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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CRD summary
The authors concluded that there was limited evidence for the potential efficacy of atypical antipsychotics on global post traumatic stress disorder symptoms and individual post-traumatic stress disorder symptoms cluster (in particular intrusion) compared with placebo. The authors’ conclusions were appropriately cautious given the small number of diverse trials included.

Authors’ objectives
To determine the effectiveness and tolerability of atypical antipsychotics in the treatment of post-traumatic stress disorder (PTSD) as a monotherapy or add-on therapy.

Searching
PubMed, the National PTSD Center Pilots database, PsycINFO and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for English peer-reviewed publications only. Search terms were reported. The abstracts library of the American Psychiatric Association, reference lists from identified articles and reviews were also searched.

Study selection
Eligible for inclusion in the review were randomised controlled trials (RCTs) that compared atypical antipsychotics (clozapine, olanzapine, risperidone, ziprasidone, quetiapine, aripiprazole, amisulpride) with placebo for the treatment of post-traumatic stress disorder (PTSD), either as a monotherapy or add-on therapy. There were no restrictions on duration of treatment, comorbidities, concomitant medications, presence of psychotic symptoms, severity and duration of PTSD, type of trauma experienced, inpatient or outpatient treatment.

The primary outcome measure was mean change in total score on the Clinician Administered PTSD Scale (CAPS), or the Davidson Trauma Scale (DTS). Secondary outcome measures were mean changes in the subscores of CAPS, response rates measured on the Clinical Global Impression-Improvement (CGI-I) score, number of drop-outs, adverse events, and weight change.

Atypical antipsychotics in the included trials were risperidone or olanzapine only. Duration of treatment ranged from five to 16 weeks. In most of the trials patients were also receiving anti-depressants. Included trials varied in the type of trauma experienced: combat only trauma; non-combat trauma (childhood abuse, sexual abuse, domestic violence); and a mixture of combat and non-combat trauma. All trials concerning combat trauma included men only.

The authors did not state how many reviewers were involved in the study selection process.

Assessment of study quality
The authors did not state whether trial quality was assessed.

Data extraction
Data were extracted in order to calculate risk ratios (RR) and 95% confidence intervals (CI) and standardised mean differences and 95%confidence intervals. Where standard deviations for mean changes were not reported, median standard deviation was used.

One reviewer extracted data, which was then checked by a second reviewer.

Methods of synthesis
Risk ratios and standardised mean differences (SMDs) were combined using a fixed-effect model. Heterogeneity was assessed using the $\chi^2$ and $I^2$ tests. Heterogeneity was explored by the removal of trials from the analysis.

**Results of the review**

Seven RCTs were included in the review (n=192 patients, sample size 15 to 65). The authors described the trials as double blinded in the review title and abstract but there was no mention of blinding in the text of the paper. It was noted that there were discrepancies between values given in the text and those shown in the figures. The values reported below are those given in the text.

**Primary outcome:** Atypical antipsychotics were associated with a statistically significant greater mean change in Clinician Administered PTSD Scale (CAPS) total score than placebo, favouring atypical antipsychotics over placebo (SMD -0.45, 95% CI -0.75 to -0.14; six RCTs); no significant heterogeneity was found.

**Secondary outcomes:** Atypical antipsychotics were associated with a statistically significant greater mean change in CAPS overall subscore (-0.27, 95% CI -0.47 to -0.07; four RCTs) and CAPS subscore of intrusion (SMD -0.37, 95% CI -0.71 to -0.03; four RCTs) compared to placebo.

There was no difference between atypical antipsychotics and placebo in terms of reported patient response rates as measured by CGI-I scores (CAPS subscore for avoidance, CAPS subscore for hyperarousal, drop-outs due to any reason, and drop-outs due to adverse events. However, it was noted that there was statistically significant heterogeneity for hyperarousal ($I^2=70.2\%$).

Atypical antipsychotics were also associated with a statistically significant greater mean change in weight compared to placebo (SMD 0.92 lbs, 95% CI 0.27 to 1.58; three RCTs). However there was evidence of statistically significant heterogeneity ($I^2=89.8\%$). The removal of one trial resulted in the removal of heterogeneity ($I^2=0\%$) and an even greater mean change weight (SMD 2.58 lbs, 95% CI 1.60 to 3.57; two RCTs).

**Authors’ conclusions**

There was limited evidence for the potential efficacy of atypical antipsychotics on global post-traumatic stress disorder symptoms and individual post-traumatic stress disorder symptoms cluster (in particular intrusion) compared with placebo.

**CRD commentary**

This review addressed a clear research question and was supported by adequate inclusion criteria. The search strategy was adequate, but it was limited to published peer-reviewed articles in English only, which increased the risk of both language and publication bias. Data extraction was performed by one reviewer and checked by a second, which reduced the risk of reviewer error and bias in this review process.

There was no assessment of trial quality, which meant that the reliability of the evidence presented could not be determined. The authors acknowledge there was possible clinical heterogeneity among trials causing different treatment effect, but the influence of potential modifiers was not explored.

The authors’ conclusions were appropriately cautious given the small number of diverse trials included.

**Implications of the review for practice and research**

**Practice:** The authors stated that the clinical significant of the results presented should be carefully interpreted and translated into clinical practice.

**Research:** The authors stated that there is a need for adequately powered, well designed RCTs that evaluate atypical antipsychotics in settings and populations that reflect real clinical practice. Future studies should compare the efficacy and safety of atypical antipsychotics used in combination with first-line treatments for PTSD, and evaluate these treatments for patients with both combat and non-combat PTSD.
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