Psychiatry Research 219 (2014) 543–549

Contents lists available at ScienceDirect

Psychiatry Research

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

Efficacy and acceptability of atypical antipsychotics for the treatment of post-traumatic stress disorder: A meta-analysis of randomized, double-blind, placebo-controlled clinical trials

Xiao-hui Liu [a,1], Xin-hui Xie [a,b,c,*,1], Ke-yong Wang [d], Hong Cui [a,*]

[a] Medical Psychology Division, Chinese PLA General Hospital & Medical School PLA, Beijing, China
[b] Department of Psychiatry, Shenzhen Kangning Hospital & Shenzhen Mental Health Center, Shenzhen, China
[c] Department of Psychiatry, Shenzhen Key laboratory of psychological health center, Shenzhen, China
[d] Department of Psychiatry, Anhui Mental Health Center, Hefei, Anhui, China

ARTICLE INFO

Article history:
Received 14 September 2013
Received in revised form
5 May 2014
Accepted 19 May 2014
Available online 2 June 2014

Keywords:
Post-traumatic stress disorder
Atypical antipsychotics
Meta-analysis
Pharmacotherapy
Randomized controlled trial

ABSTRACT

As some evidences demonstrated that atypical antipsychotics (AA) may be efficacious in treating post-traumatic stress disorder (PTSD), we preformed a meta-analysis of randomized, double-blind, placebo-controlled clinical trials (RCTs) of AAs for the treatment of PTSD. Two hundred and fifty one papers were searched and screened. Eight RCTs met the inclusion criteria. AAs may be superior to placebo in the treatment of PTSD, as indicated by the changes in Clinician Administered PTSD Scale (CAPS) total scores (weighted mean differences (WMD)= −5.89, 95% confidence interval (CI) [−9.21, −2.56], P=0.0005) and also in CAPS subscale intrusion (WMD= −2.58, 95% CI[−3.83, −1.33], $P<0.0001$) and subscale hyperarousal (WMD= −2.94, 95% CI[−5.45, −0.43], P=0.02). The acceptability measured by dropout rates between AAs and placebo showed no statistical difference (OR=1.24, 95%CI [0.78, 1.97], P=0.36). PTSD symptom cluster, especially in intrusion and hyperarousal. However, we should be careful to generalize the conclusion because of the small number of included trails. We expect more RCTs will be done in the future so as to clarify the specific value of AAs for PTSD.

1. Introduction

Post-traumatic stress disorder (PTSD) results from the exposure to a traumatic event or witnessing of a life-threatening event, such as violence, abuse, accident, war trauma, disaster, or any situation that seriously threatens the integrity of a person (Foa et al., 2000). PTSD has a highly prevalent rate of 8%, is higher (12.3%) in women (Kessler et al., 1995; Resnick et al., 1993), and associated with a high rate of comorbid psychiatric disorders (Vieweg et al., 2006). PTSD patients are six times more likely to attempt suicide than the common population (Davidson et al., 1991; Kessler et al., 1995), compared with 25% prevalence rates observed in individuals with major depressive disorder (MDD) (Asnis et al., 1993). The core symptoms of PTSD include intrusive re-experiencing, avoidance/numbing, and hyperarousal. Some patients even develop hallucinations and delusions; therefore, treatment of PTSD is complex. First-line treatment consists of psychotherapy, such as cognitive therapy, exposure therapy, stress inoculation training, and pharmacotherapy. Drug therapy includes antidepressants, specifically, selective serotonin reuptake inhibitors (SSRIs), such as sertraline and paroxetine, which have received the US Food and Drug Administration (FDA) indication (Foa et al., 2000; Hamner and Robert, 2005; Schoenfeld et al., 2004; Ursano et al., 2004). However, response rates remain below 60% and fewer than 30% of patients treated with SSRIs achieved full remission (Stein et al., 2002; Zohar et al., 2002). Of patients treated with serotonin–norepinephrine reuptake inhibitors (SNRI), such as venlafaxine ER, only 40.4% achieved remission (Davidson et al., 2006). These studies suggest that SSRIs or SNRIs may have limitations in treating PTSD patients. Fortunately, there exist emergent novel therapies that are likely to be efficacious in treating PTSD patients based on the evidence from randomized clinical trials (RCTs) or open-label trials. For example, as adjunct treatment or monotherapy, atypical antipsychotics (AAs), such as risperidone, olanzapine, quetiapine, clozapine, and aripiprazole demonstrated effectiveness in PTSD (Ashraf and Shahid, 1992; Kozaric-Kovacic et al., 2005; Padala et al., 2006; Petty et al., 2001; Pivac et al., 2004; Reich et al., 2004). However, other studies did not reveal a difference between AA- and placebo-treated patients in the improvement of PTSD

* Corresponding authors. Tel.: +86 10 66936675.
E-mail addresses: xxh.med@gmail.com (X.-h. Xie), cuih@sina.cn, hongcui@301hospital.com.cn (H. Cui).
[1] These authors contributed equally to the manuscript.

http://dx.doi.org/10.1016/j.psychres.2014.05.027
0165-1781/

clinical endpoints (Krystal et al., 2011; Rothbaum et al., 2008). From a pharmacological perspective, AAs can affect several neurotransmitter systems that have been shown to be involved in the psychophysiology of PTSD. In an earlier meta-analysis study, PTSD patients were treated with risperidone, olanzapine and placebo, and the conclusion was that AAs were effective in PTSD patients (Pae et al., 2008).

But some new important RCTs like those described in Krystal et al. (2011) and Carey et al. (2012) were published recently. These trials revealed some inconsistent results. Krystal et al. (2011) summarized their results and stated that the risperidone is not able to provide a statistical priority than placebo on global PTSD symptoms, but Carey et al. (2012) reported the significantly greater improvement on the Clinician Administered PTSD Scale after olanzapine treatment.Therefore, we performed the present meta-analysis study in order to clarify the effectiveness of AA therapies on PTSD.

2. Methods

2.1. Literature search

A literature search in the *Medline, Embase,* and *Cochrane Library* databases was performed by using the key terms "posttraumatic stress disorder", "placebo", and "atypical antipsychotics". In addition, more papers were collected by further manual snowballing searches performed by two reviewers. Only RCTs published in peer-reviewed journals were retained. We also manually searched previous meta-analyses, systematic reviews, and traditional reviews to identify studies designed to evaluate the effects of AA pharmacotherapies on PTSD (Ahearn et al., 2011; Asnis et al., 2004; Berger et al., 2009; Gao et al., 2006; Hamner and Robert, 2005; Hetrick et al., 2010; Ipser et al., 2006; Kozaric-Kovacic, 2008; Pae et al., 2008; Steckler and Risbrough, 2012; Sullivan and Neria, 2009).

2.2. Inclusion criteria

To filter irrelevant papers, the following inclusion criteria were adopted:

1. RCTs prospectively compared at least one AA with placebo or another drug.
2. Clinician administered PTSD scale (CAPS) was the primary measure of treatment outcome.
3. Patients met the DSM-IV (APA, 2000) or ICD-10 (WHO, 1992) diagnostic criteria.
4. Papers were published in peer-reviewed journals.
5. Study participants were all adults.

2.3. Methodological assessment

The quality of RCT was assessed by using the Jadad scoring system (Jadad et al., 1996).

2.4. Data abstraction and outcomes

Data were extracted independently by two observers who were blind to the research design and then cross-checked to reach consensus. The following data fields were recorded: author, journal, date of publication, geographical region, trial design, recruitment criteria, baseline characteristics, primary and secondary outcomes, and quality assessment. Primary outcomes measure was the mean change from baseline in CAPS total scores (Blake et al., 1995). Secondary efficacy measures were mean changes in CAPS subscores. Tolerability measure was the number of dropouts for any reasons related to the study. The first authors were contacted to retrieve further information if necessary.

2.5. Statistical analysis

We conducted meta-analyses on all original studies that compared the primary and secondary outcomes to obtain an overall review of the effect of AAs on PTSD patients. Dichotomous variables were analyzed using odds ratio (OR), and continuous variables were analyzed using the weighted mean differences (WMD). Pooled analyses were chosen by the fixed-effects model (the inverse variance method) or the random effects model (the inverse variance method) due to statistical heterogeneity. Statistical heterogeneity was assessed by the I^2 statistic, and threshold values of I^2 were 0–50%, and 50–100%, representing low and high heterogeneity, respectively. Subgroup analyses included: (a) the course of PTSD (b) trial design (monotherapy or adjunctive treatment), and (c) the specific AA. Meta-regression analysis was performed to explore the source of heterogeneity. We used Review Manager Software (RevMan version 5.1.) and Stata 12.0 software (Stata, College Station, TX, USA) to perform the analysis.

3. Results

3.1. Description of studies

Of the 455 patients reviewed across eight studies, 231 were assigned to the AAs group, and 224 were assigned to the placebo group to evaluate the therapeutic effects of AAs. Fig. 1 shows a flow chart summarizing the potential number of original research papers retrieved and the selection process used. Both data observers agreed on the selection and assessment methodologies. Four monotherapy RCTs of risperidone or olanzapine treatment and another four add-on therapy RCTs were categorized. Detailed information of all included trials are presented in Table 1. Meta-analysis of primary and secondary efficiency and tolerability results are presented as forest plots in Figs. 2–6.

3.2. Primary efficacy

The meta-analysis result of primary efficacy is presented in Fig. 2. The primary efficiency result is described as the mean change in total CAPS score from baseline to the end of each trial. The results indicated that in terms of efficacy, AAs are significantly superior to placebo as measured by mean changes in total CAPS scores from baseline ($P=0.0005$). Furthermore, mean change of WMD of total CAPS score is statistically different between placebo and the AAs group (WMD$=-5.89$, 95% CI from -9.21 to -2.56).

3.3. Secondary efficacy

3.3.1. CAPS intrusion

Fig. 3 presents the meta-analysis results of CAPS intrusion (I) subscore. For CAPS I subscore, the efficiency of AAs, as measured by mean changes from baseline, is significantly superior to placebo ($P<0.0001$). Furthermore, mean change in WMD of CAPS I subscore is statistically different between placebo and the AAs group (WMD$=-2.58$, 95% CI from -3.83 to -1.33).

3.3.2. CAPS avoidance

The meta-analysis results of CAPS avoidance (A) score are presented in Fig. 4. For CAPS A, the efficiency of AAs, as measured

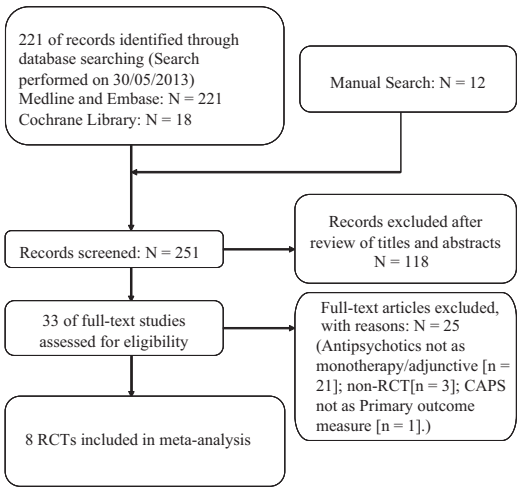

Fig. 1. Flow Chart.