The atypical antipsychotics olanzapine and risperidone in the treatment of posttraumatic stress disorder: a meta-analysis of randomized, double-blind, placebo-controlled clinical trials

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Posttraumatic stress disorder (PTSD) is a prevalent and disabling mental illness. Small studies found atypical antipsychotics (AAs) to be beneficial in the treatment of patients with PTSD regardless of psychotic symptoms who are unresponsive to conventional pharmacological treatments such as serotonin selective reuptake inhibitors. This study reports the results of a meta-analysis of existing randomized, double-blind, placebo-controlled clinical trials (RCTs) of AAs as a monotherapy or augmentation therapy for the treatment of patients with PTSD. Seven RCTs were identified through extensive scans of databases, which included PubMed, MedLine, the National PTSD Center Pilots database, PsycINFO, Cochrane Central Register of Controlled Trials, and the Abstracts Library of the American Psychiatric Association with predefined inclusion criteria. Dichotomous and continuous measures were performed using a fixed effects model, heterogeneity was assessed, and subgroup analyses were done. Data from seven RCTs involving a total of 192 PTSD patients (102 randomized to AAs and 90 randomized to placebo) were analyzed. The results show that AAs may have a beneficial effect in the treatment of PTSD, as indicated by the changes from baseline in Clinician Administered PTSD Scale total scores [standardized mean difference (SMD) = −0.45, 95% confidence interval (CI) (−0.75, −0.14), P=0.004]. In addition, the overall SMD of the mean changes in the three Clinician Administered PTSD Scale subscores was statistically significant (P=0.007) between AAs and placebo groups, favoring AAs over placebo (SMD = −0.27, 95% CI = −0.47, −0.07). In particular, the symptom of 'intrusion' was mainly responsible for this significance. Clinical significance of the results, however, should be carefully interpreted and translated into clinical practice, given that the quality and availability of currently existing RCTs included in the analysis. *Int Clin Psychopharmacol* **23:1–8 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

International Clinical Psychopharmacology 2008, **23**:1–8

Keywords: atypical antipsychotics, meta-analysis, posttraumatic stress disorder

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Received 28 February 2007 **Accepted** 9 May 2007

Introduction

Posttraumatic stress disorder (PTSD) is a highly prevalent mental disease (8%) and is a disorder predominantly experienced by women (12.3%) (Resnick *et al.*, 1993; Kessler *et al.*, 1995). Moreover, PTSD has been considered a devastating condition with a longitudinal course (McFarlane, 1988; Ursano *et al.*, 1995) and patients with PTSD also have high rates of comorbid psychiatric disorders (Vieweg *et al.*, 2006).

Patients with PTSD experience significant morbidity and mortality. Appropriate and timely interventions with either psychotherapeutic or pharmacological treatments or a combination of both therapies is necessary to minimize the worsening of the clinical outcomes.

The currently available evidence suggests that first-line pharmacotherapy is selective serotonin reuptake inhibitors (SSRIs), which includes sertraline, paroxetine, fluoxetine, and possibly the serotonin norepinephrine reuptake inhibitor venlafaxine extended release (Katzman *et al.*, 2005). Response rates, however, are limited, reaching approximately 60% among SSRI-treated patients with PTSD (Stein *et al.*, 2006). In addition, psychotic symptoms are not uncommon in patients with PTSD. These symptoms are associated with more severe symptomatology and their presence is also known to decrease the efficacy of conventional treatment (Sautter *et al.*, 1999), further indicating a possible role of atypical antipsychotics (AAs) as an adjunctive treatment. Moreover, the neurobiological pathophysiology of PTSD

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implicates a disturbed neuronal transmission of several critical neurotransmitters such as serotonin, norepinephrine, and dopamine and may indicate the relevance of pharmacotherapy based on the biological action of AAs. Increasing evidence also suggests that AAs may have antidepressant and antianxiety efficacy (Blier and Szabo, 2005; Nemeroff, 2005) as well as having a possible benefit in decreasing impairment of neurocognition and perception (Harvey and Keefe, 2001).

A paucity of adequately powered, randomized, double-blind, placebo-controlled clinical trials (RCTs) of AAs for the treatment of PTSD was found. However, small RCTs and open-label studies have tentatively demonstrated the beneficial effect of AAs for the treatment of patients with PTSD (Hamner and Robert, 2005).

Currently, larger RCTs are needed to confirm the effectiveness and tolerability of AAs for the treatment of patients with PTSD when considering the small number of existing RCTs and small treatment effect sizes observed in such trials. Although meta-analysis could not replace a well-designed, adequately powered RCT, it can complement smaller trials by pooling groups from different small studies based on a priori defined criteria for inclusion. It allows critical comparisons between studies and comparator drugs as well as giving greater statistical power than individual trials (Fineberg *et al.*, 2006).

The purpose of this study was to meta-analyze the effectiveness and tolerability of AAs to address the current evidence of their role in the treatment of PTSD as a monotherapy or add-on therapy.

Methods

Source of data

A search of the studies used the key terms 'posttraumatic stress disorder', 'placebo' and each of the AAs from the databases PubMed, MedLine, the National PTSD Center Pilots database, PsycINFO, Cochrane Central Register of Controlled Trials, and the Abstracts Library of American Psychiatric Association. The data were verified for publication in peer-reviewed journals. We also used reference lists from identified articles and reviews to find additional studies.

Inclusion criteria

We included RCTs that prospectively compared one of the AAs (clozapine, olanzapine, risperidone, ziprasidone, quetiapine, aripiprazole, amisulpiride) with placebo and were published in English in peer-reviewed journals. No requirements or restrictions were seen on duration (short term or long term) or type of treatment (mono- or add-on therapy) of AAs, comorbidity, concomitant medications, presence of psychotic symptoms, severity and duration of PTSD, types of experienced trauma, sex, minimum number of participants, and inpatient/outpatient treatment.

Efficacy measures

Primary efficacy measure

The primary efficacy measure was the mean change from baseline in the total scores on Clinician Administered PTSD Scale (CAPS) (Blake *et al.*, 1995), which was the most frequently used assessment in the included RCTs (Stein *et al.*, 2002; Hamner *et al.*, 2003; Reich *et al.*, 2004; Bartzokis *et al.*, 2005; Padala *et al.*, 2006). Change from baseline in total scores on the self-report, Davidson Trauma Scale (DTS) (Davidson *et al.*, 1997), was also included as a primary efficacy measure. DTS is proven to be similar to CAPS in scoring and apparent treatment effects (Davidson *et al.*, 2002) and is thus considered equivalent to the CAPS score (Davidson *et al.*, 2002).

Secondary efficacy measures

Included secondary efficacy measures were mean changes in subscores on the CAPS and responder rates measured by Clinical Global Impression-Improvement (CGI-I) score (Guy, 1976) rated as 'much or very much improved'.

Safety measure

The number of dropouts for any reasons, adverse events (AEs) related to study medication, and weight changes from baseline were included in the analysis when available.

Data extraction and analysis

Participants' characteristics, treatment details, study procedures, diagnostic information including comorbid conditions, all efficacy measures, dropouts, and adverse events were analyzed. Data extraction was handled first by one of the authors (C.U.P.) and then independently reassessed by K.P. We used the fixed-effect model despite a moderate heterogeneity across studies given that we had no a-priori reason to hypothesize data coming from different populations and because of the main aim of this analyses is the identification of the best estimate of a single effect size more than the range of effect sizes across populations (Munafo and Flint, 2004).

Seven RCTs were identified (Butterfield *et al.*, 2001; Stein *et al.*, 2002; Hamner *et al.*, 2003; Monnelly *et al.*, 2003; Reich *et al.*, 2004; Bartzokis *et al.*, 2005; Padala *et al.*, 2006) and data were thoroughly reviewed for the possible inclusion in the final analysis where appropriate. Given that not all studies used the same or similar efficacy measures and used different methods of presentation of study results, data selection could not be done from all included studies. Therefore, the priority was given to studies utilizing similar efficacy and safety measures. The study (Monnelly *et al.*, 2003) that reported the primary outcome measure as the Overt Aggression Scale-Modified

for Outpatients (OAS-M) was not included in the efficacy analysis.

The mean change was directly extracted from the cited studies and, if not already done, the mean changes were computed. When standard deviations (SDs) for the mean changes were not available, the weighted median SD from those studies where SD was reported was adopted.

Dichotomous [relative risk (RR) of 1 stands for no difference between drug and placebo] and continuous (standardized mean difference, SMD) measures were calculated using a fixed effects model. Heterogeneity between the studies was assessed with a χ^2 test. 95% confidence intervals (CIs) were also reported in the analysis. All directly extracted or computed data from the studies were entered into Review Manager 4.2.9 to complete meta-analysis with data synthesis and then analyzed (Cochrane Collaboration, 2006).

Results

In total, seven RCTs were included in the meta-analysis based on our inclusion criteria. Data were extracted from the original studies according to their relevance and availability. About 102 AA-treated and 90 placebo-treated participants were present. We found two monotherapy RCTs of olanzapine or risperidone treatment; the other five RCTs were all add-on therapy of AAs (one RCT for olanzapine and four RCTs for risperidone) with preexisting antidepressants or other psychotropics. The duration of treatment ranged from 5 to 16 weeks and we observed heterogeneity in the trauma types and presence of comorbid psychotic symptoms. The individual studies are summarized in Table 1.

The meta-analysis results are presented in Fig. 1 as forest plots. The results for the primary efficacy measured by CAPS total scores from six RCTs, for the secondary efficacy outcomes as measured by the responder rate from two RCTs and PTSD cluster symptoms (intrusion, avoidance, and hyperarousal) from four RCTs. Tolerability measures were based on dropout rates for any reason from six RCTs, dropout rates due to AEs from five RCTs, and weight gain from three RCTs.

Primary efficacy

As presented in Fig. 1, the add-on/monotherapy of AAs was significantly superior to placebo in improvement of global PTSD symptoms as measured by mean changes from baseline in CAPS total scores ($P = 0.004$). The SMD on the mean changes in CAPS total scores was significantly different between AAs and placebo groups, favoring AAs over placebo (SMD = −0.45, 95% CI = −0.75, −0.14). SMDs from the individual studies ranged from −0.57 to 0.18. The overall SMDs were not sufficiently large to be translated into clinical significance between AAs and placebo groups as seen in Fig. 1. The trend of plots approached the 'line of no effect', probably showing an additional indicator of 'possible borderline efficacy'. Indeed, among six RCTs included in the analysis of the primary efficacy measure, two RCTs failed to find statistically significant differences in the mean change on CAPS total score between risperidone and placebo groups (Butterfield *et al.*, 2001; Hamner *et al.*, 2003). Furthermore, four RCTs (Stein *et al.*, 2002; Reich *et al.*, 2004; Bartzokis *et al.*, 2005; Padala *et al.*, 2006) that demonstrated significant differences in the mean change on CAPS total score between AAs (risperidone and olanzapine) and placebo groups found a modest magnitude of differences. Between-study heterogeneity was not significant reaching approximately 20.8% ($P = 0.28$).

Secondary efficacy

Only two RCTs of olanzapine (monotherapy and augmentation) reported responder rates as measured by CGI-I scores (much or very much improved). The likelihood of nonresponse (RR = 0.84, 95% CI = 0.52–1.36) in the AA group compared with placebo group was not significantly different ($P = 0.48$).

Four RCTs of risperidone were included in the analysis of cluster symptoms of PTSD measured by differences in mean change in CAPS subscores on intrusion, avoidance, and hyperarousal, in which risperidone was found to be significantly superior ($P = 0.03$) to placebo in reduction of the CAPS subscore on intrusion (SMD = −0.37, 95% CI = −0.71–0.03). Risperidone treatment, however, failed to establish significant differences in the reduction of scores on avoidance ($P = 0.48$) and hyperarousal ($P = 0.07$) compared with placebo. The overall SMD on the mean changes in the three CAPS subscores was statistically significant ($P = 0.003$) between AA and placebo groups, favoring AAs over placebo (SMD = −0.27, 95% CI = −0.47–0.07). As observed in CAPS total score, however, visual inspection of SMDs on CAPS subscores showed similar approaches toward the 'line of no effect'. Overall there was no heterogeneity (15.2%, $P = 0.30$) between studies.

Tolerability

No significant difference was observed between AAs and placebo groups on the likelihood of discontinuation from the study in terms of dropout rates for any reason (RR = 1.34, 95% CI = 0.82–2.19) or AEs associated with treatments (RR = 2.13, 95% CI = 0.58–7.87). The SMD on weight change was, however, significantly higher in AA groups [two RCTS for olanzapine (Butterfield *et al.*, 2001; Stein *et al.*, 2002) and one RCT for risperidone (Reich *et al.*, 2004)] than in the placebo group (SMD = 0.92, 95% CI = 0.27–1.58) and heterogeneity was found between studies ($P < 0.0001$, 89.8%). When excluding the RCT of Reich *et al.* (2004) from the

Table 1 Summary of randomized, double-blind, placebo-controlled clinical trials of atypical antipsychotics (AAs) for the treatment of patients with posttraumatic stress disorder

Study	Drug/mean dose (mg/day)	Duration (weeks)	Sex	Number (AA : placebo)/age (years)	Major existing medication	Trauma type	Comorbid psychotic symptoms	Outcomes	Results[a] (AA versus Placebo)	Responder[c]
Stein *et al.* (2002)	Olanzapine/ 15	8	Men only	10 (55.2) : 9 (51.1)	SSRIs	Combat	NR	CAPS total score	CAPS ($P<0.05$)	CGI-I score
								PSQI score	PSQI ($P<0.01$)	
								CES-D score	CES-D ($P<0.03$)	
Bartzokis *et al.* (2005)	Risperidone/ initiation 1 and fixed 3 after gradual titration	16	Men only	33 : 32 (51.6 in both groups)	Antidepressants	Combat	NR	CAPS total scores	CAPS ($P<0.05$)	NR
								CAPS subscores	CAPS H ($P<0.01$)	
								PANSS-P score	PANSS-P ($P<0.01$)	
								HAM-A score	HAM-A ($P<0.001$)	
								HAM-D scores		
Reich *et al.* (2004)	Risperidone/ 1.4	8	Women only	12 (30.6) : 9 (24.2)	Antidepressants	Childhood abuse	NR	CAPS total Scores	CAPS ($P=0.015$)	NR
								CAPS subscores	CAPS I ($P<0.001$)	
									CAPS H ($P=0.006$)	
Butterfield *et al.* (2001)	Olanzapine/ 14 (mean peak dose)	10	Only 1 man in olanzapine group	10 (44.6) : 5 (40.4)	Monotherapy	Mixed combat and physical/sexual abuse	NR	SIP		
								SPRINT DTS TOP-8 SDS	All not significant	CGI-I score
Monnelly *et al.* (2003)	Risperidone/ 0.6	6	Men only	7 (48.9) : 8 (53.5)	Antidepressants	Combat	NR	OAS-M total score	OAS-M I ($P=0.04$)	NR
								OAS-M subscores	PCL-M ($P=0.02$)	
								PCL-M total score	PCL-M I ($P=0.001$)	
								PCL-M subscores		
Padala *et al.* (2006)	Risperidone/ 2.6	10	Women only	11 (39.2) : 9 (43.8)	Monotherapy	Sexual assault/domestic violence	NR	TOP-8 total score	TOP-8 ($P=0.03$)	NR
								CAPS total score HAM-A score HAM-D score	CAPS ($P=0.04$)	
Hamner *et al.* (2003)	Risperidone/ 2.5	5	Men only	19 (50.8) : 18 (53.7)	Antidepressants	Combat	Yes	PANSS total score	PANSS ($P<0.05$)	NR
								PANSS subscores	PANSS-GP ($P<0.05$)	
								CAPS total score	CAPS I ($P<0.05$)[b]	
								CAPS subscores		

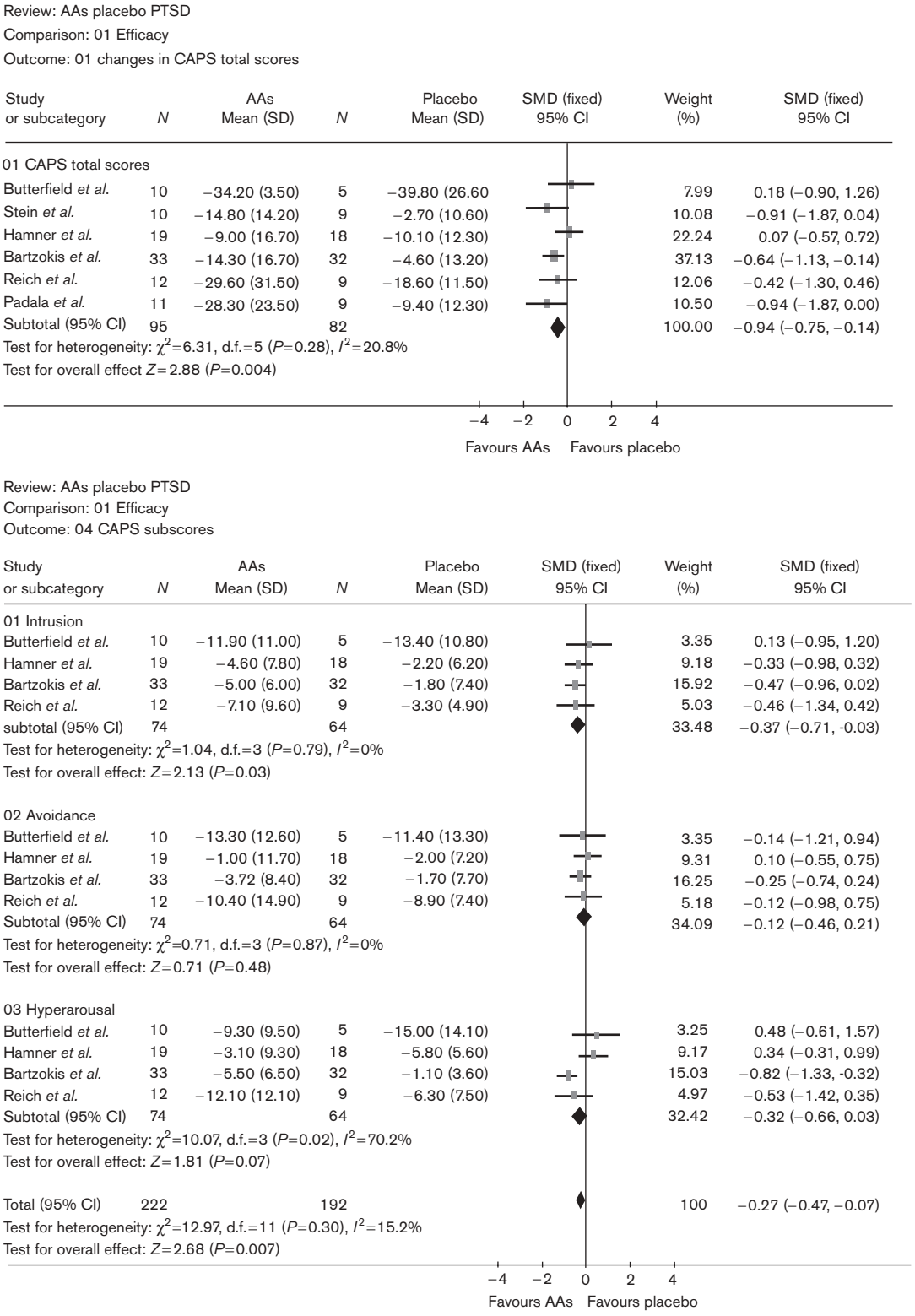
[a]Presented only positive outcome of drug treatment versus placebo.
[b]Completer analysis.
[c]Rated as much or very much improved.
CAPS, Clinician Administered PTSD Scale (I, intrusion subscale; CES-D, Center for Epidemiologic Studies Depression Scale; CGI-I, Clinical Global Impression-Improvement score; DTS, Davidson Trauma Scale; H, hyperarousal subscale); HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; NR, not reported; OAS-M total score; OAS-M, Overt Aggression Scale-Modified for Outpatients (I, intrusion subscale); PANSS, Positive and Negative Syndrome Scale (P, positive symptom subscale); PCL-M, Patient Checklist for PTSD-Military Version; PSQI, Pittsburgh Sleep Quality Index; SDS, Sheehan Disability Scale; SIP, structured interview for PTSD; SPRINT, short PTSD rating interview; SSRIs, selective serotonin reuptake inhibitors; TOP-8, treatment outcome PTSD.

analysis, the heterogeneity was removed ($P = 0.84$, 0%) and the SMD on weight change increased reaching 2.58 (95% CI = 1.60–3.57), suggesting the study was responsible for the heterogeneity.

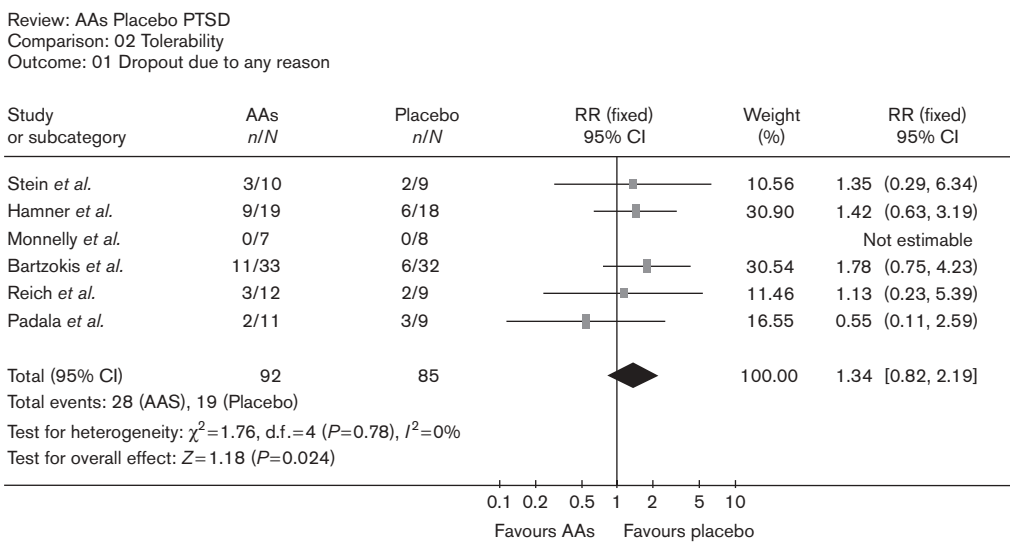
Discussion

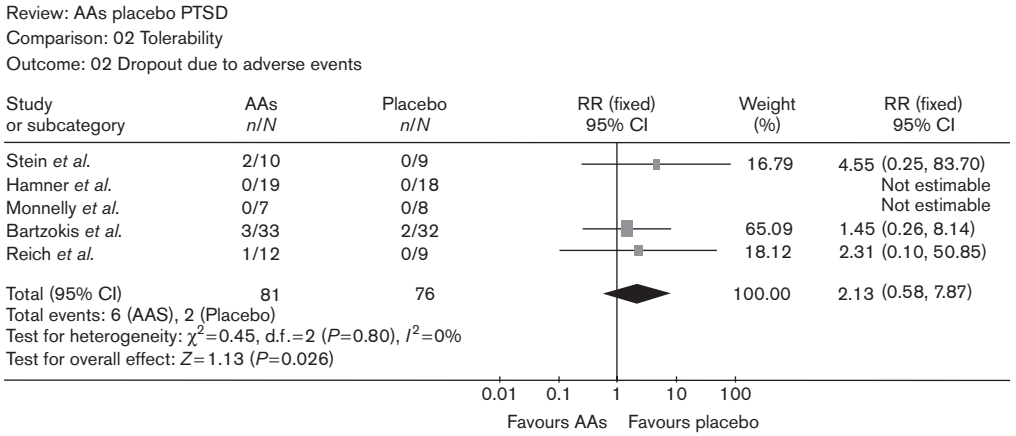
This is the first meta-analysis reporting the potential efficacy and tolerability of AAs (risperidone and olanzapine) as an add-on therapy or monotherapy in the

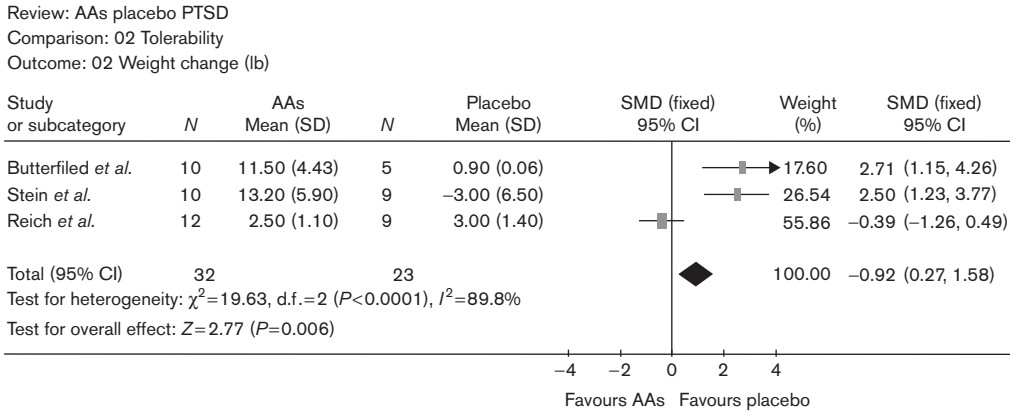
Fig. 1



The results of meta-analysis from seven randomized, double-blind, placebo-controlled clinical trials of atypical antipsychotics (AAs) for posttraumatic stress disorder (PTSD). CAPS, Clinician Administered PTSD Scale; CI, confidence interval; RR, relative risk; SD, standard deviation; SMD, standardized mean difference. The middle vertical line indicates 'line of no effect' and displayed data on the left side of the 'line of no effect' represents favoring AAs over placebo.







treatment of patients with PTSD. We found supporting evidence for efficacy of AAs on global PTSD symptoms and individual PTSD symptom clusters, in particular intrusion based on the findings of mean change from baseline to the end of study in CAPS total scores and CAPS cluster subscores, when comparing drug with placebo treatment. Responder rate, however, did not show any significant difference between AA and placebo groups, but this was calculated for two studies only. Concerning tolerability, the forest plots on dropouts concerning medication compliance demonstrated a trend toward favoring placebo group over AAs group, although it was not statistically significant, the SMD on mean change from baseline in weight highly favored placebo group over AAs group with robust significance.

Psychotic symptoms may be commonly observed in patients with PTSD, although they are not included in

the diagnostic criteria for PTSD. Moreover, AAs have frequently been prescribed for patients with PTSD comorbid with psychotic symptom or behavioral disturbances because of the broad psychotropic effects of AAs (Hamner and Robert, 2005). Contemporary evidence-based pharmacological treatment guidelines, however, (Bandelow *et al.*, 2002; American Psychiatric Association, 2004; Baldwin *et al.*, 2005; Canadian Psychiatric Association, 2006) suggest that AAs should be carefully considered when concomitant psychotic symptoms are present or when first-line approaches have been ineffective in controlling PTSD symptoms. Our meta-analytic results on the mean changes on CAPS total scores confirm these recommendations. The included studies in our meta-analysis used mainly add-on therapy to pre-existing antidepressants, which means paucity of RCT data on AA monotherapy for PTSD, thereby limiting generalization of the results. In fact, the results from two RCTs of AA monotherapy are inconsistent, where the RCT of olanzapine monotherapy (Butterfield *et al.*, 2001) failed to differentiate from placebo on all efficacy measures, whereas another RCT of risperidone monotherapy (Padala *et al.*, 2006) demonstrated superior efficacy measured by changes on CAPS total score compared with placebo. When excluding two monotherapy RCTs from the analysis, the overall SMD on CAPS total score became -0.44 ($P = 0.01$), whereas it turned out statistically nonsignificant with an overall SMD of -0.45 ($P = 0.45$) if we excluded four add-on therapy RCTs, indicating a paucity of monotherapy RCT data and possible inadequate efficacy of AA monotherapy for the treatment of PTSD. Therefore, we could not arrive at any conclusion on whether or not either add-on therapy of AAs or monotherapy with AAs would be superior over each treatment.

Our results also showed that the add-on therapy of risperidone for patients with PTSD may have differential efficacy in PTSD cluster symptoms, in particular intrusion as measured by CAPS subscores (SMD = -0.37), whereas there was no significant difference on avoidance and hyperarousal. The overall SMD for three CAPS subscores was -0.27 and when excluding intrusion subscore from the analysis it decreased to -0.22 without statistical significance ($P = 0.08$), suggesting that the intrusion CAPS subscore mainly accounted for the overall effect. In line with this result, intrusion was frequently and robustly associated with statistical significance than hyperarousal favoring AAs over placebo in the studies (Hamner *et al.*, 2003; Monnelly *et al.*, 2003; Reich *et al.*, 2004; Bartzokis *et al.*, 2005). It has been suggested that intrusion has a different neurobiological pathophysiology compared with the remaining PTSD symptomatology (Blomhoff *et al.*, 1998), and it is closer to psychotic symptoms, which could explain the larger effect of antipsychotics we observed on this aspect.

We failed to find any significant difference in responder rate between AA and placebo treatments. This is likely due to the small numbers of participants and studies. In addition, it should be also remembered that no studies used the conventional criteria of responder '$\geq 30\%$ reduction from baseline in CAPS total score' but only used CGI-I score of 'much or very much improved'. The marginal significance in depression rating scale scores suggests a limited efficacy of AAs on PTSD-associated with depression, although it was not reported in the results section due to limited data and differences in outcome measure (Stein *et al.*, 2002; Bartzokis *et al.*, 2005) (SMD = -0.45; 95% CI = -0.89, -0.01; $P = 0.04$).

It was found that the likelihood of early discontinuation from the study due to any reasons or AEs was numerically higher in the AA group compared with the placebo group, which might indirectly suggest the unfavorable tolerability for AA group versus placebo group, although those were not statistically different between the two treatment groups. Weight gain was evidently more robust in the AA group than the placebo group (SMD = 0.92, $P = 0.006$), in particular, when including only olazapine RCTs (SMD = 2.58, $P < 0.00001$) in the analysis, the SMD was strikingly increased by 180.4%. This tolerability finding clearly suggests that the use of AAs in patients with PTSD should be weighed against the wide range of side effects, including extrapyramidal symptoms and metabolic complications such as weight gain, diabetes, and hyperlipidemias (Hamner and Robert, 2005).

Our study has several shortcomings. The sample size of individual studies varied, ranging from 15 to 65, in total 192 in both AA and placebo groups. Indeed, among six RCTs included in the efficacy outcome analysis for the mean change on CAPS total score, only one RCT had more than 60 participants in both treatment groups and the other five RCTs had less than 40 in both treatment groups. Publication bias should be also considered. Despite the formal test of heterogeneity that has been reported across our analyses, we observed noticeable differences in the primary and secondary outcome measures among identified individual studies, which made us unable to include all the identified studies for outcome analysis. In addition, we also noted considerable difference between observed SMDs in mean change on CAPS total score, which indicates possible clinical heterogeneity between studies that might have arisen from different participants (sex and trauma type) and study characteristics (diagnostic criteria and interview). We included only published papers and the main antipsychotics included in the analyses were olanzapine and risperidone, which might limit generalization of the results. The duration of treatment may have affected our analysis results considering that PTSD need longer term pharmacological treatment. The aforementioned

limitations may be pivotal in the validation of combining individual studies under our single meta-analysis.

Currently, a placebo-controlled trial of adjunctive quetiapine for patients with refractory combat PTSD (defined as a less than 30% reduction in CAPS scores or a minimum CAPS score of 50 at week 8) targeting 212 participants is under investigation in the United States. Adequately powered, well-designed RCTs will have both clinician and patient information sufficient to determine the use of AAs in real clinical practice. Intensive investigation on differential efficacy and AEs between AAs in conjunction with first-line treatment agents for PTSD will also advance our knowledge in this area. Preliminary evidence also suggests that the response of pharmacological treatment may vary in accordance with trauma types, in particular less efficacy of SSRIs with combat PTSD versus noncombat PTSD (Hertzberg *et al.*, 2000), and that psychotic symptoms commonly occur in combat-related PTSD (Kozaric-Kovacic and Borovecki, 2005). Hence new studies on the differential efficacy of AAs might be explored.

In conclusion, we found limited evidence for the potential efficacy of AAs on global PTSD symptoms and individual PTSD symptom cluster, in particular intrusion, compared with placebo treatment. AA add-on therapy or monotherapy, however, appeared not to posit comparable tolerability compared with placebo, despite no statistical differences in between-treatment groups but 'weight gain' was robustly unfavorable to AAs compared with placebo. Clinical relevance and significance relative to our results should be carefully taken into consideration.

Acknowledgement

This study was not supported by any pharmaceutical companies.

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