Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

CRD summary
The authors concluded that antipsychotic drugs differed in many properties and could not be categorised into first- and second-generation groupings; the suggested hierarchies should help clinicians adapt choice of antipsychotics to individual patients’ needs. Limitations such as substantial differences between the included studies and limited generalisability of the findings made it difficult to determine the reliability of these conclusions.

Authors’ objectives
To assess the efficacy and tolerability of 15 antipsychotic drugs in the treatment of schizophrenia.

Searching
The Cochrane Schizophrenia Group's specialised register (available up to August 2009) was searched and five additional electronic sources were searched up to September 2012 for published and unpublished studies. Search terms were reported. The US Food and Drug Administration website, reference lists of other reviews and websites of pharmaceutical companies were searched.

Study selection
Eligible studies were randomised controlled trials (RCTs) in people with schizophrenia or related disorders (schizoaffective, schizophreniform or delusional disorder). Trials had to compare orally administered antipsychotics (as monotherapy) with each other or versus placebo. The 15 eligible antipsychotic drugs were listed in the review. Trials in patients with predominant negative symptoms, concomitant medical conditions or treatment resistance and trials in patients with stable illness were excluded from the review. Trials conducted in China were considered prone to potential bias and were excluded.

The primary outcome of interest was mean overall change in symptoms after six weeks treatment. There were six secondary outcomes of interest including all-cause discontinuation, weight gain and use of anti-Parkinson drugs.

Included studies were published between 1955 and 2012. The mean age of patients was 38.4 years. Where reported, average duration of illness ranged from one to 40 years and treatment durations ranged from four to 78 weeks. Studies included first-generation antipsychotic drugs (haloperidol and chlorpromazine), second-generation drugs (amisulpride, aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone and zotepine) and placebo.

At least two reviewers independently screened studies for inclusion. Discrepancies were resolved through consensus or referral to a third reviewer.

Assessment of study quality
Trial risk of bias was assessed according to the Cochrane risk of bias methods with criteria on blinding, sequence generation, allocation concealment, completeness of outcome data, selective reporting and other biases. Only trials that were at least single-blinded and were not at high risk of bias because of sequence generation or unclear allocation concealment were included in the review.

Two of five reviewers assessed trials for risk of bias.

Data extraction
The mean overall change in symptoms (based on change from baseline on the Positive and Negative Syndrome Scale or Brief Psychiatric Rating Scale) were extracted along with their standard deviations. Data were extracted on an intention-to-treat basis where possible. Data were extracted after six weeks treatment or, where these data were not available, extracted between four to 12 weeks. Where standard deviations were not reported, either authors were contacted for
missing data or standard deviations were estimated from other data. Secondary outcome data were extracted.

At least two reviewers independently extracted outcome data.

**Methods of synthesis**

Direct pairwise comparisons were performed using a random-effects model. Continuous outcomes were combined to calculate standardised mean differences (SMD) using Hedges’ adjusted g (SMD of -0.2 was considered small, -0.5 medium and -0.8 large). Binary outcomes were combined to calculate odds ratios (OR). Pooled 95% confidence intervals (CI) or credible intervals (CrI) were calculated. Numbers needed to harm (NNH) and numbers needed to treat (NNT) were calculated.

A Bayesian hierarchical model using Markov Chain Monte Carlo methods was used to assess direct and indirect treatment comparisons combining standardised mean differences, odds ratios and 95% CrIs. Previously published methods were used to rank treatment efficacy using the surface under the cumulative ranking probabilities that compared each intervention to an imaginary intervention that was always the best without uncertainty. Consistency was assessed through comparison between direct and indirect evidence.

Statistical heterogeneity was assessed through visual inspection of forest plots and using the I² statistic. A priori sensitivity analyses were performed for the primary outcome by excluding single-blind studies, studies that compared high versus low drug doses and by excluding studies in first-episode populations. Meta-regression and post-hoc sensitivity analyses were performed (as reported in the review).

Publication bias was assessed using funnel plots.

**Results of the review**

The review included 212 RCTs (43,049 patients). Most trials were at low or unclear risk of bias for blinding, randomisation and allocation concealment. Around half were at high risk of bias for incomplete outcome data and selective reporting. Only one trial was at low risk of bias for all criteria; most were at high risk of bias for at least one criterion. The overall proportion of withdrawals in the included studies was 35%.

Compared to placebo, all antipsychotic drugs were statistically significantly more effective in improving symptoms. Effect sizes ranged from -0.33 to -0.88. Surface under the cumulative ranking probabilities ranked clozapine as the most effective drug.

All drugs except zotepine were statistically significantly better than placebo for all-cause discontinuation (a measure of drug acceptability). Odds ratios ranged from 0.43 (amisulpride; NNT=6) to 0.80 (haloperidol; NNT=20).

All drugs except haloperidol, ziprasidone and lurasidone resulted in significantly more weight gain than placebo. Effect sizes ranged from -0.17 for aripiprazole to -0.74 for olanzapine.

Extrapyramidal side-effects were not statistically significantly different between placebo and sertindole, olanzapine, quetiapine, aripiprazole, iloperidone, amisulpride and asenapine. Haloperidol resulted in significantly more extrapyramidal side-effects compared to any other antipsychotic drug (effect sizes for significant results ranged from 0.06 to 0.52; NNH ranged from 5 to 11). Zotepine, chlorpromazine, lurasidone, risperidone and paliperidone were among the least well tolerated drugs compared to other antipsychotics. Clozapine resulted in fewer extrapyramidal side-effects compared to other drugs and placebo (ranked as number one according to surface under the cumulative ranking probabilities).

There was some inconsistency between direct and indirect results but the authors did not consider that this was substantial enough to change the results. Other results including findings from meta-regression and sensitivity analyses were reported in the review.

There was evidence of publication bias according to funnel plots.

**Authors’ conclusions**

Antipsychotic drugs differ in many properties and can therefore not be categorised into first-generation and second-
generation groupings. The suggested hierarchies should help clinicians to adapt choice of antipsychotic drug to the needs of individual patients and should lead to modification of clinical practice guidelines.

**CRD commentary**

The review question and supporting inclusion criteria were clearly defined. There was a comprehensive search of the literature and this included a search for unpublished data which reduced potential for missed data. Trial quality was assessed using previously published criteria but most trials appeared to be at some risk of bias. Each stage of the review process was undertaken in duplicate which minimised potential for reviewer error and bias.

The evidence base was large but there was substantial variability across studies. The authors undertook considerable additional analyses in an attempt to investigate potential causes of variability. Various methods were used to assess several direct and indirect comparisons. Inherent uncertainties that surround indirect comparisons should be taken into account when interpreting these findings. The authors acknowledged that the differences in efficacy between drugs were small, particularly when compared to effect sizes for side-effects. They acknowledged that the findings could not be generalised to young people with schizophrenia, patients with predominant negative symptoms, treatment-resistant patients and stable patients. The authors mentioned that the meta-regression with percentage of withdrawals as a moderator could not rule out potential bias associated with high attrition in schizophrenia trials.

This was a comprehensive review that included a large evidence base. The authors acknowledged some of the limitations of the evidence (including small effect sizes). The authors’ conclusions reflect the differences between various antipsychotic drugs. However, there were substantial differences between studies, uncertainties surrounding indirect comparisons and the generalisability of the findings was limited so it was unclear which populations would benefit and to what extent; this made it difficult to determine the reliability of the authors’ conclusions.

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

**Practice:** The authors stated that the differences in efficacy between drugs were possibly substantial enough to be clinically relevant.

**Research:** The authors stated that future multiple treatment meta-analyses could focus on long-term trials.

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