Efficacy of second-generation-antipsychotics in the treatment of negative symptoms of schizophrenia: a meta-analysis of randomized clinical trials

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CRD summary
The authors concluded that most antipsychotics were significantly effective in the treatment of the negative symptoms of schizophrenia, and amisulpride and ziprasidone were slightly better than the others. Second-generation antipsychotics were significantly better than haloperidol. Despite a lack of quality assessment, the authors’ conclusions reflect the evidence and are likely to be reliable.

Authors' objectives
To assess whether second-generation antipsychotics were effective for treating the negative symptoms of schizophrenia.

Searching
Five databases, including PubMed and Cochrane Central Register of Controlled Trials (CENTRAL), were searched up to November 2006, for studies in English. Cross-reference searches were performed, and the search terms were reported.

Study selection
Randomised controlled trials (RCTs) assessing the efficacy of antipsychotics, in patients diagnosed with schizophrenia or schizoaffective disorder, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV or DSM-III-R) or the World Health Organization's International Classification of Diseases (ICD-10), were eligible for inclusion. Trials had to be placebo-controlled and double-blind, and they had to report efficacy for the negative symptoms of schizophrenia. Patients had to receive no more than one antipsychotic medication. Trials of those who were resistant to treatment or who had a history of no response to any antipsychotic medication, were excluded. Additional exclusion criteria were reported. Outcomes had to be reported using standardised scales, including the Scale for the Assessment of Negative Symptoms (SANS) and the modified version of the SANS.

In the included trials, the mean participant age range from 33 to 51 years. Most patients were male; some were outpatients and some were in-patients. The treatments were haloperidol, olanzapine, quetiapine, amisulpride, zotepine, ziprasidone, risperidone, and chlorpromazine, and the dosages varied significantly between trials. Control treatments were placebo or haloperidol. Concomitant medications were permitted in most trials. Trials lasted between six weeks and one year. Where reported, wash-out periods ranged from zero to four weeks.

Trials were selected in duplicate by two reviewers. Disagreements were resolved by clinicians.

Assessment of study quality
The authors did not report an assessment of trial quality.

Data extraction
Data on the outcome of interest (the mean change in negative symptoms score from baseline) were extracted to calculate mean differences, on an intention-to-treat basis, with the last observation carried forward. Attempts were made to contact trial authors where data were missing.

The authors did not state how many reviewers extracted the data.

Methods of synthesis
Standardised mean differences and 95% confidence intervals were calculated, with Cohen's d, using a random-effects meta-analysis. Heterogeneity was assessed using Cochran's Q and I².

Subgroup analyses by drug and by control (placebo or haloperidol) were performed. Publication bias was assessed using Begg's and Egger's tests. Where necessary, standard deviations were imputed using probabilities. Sensitivity analysis
excluding a trial with design issues was performed.

**Results of the review**

**Antipsychotics versus placebo:** There were 16 trials of first- and second-generation antipsychotics, with 3,957 patients (from table 3, which did not match the number of patients in table 1). Compared with placebo, active treatment was associated with a moderate positive effect (SMD 0.40, 95% CI 0.34 to 0.45). There was no evidence of heterogeneity ($I^2=0$). Subgroup analyses showed similar results for olanzapine and risperidone. The effect size was statistically significant and low to moderate for haloperidol (SMD 0.34, 95% CI 0.21 to 0.48; six trials), quetiapine (SMD 0.35, 95% CI 0.22 to 0.48; three trials), and zipotepine (SMD 0.28, 95% CI 0.05 to 0.51; three trials; the confidence interval in the forest plot differed from that in the text and table 3, and the negative 0.05 seems to have been an error). The effect for chlorpromazine (one trial) was not statistically significant, compared with placebo.

**Second-generation antipsychotics versus haloperidol:** There were 10 trials, with 2,085 patients (from table 4, which did not match the number of patients in table 1). Compared with haloperidol, second-generation antipsychotics were associated with a statistically significant positive effect (SMD 0.15, 95% CI 0.04 to 0.26). There was evidence of heterogeneity ($I^2=46$%). Subgroup analyses favoured ziprasidone, risperidone and olanzapine (two trials each), but quetiapine was significantly less effective than haloperidol (SMD -0.22, 95% CI -0.40 to -0.05; two trials). Trends favoured amisulpride and zipotepine, over haloperidol (one trial each). Sensitivity analysis, excluding one trial, did not significantly alter these results.

**Authors' conclusions**

The authors concluded that most antipsychotics (amisulpride, haloperidol, olanzapine, quetiapine, risperidone, ziprasidone and zotepine) were significantly effective, and amisulpride and ziprasidone were slightly better than the others. Second-generation antipsychotics were significantly better than haloperidol.

**CRD commentary**

The review question and inclusion criteria were generally clear. Several databases were searched and attempts were made to minimise error and bias when selecting the trials. It was unclear if similar attempts were made when extracting the data. No quality assessment of the trials was reported, but all were RCTs, and most were placebo controlled. A relatively large number of trials was included in the main analysis.

The synthesis methods seem to have been appropriate. The direction and magnitude of the effects were interpreted, and the pooled estimates for the drugs that were considered effective were small to moderate. No evidence of high statistical variation was found. Attempts were made to explore heterogeneity and consistency, using appropriate methods. The results of the subgroup analyses were reported, but they were limited by the small number of trials in each subgroup, as acknowledged by the authors. They noted that the results of these analyses with few trials could be changed by the publication of new RCTs, particularly with longer follow-up, as the follow-up for some trials was short. They suggested that the results of the haloperidol-controlled analyses should be interpreted with caution, due to the few trials included.

Despite a lack of quality assessment, the authors' conclusions reflect the evidence and are likely to be reliable.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that more trials evaluating the effects of chlorpromazine, on the negative symptoms of schizophrenia, should be carried out, and the results included in future meta-analyses.

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