BRIEF REPORT

Aripiprazole in the treatment of posttraumatic stress disorder. An open-label trial

Aripiprazol no tratamento do transtorno de estresse pós-traumático. Um ensaio clínico aberto

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Abstract

Objective: *Post traumatic stress disorder is frequent in the general population (7.8%-lifetime-USA). The selective serotonin reuptake inhibitors are the first choice of treatment but result in low remission rates. This study aims to evaluate the effect of aripiprazole monotherapy for the treatment of post traumatic stress disorder.* ***Method:*** *Thirty-two patients diagnosed with post traumatic stress disorder were included in a 16-week open label trial of aripiprazole. They were evaluated at baseline, week 8, and 16 with the Clinician-Administered PTSD Scale, Beck Depression Inventory, Beck Anxiety Inventory, Medical Outcome Study Short Form 36, and Social Adjustment Scale. Statistical analysis were performed with an intention-to-treat approach and last observation carried forward. A general linear model for repeated measures comparing the factor with 3 continuous measures from baseline, 8 and 16 weeks was used. A between-subject factor was included* ***Results:*** *Nine patients discontinued the treatment. The mean aripiprazole dose was 9.6 (± 4.3) mg/day. The mean scores at baseline and* endpoint *for all measures were: Clinician-Administered PTSD Scale - 82.7 (± 23.1) and 51.4 (± 31.4) (F = 11.247, p = 0.001); Beck Anxiety Inventory - 31.7 (± 13.4) and 25.4 (± 18.2) (F = 8.931, p = 0.011); Social Adjustment Scale - 2.4 (± 0.45) and 2.27 (± 0.57) (F = 8.633, p = 0.012); Medical Outcome Study Short Form 36 - 76.6 (± 14.11) and 94.01 (± 25.06) (F = 10.127 p = 0.007); and Beck Depression Inventory - 26.06 (± 11.6) and 21.35 (± 12.6) (F = 1.580, p = 0.042). In all measurements, the differences were statistically significant.* ***Conclusions:*** *Patients achieved a good response to treatment with aripiprazole, but placebo-controlled studies are needed for more accurate results.*

Descriptors: *Aripiprazole; Patients; Stress disorders, post-traumatic; Treatment; Randomized controlled trial*

Resumo

Objetivo: *O transtorno de estresse pós-traumático é um quadro prevalente (7,8%-lifetime-EUA) que provoca grande prejuízo aos pacientes. Os inibidores seletivos de recaptação de serotonina, medicação de primeira escolha para o tratamento, mostram baixos índices de remissão. Este estudo pretende apresentar uma diferente escolha de medicamento para tratar o transtorno de estresse pós-traumático.* ***Método:*** *Trinta e dois pacientes com transtorno de estresse pós-traumático receberam aripiprazol por 16 semanas. Foram submetidos na entrada, 8 e 16 semanas às escalas* Clinician-Administered PTSD Scale, Beck Depression Inventory, Beck Anxiety Inventory, Medical Outcome Study Short Form 36 *e* Social Adjustment Scale*. Foi usado o modelo linear generalizado para medidas repetidas comparando o fator com as três medidas contínuas nos três pontos de avaliação. Foi feita uma comparação entre sujeitos (grupo tratamento) usando modelo linear generalizado univariado. Usamos a intenção de tratamento e a estratégia da última observação com* endpoint *(*Last Observation Carried Forward*).* ***Resultados:*** *Nove pacientes descontinuaram antes da segunda avaliação. A dose média foi 9,6 (± 4,3) mg/dia. As medidas na entrada e no final do tratamento foram:* Clinician-Administered PTSD Scale *– 82,7 (± 23,1) e 51,4 (± 31,4) (F = 11,247, p = 0,001);* Beck Anxiety Inventory *– 31,7 (± 13,4) e 25,4 (± 18,2) (F = 8,931, p = 0,011);* Social Adjustment Scale *– 2,4 (± 0,45) e 2,27 (± 0,57) (F = 8,633, p = 0,012);* Medical Outcome Study Short Form 36 *– 76,6 (± 14,11) e 94,01 (± 25,06) (F = 10,127 p = 0,007); e* Beck Depression Inventory *– 26,06 (± 11,6) e 21,35 (± 12,6) (F = 1,580, p = 0,042). Em todas as medidas, as diferenças foram estatisticamente significativas.* ***Conclusões:*** *O aripiprazol alcançou uma boa resposta em pacientes com transtorno de estresse pós-traumático, mas para resultados mais acurados ainda são necessários estudos controlados com placebo.*

Descritores: *Aripiprazol; Pacientes; Transtornos de estresse pós-traumáticos; Tratamento; Ensaios clínicos controlados aleatórios*

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Introduction

Posttraumatic Stress Disorder (PTSD) affects approximately 10% of the female population and 5% of males in the US.[1] Data from the National Comorbidity Survey (NCS)[1] involving a representative community sample of 5,877 individuals aged 15 to 54 from the US showed a 7.8% lifetime prevalence of PTSD. Combat exposure and witnessing among men, and rape and sexual molestation among women were the kinds of trauma most often associated with PTSD.

The serotonin reuptake inhibitors (SSRIs) are the recommended first-line therapy for the treatment of PTSD. They are effective across all PTSD symptom clusters and improve both quality of life and functional impairment.[2] Despite their efficacy data, approximately 20 to 40% of PTSD patients fail to respond to treatment. Remission rates with SSRIs after 12 weeks are relatively low, at 30% or less.[3] Many chronic PTSD patients, especially male combat veterans, have a partial or minimal response to antidepressants.[4] Studies with antidepressants indicate that PTSD among combat veterans is difficult to treat and often requires additional psychotropic medications.[4]

The search for new treatment options in PTSD is required because of the lack of an effective gold standard treatment. The antidepressants with dual mechanisms such as mirtazapine (noradrenergic and specific serotoninergic antidepressant)[5] and venlafaxine (serotoninergic and noradrenergic reuptake inhibitor - SNRI)[6] were associated with preliminary positive results; mood stabilizers and anticonvulsants were also tested[7] and were shown to have potential for further studies.

There is growing evidence supporting the use of atypical antipsychotic agents as adjunctive therapy in PTSD. Olanzapine,[8] risperidone[9] and quetiapine[10] were shown to improve scores of Clinician Administered Posttraumatic Scale (CAPS) total scale and subscales, as well as psychotic symptoms. In addition, there is evidence that 36-46% of patients with PTSD also suffer from psychotic symptoms.[11] PTSD is associated with abnormalities in serotonin, norepinephrine, and dopamine systems, among others.[12] Aripiprazole is a novel and efficacious antipsychotic with 5-HT2A antagonist effect and partial agonist activity at the 5-HT1A and D2 receptors.[13]

Lambert reported the case of five patients with PTSD who were treated with aripiprazole. The drug was well-tolerated and was effective in the management of sleep disturbances, such as nightmares and agitated behaviors during sleep, and was also helpful in the management of hyper-arousal. Except for one patient who experienced a paradoxical excitation response to the medication.[14] Padala et al. also reported cases of success using aripiprazole to treat patients with PTSD, but as an adjunctive therapy.[15]

Recently, Villarreal et al. have reported the results of a twelve-week, open-label, flexible dose trial of aripiprazole monotherapy conducted to assess the efficacy of the latter in core PTSD symptoms and associated psychiatric symptoms, including anxiety, depression and positive psychotic symptoms.[11] Of twenty-two subjects with DSM-IV diagnosis of PTSD, fourteen completed the trial. Eight subjects dropped out due to side-effects. Significant improvements were seen on CAPS total and its subscales. Fourteen participants were classified as responders, defined as improvement of 20% or above on CAPS total score. Of the thirteen subjects who completed final ratings, CAPS total scores improved significantly ($p = 0.011$). 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 effect observed was somnolence.[11]

The pharmacological profile of aripiprazole and previous positive results led us to study drug in PTSD. Our main objective was to evaluate the aripiprazole monotherapy efficacy to treat PTSD symptoms.

Method

This study was conducted at the Program for Victims of Violence at the Department of Psychiatry of the Universidade Federal de São Paulo (Unifesp)-Brazil. It has been approved by the local Institutional Review Board.

1. Sample

The first thirty-two consecutive outpatients who met the inclusion and exclusion criteria and accepted to sign the consent form comprised the final sample.

The inclusion criteria were: age from 18 to 60 years, diagnosis of PTSD according to DSM-IV criteria confirmed by structured clinical interview for DSM-IV (SCID-I) applied by a trained psychiatrist. Women with a childbearing potential had to be using a reliable contraceptive method during the study. The exclusion criteria were: diagnosis of schizophrenic disorder, delusional disorder, bipolar disorder, psychotic depression episode and psychoactive substance dependency disorder in the previous 6-month period, instable medical diseases and pregnancy. Fourteen patients were receiving a SSRI, nine combined with benzodiazepines, four combined with low doses of typical antipsychotics, four patients were using benzodiazepines alone, seven patients were drug naïve and seven had used psychoactive drugs in the past but were not medicated at the moment of evaluation. All patients ($n = 18$) who were receiving psychoactive medications at inclusion entered a washout period, which lasted according to the medications being taken, half-lives and current dosage (from one week to 5 weeks for fluoxetine to avoid interactions and discontinuation syndrome.

2. Main outcome measures

Our primary outcome measure was the CAPS means and standard deviations at baseline and endpoint.

A 30% decrease on CAPS scores at endpoint compared to baseline was defined as response criteria.

Secondary outcome measures were improvement on depressive and anxiety symptoms measured by BDI and BAI scores at endpoint and compared to baseline, as well as improvement on quality of life and social adjustment measured by SF-36 and SAS scores at endpoint and compared to baseline.

3. Procedures

At baseline, patients were submitted to a socio-demographic inventory and to a psychometric evaluation, being the latter reapplied at weeks 8 and 16. The psychometric evaluation consisted of the CAPS and self-reporting instruments. CAPS validated to Brazilian Portuguese (manuscript under preparation) was administered by a trained researcher (MCPC) to measure PTSD symptoms severity. Self-reporting instruments included the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI), the Medical Outcome Scale short form (MOS-SF-36) and the Social Adjustment Scale (SAS) to evaluate depressive and the anxiety symptoms severity, quality of life and social adjustment, respectively.

An initial 7.5 mg single dose of aripiprazole was prescribed and patients were seen every two weeks. The dosage could be increased or decreased depending on tolerance to side-effects (the maximum dosage allowed was 15 mg/day). After a 16-week period, the drug was discontinued over a two week period.

4. Statistical analysis

All data were analyzed using SPSS (version 13.0). For missing data we used the last observation carried forward strategy for an intention-to-treat analysis. The frequencies of nominal variables from all patients were calculated. CAPS scores from baseline and endpoint were stratified according to severity. Nominal data were analyzed using the chi-square test and the Fisher test when there were cells that counted less than five or at least one cell counted zero subjects.

A univariate General Linear Model (GLM) for repeated measures was used to compare each of the scales as 3 continuous measures (baseline, week 8 and 16).The between-subject factor was defined as the independent variable (treatment group). The confidence level used for all comparisons was 5% ($p < 0.05$). All observed Power as a type II error function were presented with minimum values of significance for each comparison.

Results

Thirty-two outpatients comprised the final sample. Twenty-four (75%) were women and 8 (25%) were men. Eighteen (56.3%) were married, eight (25%) were single, and six (18.7%) were widowed or divorced. Their mean age was 38.41 (± 10.97) years old, and the mean time since trauma happened was 50.87 (± 77.21) months. Three (9.4%) patients had been victims of sexual abuse, four (12.5%) had been kidnapped, four (12.5%) had been held hostage in prison rebellions, 7 (21.88%) had lost a close person in homicide and 8 (18.75%), had suffered a homicide attempt. PTSD symptoms means duration was 50.93 (± 77.17) months, ranging from 2 months to 30 years of history.

Nine (28%) patients discontinued the treatment before the second assessment. Six of them (18.7%) discontinued the medication because of adverse events (anxiety, psychomotor agitation, nausea, and insomnia). Three patients who abandoned treatment could not be contacted. Using GLM for repeated measures we did not detect any effect of the between subject factor ($F_{(8,18)} = 0.846$; $p = 0.613$; observed power 0.260) but found a significant effect of CAPS ($F = 13.169$; $p = 0.002$; observed power 0.980), BAI ($F = 5.065$; $p = 0.025$; observed power 0.810), BDI ($F = 3.895$; $p = 0.039$; observed power 0.802) and SF-36 ($F = 6.114$; $p = 0.018$; observed power 0.867) on final outcome.

The mean aripiprazole maximum tolerated dosage was 9.6 (± 4.3) mg/day, with a dose range of 3.75 to 15 mg/day.

Using intention-to-treat analysis with last observation carried forward (LOCF) for missing values we found a CAPS mean scores at baseline of 82.7 (± 23.1) and 51.4 (± 31.4) on endpoint, what represents a 38% reduction from baseline. When comparing the data using a univariate GLM, the difference between scores before and after treatment was statistically significant ($F = 11.247$, $p = 0.001$, Observed Power = 1.000). When applying a response criteria of 30% decrease at CAPS mean score from baseline, 17 (53.1%) patients were classified as responders.

Considering that a CAPS score higher than 50 was still in the PTSD range, only six (19%) patients remitted (CAPS < 20), and twelve (12/38%) patients had mild PTSD symptoms (CAPS < 39) after the treatment. For an additional analysis, we classified patients according to severity strata based on CAPS scores. At baseline strata were composed of 20 patients with an extremely severe PTSD (CAPS > 80), eight with severe PTSD (CAPS from 60 to 79), three with moderate PTSD (CAPS from 40 to 59), and one with a mild PTSD (CAPS from 20 to 39). After treatment, using LOCF, six patients had extremely severe PTSD, six had severe PTSD, eight had moderate PTSD; seven mild PTSD, and five patients had subclinical PTSD (CAPS < 19). Extremely severe and severe PTSD strata were associated at baseline and end of treatment (chi-square = 22.793, $p < 0.030$). The difference was due to extreme, severe and mild PTSD symptom cases.

The mean BAI score at baseline was 31.7 (± 13.4) and at end-point it was 25.4 (± 18.2) ($F = 8.931$, $p = 0.011$, Observed Power = 0.988). The SAS mean index score at baseline was 2.4 (± 0.45) and at endpoint 2.27 (± 0.57) ($F = 8.633$, $p = 0.012$, observed power = 0.990). The MOS SF-36 mean score at baseline was 76.6 (± 14.11) and at endpoint 94.01 (± 25.06) ($F = 10.127$, $p = 0.007$ observed power = 1.000). The mean BDI score at baseline was 26.06 (± 11.6) and at the end-point 21.35 (± 12.6) which was shown to be a statistically significant difference ($F = 1.580$, $p = 0.042$, observed power = 0.830). In all measurements the differences between baseline and endpoint means were statistically significant.

Discussion

Patients with PTSD showed a response to aripiprazole in this open trial with numbers that are at least comparable to those obtained with the first-line agents (SSRIs). Patients improved regarding not only specific PTSD symptoms, but also depressive and anxiety symptoms, social adjustment and quality of life. Although many patients were still symptomatic after the trial, some of those who tolerated medication side effects and completed the trial had a positive response to treatment. For a small number of patients the severity of PTSD or depressive symptoms have worsened from baseline or remained the same after 16 weeks of treatment. A significant number of patients (28%) discontinued treatment, many of which due to side effects. Those who discontinued had more severe depressive symptoms at baseline. This is a difficult-to-interpret finding as aripiprazole has been show to effectively treat unipolar depressive disorder, and was recently approved by the FDA to treat this condition. We could hypothesize that PTSD-depressive syndrome comorbidity behaves differently from unipolar depressive disorder on which aripiprazole was recently approved to treat.

Our results are encouraging for future prospective double-blind, placebo-controlled, randomized trials specifically designed to test aripiprazole efficacy. In addition, further studies should identify subgroups of patients with a greater chance of better response, for example those with more dissociative or psychotic symptoms. Finally, an investigation into whether aripiprazole as adjunct therapy of an SSRI has a better profile than a monotherapy for those patients with depression disorder as comorbidity should be conducted.

A weakness of this study is the length of follow-up and drug use continuation; as PTSD symptoms continued to improve slowly up to nine months after the beginning of treatment. Also, it is an open trial, which limited our possibility of drawing conclusions. Some patients had a very fast response to medication evaluated clinically, but some could not stand the gastrointestinal symptoms even with doses as low as 3.75 mg/day; most dropouts included those presenting the most severe depressive symptoms, which again reinforces the need to evaluate specific groups of patients that will respond better to aripiprazole monotherapy.

Disclosures

Writting group member	Employment	Research grant[1]	Other research grant or medical continuous education[2]	Spekear's honoraria	Ownership interest	Consultant/ Advisory board	Other[3]
Marcelo Feijo Mello	UNIFESP	Eli Lilly do Brasil* Servier*	Eli Lilly do Brasil* Servier*	Eli Lilly do Brasil* Servier*	---	---	---
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** Modest*
*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*
Note: UNIFESP = Universidade Federal de São Paulo.
For more information, see Instructions for authors.

References

1. Kendler KS, Kessler RC, Walters EE, MacLean C, Neale MC, Heath AC, Eaves LJ. Stressful life events, genetic liability, and onset of an episode of major depression in women. *Am J Psychiatry.* 1995;152(6):833-42.
2. Davidson JR. Pharmacologic treatment of acute and chronic stress following trauma: 2006. *J Clin Psychiatry*. 2006;67(Suppl 2):34-9.
3. Davidson J, Rothbaum BO, Tucker P, Asnis G, Benattia I, Musgnung JJ. Venlafaxine extended release in posttraumatic stress disorder: a sertraline- and placebo-controlled study. *J Clin Psychopharmacol*. 2006;26(3):259-67.
4. Davidson JR, Weisler RH, Butterfield MI, Casat CD, Connor KM, Barnett S, van Meter S. Mirtazapine vs. placebo in posttraumatic stress disorder: a pilot trial. *Biol Psychiatry*. 2003;53(2):188-91.
5. Davidson J, Lipschitz A, Musgnung J. Treatment of PTSD with venlafaxine XR, sertraline, or placebo: a double-blind comparison. *Int J Neuropsychopharmacol*. 2004;7(Suppl 1):S364-5.
6. Berlant J, van Kammen DP. Open-label topiramate as primary or adjunctive therapy in chronic civilian posttraumatic stress disorder: a preliminary report. *J Clin Psychiatry*. 2002;63(1):15-20.
7. Brady K,Pearlstein T, Asnis GM, Baker D, Rothbaum B, Sikes CR, Farferl GM. Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. *JAMA*. 2000;283(14):1837-44.
8. Bartzokis G, Lu PH, Turner J, Mintz J, Saunders CS. Adjunctive risperidone in the treatment of chronic combat-related posttraumatic stress disorder. *Biol Psychiatry*. 2005;57(5):474-9.
9. Kozaric-Kovacic D, Pivac N. Quetiapine treatment in an open trial in combat-related post-traumatic stress disorder with psychotic features. *Int J Neuropsychopharmacol*. 2007;10(2):253-61.
10. Campbell ML, Morrison AP. The psychological consequences of combat exposure: the importance of appraisals and post-traumatic stress disorder symptomatology in the occurrence of delusional-like ideas. *Br J Clin Psychol*. 2007;46(Pt 2):187-201.
11. Villarreal G, Calais LA, Cañive JM, Lundy SL, Pickard J, Toney G. Prospective study to evaluate the efficacy of aripiprazole as a monotherapy in patients with severe chronic posttraumatic stress disorder: an open trial. *Psychopharmacol Bull*. 2007;40(2):6-18.
12. Ruiz JE, Barbosa Neto J, Schoedl AF, Mello MF. Psychoneuroendocrinology of posttraumatic stress disorder. *Rev Bras Psiquiatr*. 2007;29(Suppl 1):S7-12.
13. Hirose T, Uwahodo Y, Yamada S, Miwa T, Kikuchi T, Kitagawa H, Burris KD, Altar CA, Nabeshima T. Mechanism of action of aripiprazole predicts clinical efficacy and a favourable side-effect profile. *J Psychopharmacol*. 2004;18(3):375-83.
14. Lambert MT. Aripiprazole in the management of post-traumatic stress disorder symptoms in returning Global War on Terrorism veterans. *Int Clin Psychopharmacol*. 2006;21(3):185-7.
15. Padala PR, List D, Petty F, Bhatia SC. Adjunctive aripiprazole in combat-related posttraumatic stress disorder. *Ann Pharmacother*. 2007;41(10):1744.