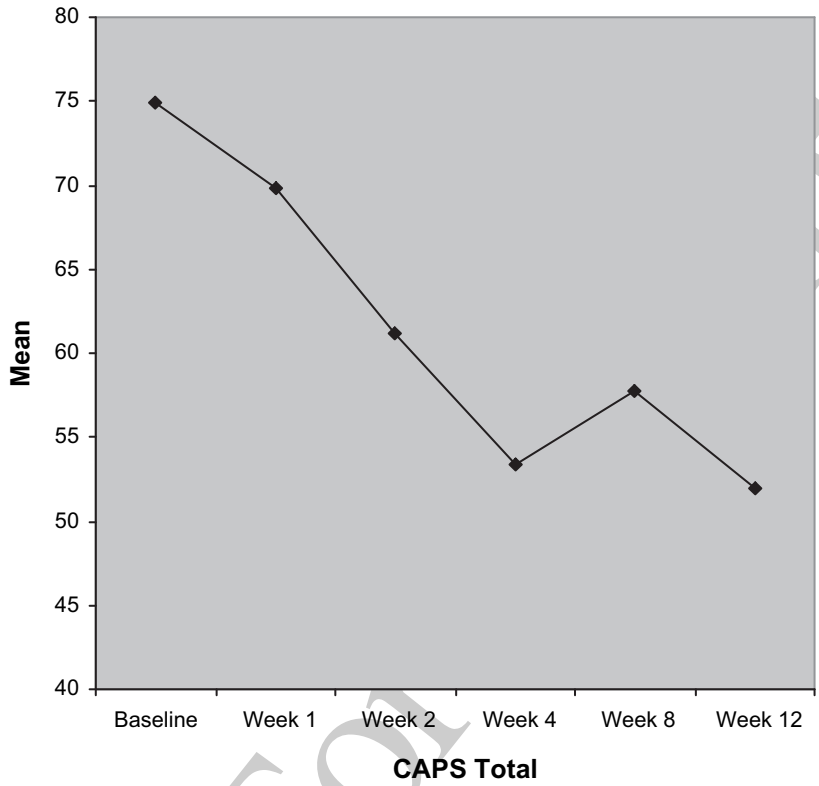
Of the 22 subjects who participated in the study, 14 (64%) were classified as responders, defined by a 20% or greater improvement on CAPS total score. Furthermore, eight subjects (36%) had a 30% or greater improvement in CAPS-total score. Two of those subjects achieved remission of PTSD symptoms as defined by a CAPS total score of <20,[44] and three others had a final CAPS total score of ≤ 26.

Of the 14 subjects who completed 12-weeks of treatment, three had a CGI-I of 1 (very much improved), nine had a CGI-I of 2 (much improved) and two had a CGI-I of 3 (minimally improved). Of the eight subjects that dropped out one had CGI-I of 2 (much improved), two had a CGI-I of 3 (minimally improved), two had a CGI-I = 4 (no change), and three had CGI-I = 5 (minimally worse).

Fifteen subjects (68%) had previous trials of two or more antidepressants; 9/14 in the completer group and 6/8 in the noncompleter group. Three subjects (14%) had previous trials of atypical antipsychotics; 1/14 in the completer group and 2/8 in the noncompleter group.

FIGURE 1

TOTAL CAPS SCORES ACROSS STUDY VISITS



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Withdrawls

Eight subjects dropped-out due to side effects. One (1) due to somnolence and blurred vision; three (3) due to anxiety and restlessness; one (1) due to asthenia; one (1) due to insomnia; one (1) due to insomnia and asthenia; and one (1) due to anxiety and insomnia.

Tolerability and Safety

There were no significant changes in vital signs, weight, abnormal movement scales, or sexual function measures between baseline and final visit (Table 4). Treatment-Emergent adverse experiences tended to be transient and mild in intensity, and did not pose significant problems or distress except in those subjects that dropped. The most common side effects reported in this study were somnolence, experienced by 12 subjects (54.5%), restlessness, experienced by 11 subjects (50%), insomnia, experienced by 8 subjects (36.4%), asthenia, experienced by 7 subjects (31.8%), anxiety, blurred vision and dry mouth, experienced by 6

TABLE 3

CHANGES IN CLINICAL VARIABLES FOR COMPLETERS FROM BASELINE TO FINAL VISIT $N = 13$

VARIABLE	BASELINE MEAN (SE)	WEEK 12 MEAN (SE)	SIGNIFICANCE
CAPS-RXP	16 (2)	8 (2)	.005*
CAPS-AVD	32 (2)	18 (3)	.000*[a]
CAPS-HYP	25 (1)	13 (1)	.000*[a]
CAPS-Total	73 (4)	39 (5)	.000*[a]
PANSS-P	15 (1)	11 (0.6)	.001*[b]
PANSS-N	13 (1.2)	13 (0.9)	.480
PANSS-G	37 (1.2)	27 (1.3)	.000*[a]
PANSS-Total	64 (3)	51 (3)	.000*[a]
HAM-D	21 (1.6)	11 (1.3)	.000*[a]
HAM-A	24 (1.3)	13 (1.45)	.000*[a]
DTS	80 (7.2)	44 (8.1)	.000*[a]
Sleep Duration (PSQI)	2.30 (0.213)	1.40 (0.306)	.001*[b]
PTSD Component (PSQI)	15.1 (1.49)	7.7 (2.35)	.005*

Pittsburg Sleep Quality Index (note: this is a composite score, lower numbers indicate more hours of sleep). CAPS-RXP, CAPS reexperiencing subscale; CAPS-AVD, CAPS avoidance/numbness subscale; CAPS-HYP, CAPS hyperarousal subscale; PANSS-P, PANSS positive subscale; PANSS-N, PANSS negative subscale; PANSS-G, PANSS general subscale; HAM-D, Hamilton Depression Rating Scale; HAM-A, Hamilton Anxiety Scale; DTS, Davidson Trauma Scale.
RM ANOVA *$P < .01$.
[a]Retains significance at $P < .01$ level with Bonferroni correction.
[b]Retains significance at $P < .05$ level with Bonferroni correction.

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TABLE 4

CHANGES IN SAFETY MEASURES FOR ENTIRE SAMPLE FROM BASELINE TO FINAL VISIT INCLUDING LAST OBSERVATION CARRIED FORWARD (LOCF) $N = 22$

VARIABLE	BASELINE MEAN (SE)	WEEK 12 (SE)	SIGNIFICANCE
Diastolic BP	72.36 (1.97)	72.32 (2.01)	.978
Systolic BP	130.27 (4.14)	128.73 (3.05)	.603
Pulse	75.32 (2.62)	74.64 (2.64)	.792
Temperature	97.68 (0.17)	97.66 (0.18)	.915
Weight	186.28 (9.14)	188.34 (8.74)	.206
ASEX	19.54 (1.09)	20.73 (1.26)	.215
AIMS	0.864 (0.43)	1.32 (0.65)	.338
Barnes	3.27 (0.36)	3.91 (0.68)	.357
SAS	12.82 (0.50)	12.77 (0.54)	.912

LOCF, Last observation carried forward; ASEX, Arizona Sexual Experiences Scale; AIMS, Automatic Involuntary Movement Scale; Barnes, Barnes Akesthesia Scale; SAS, Simpson-Angus Scale.
*$P < .05$.

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subjects each at 27.3% each, respectively. Percentages reflect those subjects who reported, at least once, any of the above treatment-emergent adverse events.

DISCUSSION

The results of this open label trial suggest that aripiprazole is potentially helpful in the treatment of PTSD. All 22 subjects had chronic PTSD with 68% (15 subjects) having been treated with two or more antidepressants suggesting that they may have been treatment resistant to pharmacological treatments. It is also important to note that 21 of 22 subjects had military-related PTSD. None of the subjects reported lack of efficacy as a reason for withdrawing from the study, but CGI-I scores indicate that these subjects had a less favorable response to the medication than completers. Treatment-emergent adverse events were not significant in those subjects that completed the 3-month study. Furthermore, of the 22 subjects enrolled, 21 subjects (95%) completed at least 4 weeks of treatment. The most common side effects were sedation and psychomotor activation. The attrition rate due to adverse events may be related to higher psychophysiologic sensitivity to psychotropic medications typically seen in combat Veterans. Patients with PTSD often tend to somatize and report more physical symptoms than with other psychiatric disorders.[45–48] Another possible reason for the high attrition rate may be the 10 mg starting dose, suggesting that beginning treatment with a lower dose (5 mg or less) may increase tolerability. General observations of this study are: 1) Aripiprazole exhibited a positive effect on all the three PTSD symptom clusters; 2) Improved psychotic, depressive, anxiety and general psychopathology symptoms; and 3) Most of the subjects who completed the study 85% (11/13) were rated as very much or much improved, two of them achieving PTSD remission criteria as defined by a CAPS total score of ≤ 20.[44]

Given the inherit limitation of an open-label study, the fact that self-rated DTS scores paralleled the CAPS-total scores (see Table 2) provides additional support about the efficacy of aripiprazole in treating PTSD symptoms. The fact that 2 subjects achieved remission with three others coming fairly close is remarkable given the chronicity of the illness, symptom severity of the study population, and the monotherapy design of the research project.

There is evidence that a significant proportion of PTSD patients suffer from psychotic symptoms, ranging from 36 to 46%.[16–19] Although patients with comorbid psychotic disorders were excluded from this study, PANSS scores indicate that the sample had psychotic symptoms that were subthreshold for diagnosis of a psychotic disorder. Furthermore, our PANSS results are consistent with the studies done by

Hamner and et al.[21,27] Moreover, our results parallel those of Hamner's study with Quetiapine.[27] Similarly, he reported that PTSD subjects had high symptom burdens (high PANSS-total scores) and saw improvement in PANSS-total, PANSS-positive and PANNS general psychopathology, but not in the PANSS-negative subscale. The reductions in PANSS total and positive scores suggest that aripiprazole improves psychotic symptoms in this population.

The improvement in depression and anxiety observed in our study is also noteworthy. In a study adding aripiprazole to an SSRI in patients with depression and anxiety who had had an incomplete response to several SSRI's, 59% were rated as much or very much improved on the CGI-I rating scale and showed a response as early as week 1.[49] A retrospective chart review of 30 treatment resistant unipolar depression patients[50] found that 46.7% were rated much improved or very much improved when aripiprazole was added. Of particular interest in this study was the fact that these patients had failed multiple antidepressant trials and had also failed augmentation with at least another atypical antipsychotic.

Interestingly, in the present study there is improvement in sleep duration and decrease in the PTSD component of the PSQI that matches the improvement seen in the CAPS total and all it's subscales. Despite insomnia being a common side effect of aripiprazole, the decrease in re-experiencing (i.e., intrusive thoughts, nightmares, flashbacks) and hyperarousal symptoms probably allowed this cohort of subjects to sleep better (longer) than without aripiprazole. In addition, somnolence was frequently reported and was not an issue for most subjects in this study but may have yielded a beneficial effect that could have resulted in the improvement in sleep duration. Although, the results did not remain significant when a Bonferroni correction was made, a larger sample size may be needed to maintain significance.

The results of this study should be taken with caution due to the open label nature of the study. Nonetheless, these preliminary results are encouraging given the reported poor response of veterans with PTSD to serotonin reuptake inhibitors.[11–14] A double-blind, placebo-controlled trial of aripiprazole in PTSD is warranted. ✤

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