Journal of Psychiatric Research 56 (2014) 72–81

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Review

The potential role of atypical antipsychotics for the treatment of posttraumatic stress disorder☆

Changsu Han [a], Chi-Un Pae [b, c, *], Sheng-Min Wang [b], Soo-Jung Lee [b], Ashwin A. Patkar [c], Praksh S. Masand [d], Alssandro Serretti [e]

[a] Department of Psychiatry, Korea University, College of Medicine, Seoul, Republic of Korea
[b] Department of Psychiatry, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea
[c] Department of Psychiatry and Behavioural Sciences, Duke University Medical Center, Durham, NC, USA
[d] Global Medical Education, New York, NY, USA
[e] Institute of Psychiatry, Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy

ARTICLE INFO

Article history:
Received 4 March 2014
Received in revised form
14 April 2014
Accepted 2 May 2014

Keywords:
Meta-analysis
Atypical antipsychotics
Posttraumatic stress disorder
Efficacy
Tolerability

ABSTRACT

Despite the fact that the majority of currently available treatment guidelines propose antidepressants as the first-line pharmacological therapy for posttraumatic stress disorder (PTSD), a substantial portion of patients fail to show an adequate response following this type of treatment. In this context, a number of small, open-label studies and randomized controlled clinical trials (RCTs) have found atypical antipsychotics (AAs) to be a beneficial treatment for patients with PTSD. Thus, the present meta-analysis was conducted to enhance the sample size power and further the current understanding of the role of AAs for the treatment of PTSD. An extensive search of several databases identified 12 appropriate RCTs and available data from 9 of these ($n = 497$) were included in the final meta-analysis. AAs may have potential benefits for the treatment of PTSD as indicated by changes from baseline of the total score on the Clinician Administered PTSD Scale (CAPS; standardized mean difference [SMD] = −0.289, 95% confidence intervals [CIs] = −0.471, −0.106), $P = 0.002$). Additionally, AAs were found to be significantly more effective ($P < 0.0001$) than a placebo in terms of change from baseline for the intrusion sub-score on the CAPS (SMD = −0.373, 95% CIs = −0.568, −0.178) but there were no significant reductions for the avoidance and hyperarousal sub-symptoms. The responder rate and rate of improvement of depressive symptoms were also significantly higher in the AA group than the placebo group ($P = 0.004$ and $P < 0.0001$, respectively). However, the present results should be interpreted carefully and be translated into clinical practice only with due consideration of the limited quality and quantity of existing RCTs included in this analysis.

1. Introduction

Posttraumatic stress disorder (PTSD) is a prevalent and chronic mental disorder that has a high rate of comorbid psychiatric and medical symptoms (Amital et al., 2006; Berry et al., 2013; Chibnall and Duckro, 1994; Kessler et al., 2005; O'Toole et al., 1998; Roy-Byrne et al., 2004). In fact, one in four individuals exposed to trauma is likely to develop PTSD, and most of these patients will require long-term treatment for up to 12–24 months (Bandelow et al., 2012). PTSD patients often experience several domains of symptoms including re-experience of the traumatic event (i.e., intrusion, flashbacks, and nightmares), avoidance (i.e., inability to remember important aspects of the trauma and emotional numbness), and hyperarousal (i.e., irritability, outbursts of anger, difficulty sleeping, and hypervigilance). These symptoms substantially impact an individual's personal, social, financial, and occupational capacities and often cause increases in health care utilization, family disconnection, medical expenses, and public health care costs (Bunting et al., 2013; Eisenman et al., 2003; Leserman et al., 2005).

Most pharmacological guidelines suggest that first-line pharmacotherapy should include selective serotonin reuptake inhibitors

☆ The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/PflvAY.

* Corresponding author. Department of Psychiatry, Bucheon St. Mary's Hospital, The Catholic University of Korea College of Medicine, 2 Sosa-Dong, Wonmi-Gu, Bucheon 420717, Kyeonggi-Do, Republic of Korea. Tel.: +82 32 340 7067; fax: +82 32 340 2255.
E-mail address: pae@catholic.ac.kr (C.-U. Pae).

http://dx.doi.org/10.1016/j.jpsychires.2014.05.003
0022-3956/

(SSRIs) and, more recently, venlafaxine extended-release, a serotonin norepinephrine reuptake inhibitor (SNRI), has also been identified as a promising agent for the treatment of PTSD (American Psychiatric Association, 2004; Baldwin et al., 2005; Bandelow et al., 2012; Canadian Psychiatric Association, 2006; Schaffer et al., 2012). However, the current pharmacotherapy options for PTSD often do not result in satisfactory clinical outcomes, as evidenced by several controlled or open-label clinical trials and a handful of meta-analyses that used various selection criteria (Ipser and Stein, 2012; Pae et al., 2008a; Watts et al., 2013). Indeed, a remission rate of 30% and a response rate of 60% for SSRI-treated patients with PTSD can be considered inadequate (Bajor et al., 2011; Ipser and Stein, 2012).

The incidences of psychotic symptoms (defined as hallucinations of all modalities, delusional beliefs, and changes in mood and behavior) identified in PTSD patients by epidemiological studies are relatively high, although they range various from 11 to 67% median rate = 39%; (Berry et al., 2013). These psychotic symptoms are associated with more severe symptomatology and decrease the efficacy of conventional treatments (Berry et al., 2013) which indicates that atypical antipsychotics (AAs) may have a role in the treatment of PTSD. In fact, various AAs have shown positive antidepressant and anti-anxiety effects in a number of small-scale open-label studies (OLSs) and randomized controlled clinical trials (RCTs) (Han et al., 2013; Pae et al., 2013; Pae and Patkar, 2013; Pae et al., 2008b); however, the most largest RCT for PTSD (Krystal et al., 2011) has also failed to separate the efficacy of risperidone from placebo. Although small RCTs and OLSs have demonstrated the potential beneficial effects of AAs for the treatment of PTSD, there is a lack of adequately powered RCTs investigating the efficacy of AAs for treatment of PTSD (Bajor et al., 2011; Pae et al., 2008a).

The current meta-analysis cannot replace a well-designed adequately powered RCT but it can complement available knowledge by pooling data from various small RCTs conducted using a priori inclusion criteria. Moreover, a meta-analysis enables critical comparisons between studies and among competitive drugs as well as achievement of greater statistical power relative to individual trials (Huf et al., 2011). Several meta-analyses have reported favorable results in patients with PTSD following the use of AAs (Ahearn et al., 2011; Ipser and Stein, 2012; Pae et al., 2008a; Watts et al., 2013); however, the majority of large RCTs investigating PTSD (Krystal et al., 2011) failed to find an increased efficacy of risperidone compared to placebo. Furthermore, risperidone did not result in significant improvements in depression and anxiety compared to placebo in these studies.

Therefore, the aim of the present study was to conduct a meta-analysis evaluating the effectiveness and tolerability of AAs for the treatment of PTSD and to further clarify the current position of AAs in this manner based on the most recent RCTs.

2. Methods

2.1. Sources of data

A search of past studies was conducted for AAs (clozapine, olanzapine, risperidone, ziprasidone, quetiapine, aripiprazole, blonanserin, amisulpiride, paliperidone, lurasidone, asenapine, and iloperidone) using key terms associated with PTSD ("post-traumatic", "stress", "disorder", and "PTSD") in the following databases: PubMed, Embase/Medline, PsycINFO, and Cochrane Library. Reference lists from identified articles and reviews were also utilized to find additional studies. Abstracts identified by the literature search were independently screened by two authors of this article (S.M.W. and S.J.L.); potentially eligible papers were then re-evaluated by two other authors (C.H. and C.U.P.) to determine whether they clearly met the selection criteria. If a disagreement occurred, the article in question was discussed and a consensus was reached by the second set of review authors.

2.2. Inclusion criteria for meta-analysis

Only RCTs that prospectively compared one of the searched AAs to a placebo in patients with PTSD diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and that were published in English-language, peer-reviewed journals were included in the present meta-analysis. There were no requirements or restrictions regarding the duration (short-term or long-term) of AA treatment (monotherapy or add-on therapy), comorbidity of symptoms, concomitant medications, presence of psychotic symptoms, severity of PTSD, types of experienced trauma, gender, minimum number of subjects, or treatment basis (i.e., inpatient or outpatient).

2.3. Data extraction for meta-analysis

The characteristics of the participants, treatment details, study procedures, and diagnostic information including comorbid conditions, efficacy measures, dropouts, and adverse events (AEs) were evaluated. Data extraction was first handled by C.U.P. and then reassessed independently by C.H. Mean changes in the rating scales were extracted from the cited studies; if mean changes were not available they were computed. Likewise, if a standard deviation (SD) for the mean change was not available then the weighted median SD from studies in which the SD was reported (or calculations with other available statistical values such as mean 95% confidence intervals (CIs), or t-values) was adopted. The precise extraction of SD data is a crucial point when conducting a meta-analysis and, in fact, if SDs are not available from an original study then that study can be excluded. However, this would drastically reduce the significance of the results via a decrease of statistical power and, therefore, it is an acceptable and commonly used method in this field to produce an estimate based on the weighted average of available studies. Additionally, the quality of the RCTs was assessed using the Jadad score (Jadad et al., 1996).

2.3.1. Primary efficacy measure

The primary efficacy measure was the mean change from baseline of total scores on the Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995), which was the most frequently used assessment tool in the included RCTs of PTSD (Bartzokis et al., 2005; Carey et al., 2012; Hamner et al., 2003; Krystal et al., 2011; Padala et al., 2006; Reich et al., 2004; Stein et al., 2002). The change from baseline of total scores on the self-reported Davidson Trauma Scale (DTS) (Davidson et al., 1997) was also included as a primary efficacy measure. The DTS has been demonstrated to be similar to the CAPS regarding scoring procedure and apparent treatment effects, and the score on this scale is considered to be equivalent to the CAPS score (Davidson et al., 2002).

2.3.2. Secondary efficacy measures

The principal secondary efficacy measures were the mean changes from baseline of the sub-scores on the CAPS; intrusion, avoidance, and hyperarousal. Furthermore, responder rates were calculated using the Clinical Global Impression-Improvement (CGI-I) score which were assessed as "much or very much improved" or "no or mild symptoms of PTSD" measured by the total score on the CAPS at the end of treatment. Improvements in depression were also assessed using the mean changes from baseline of the total scores on the Montgomery–Åsberg Depression Rating Scale