A meta-analysis of the efficacy of second-generation antipsychotics

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CRD summary
This review assessed the efficacy of second-generation antipsychotics (SGAs) compared with first-generation antipsychotics (FGAs) for patients with schizophrenia. The authors concluded that some SGAs are more efficacious than FGAs and, therefore, SGAs are not a homogeneous group. This appears to have been a relatively well-conducted systematic review and the authors’ conclusions are likely to be reliable.

Authors’ objectives
To assess the efficacy of second-generation antipsychotics (SGAs) compared with first-generation antipsychotics (FGAs), and to perform a meta-analysis of trials comparing SGAs for patients with schizophrenia.

Searching
MEDLINE (from 1966 to May 2002), International Pharmaceutical Abstracts (from 1970 to March 2002), CINAHL (from 1982 to April 2002), PsycINFO (from 1987 to January 2002) and the Cochrane Database of Systematic Reviews (Issue 2, 2002) were searched. The authors also searched the reference lists of journal articles and the U.S. Food and Drug Administration website, and included data obtained through the Freedom of Information Act, poster presentations, and unpublished data from Cochrane reviews or other meta-analyses, conference abstracts and manuscripts submitted for publication. Experts in the field were contacted for additional research, while drug manufacturers were contacted for company monographs. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. All of the included studies were RCTs; 95% of which were double-blind. Five RCTs were open or single-blind.

Specific interventions included in the review
Trials comparing the following SGAs with any FGA or another SGA were eligible for inclusion: amisulpride, aripiprazole, clozapine, olanzapine, quetiapine fumarate, remoxipride hydrochloride, risperidone, sertindole, ziprasidone hydrochloride and zotepine.

Participants included in the review
Trials of patients with schizophrenia, or trials involving predominantly schizophrenia patients but including some patients with schizoaffective disorder, were eligible for inclusion. Almost all of the included studies were of adult patients.

Outcomes assessed in the review
Trials that presented quantitative data on symptomatic improvement that would allow the calculation of the effect size were eligible for inclusion.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors assessed validity based on the following criteria: blinding, concealment of allocation, method of randomisation, sample size, internal validity, external validity, statistical analysis, and completeness and clarity of data. The authors did not state how the validity assessment was performed.
Data extraction
Two authors independently extracted data on the mean, sample size and standard deviation from all primary studies.

Effect sizes (SGA minus FGA divided by their pooled standard deviation) were calculated from the 30-item Positive and Negative Syndrome Scale (PANSS), or the 18-item Brief Psychiatric Rating Scale (BPRS) change adjusted for baseline by analysis of covariance. When this score was not available, change scores (baseline minus end point score) or, when both were unavailable, end point scores were used. The Clinical Global Rating was used when neither the PANSS nor BPRS were available. Intention-to-treat analyses were used where possible. The authors compared their effect sizes with those from other systematic reviews.

Methods of synthesis
How were the studies combined?
Fixed-effect models were used to combine the data except when significant heterogeneity was present, in which case random-effects models were used. Dose-response curves were constructed from fixed-dose random assignment double-blind studies of SGAs (and FGAs using haloperidol equivalents) to identify the therapeutic dose range. In randomised, multiple fixed-dose studies, all doses greater than approximately 60% of the therapeutic dose were pooled. The authors conducted a meta-analysis of high dose versus medium dose from randomised, double-blind, fixed-dose FGA studies.

The comparator doses were converted to haloperidol equivalents and investigated as continuous and dichotomous variables, based on a haloperidol cut-off point of 12 mg/day or less versus more than 12 mg/day. These were analysed across all drugs, then for each drug individually. A meta-analysis, based on a two-factor analysis of variance, was conducted to analyse the effect of the dichotomised haloperidol (or all drugs) dose for three drug groups.

The authors generated a funnel plot and examined Kendall's tau and Spearman rank-order correlations of effect versus sample size for presence of publication bias. Rosenthal's fail-safe number technique was used to estimate the number of non significant unpublished studies necessary to change a significant effect size difference to non significant for the significantly different SGAs.

How were differences between studies investigated?
The authors used sensitivity analyses and meta-regression to assess the effect of study characteristics on the results. The characteristics investigated were: study design, i.e. double-blind versus open or single-blind; study duration; completeness of reporting; peer-reviewed publications versus non-peer reviewed publications; quality of the study; global rating versus PANSS or BPRS continuous scales; and the exclusion of certain drugs.

Results of the review
The review included 124 RCTs comparing SGAs with FGAs, and 18 studies comparing different SGAs. There were 22 trials of risperidone, 14 trials of olanzapine, 31 trials of clozapine, 4 trials of sertindole, 5 trials of quetiapine, 12 trials of amisulpride, 4 trials of ziprasidone, 3 trials of aripiprazole, 12 trials of zotepine and 17 trials of remoxipride.

The mean effect size of haloperidol (an FGA) versus placebo, was 0.60 (95% confidence interval, CI: 0.44, 0.76); this was equivalent to about 13 PANSS points or 8 BPRS points.

The mean effect sizes of clozapine, amisulpride, risperidone and olanzapine were statistically significantly greater than the effect sizes of FGAs: 0.49 (95% CI: 0.32, 0.67), 0.29 (95% CI: 0.16, 0.41), 0.25 (95% CI: 0.18, 0.33) and 0.21 (95% CI: 0.14, 0.28), respectively. The effect sizes of the remaining six SGAs were not statistically significantly different from FGAs.

The sensitivity analyses and meta-regression showed essentially identical results.

There was no evidence that the haloperidol dose (or all FGA comparators converted to haloperidol-equivalent doses) affected these results.

The funnel plots generally showed no gross asymmetry, except for those of clozapine and risperidone; this suggested that smaller studies reported better efficacy for SGAs. The number of non significant unpublished studies necessary to
change a significant effect size difference to non significant for the significantly different SGAs was 374 for clozapine, 81 for amisulpride, 139 for olanzapine and 286 for risperidone.

Authors' conclusions
Some SGAs are more efficacious than FGAs. Therefore, SGAs are not a homogeneous group.

CRD commentary
The review question was clear in terms of the study design, participants, interventions and outcomes of interest. Several electronic databases were searched, unpublished data were sought from various sources, and no language restrictions were applied to the search strategy. Thus, the potential for publication bias and language bias was reduced. Publication bias was assessed. The quality of the included studies was assessed using appropriate criteria. The authors did not state how the studies were assessed for relevance or how the quality assessment tool was applied; therefore, the potential for reviewer error or bias cannot be assessed. However, two reviewers independently extracted the data from the studies, thus reducing the potential for reviewer error or bias.

No details of the individual studies were given, although brief study details were provided in a web supplement. Appropriate measures of effect were calculated. The authors assessed statistical heterogeneity and used sensitivity analyses and meta-regression to investigate sources of heterogeneity. This appears to have been a relatively well-conducted systematic review and the authors' conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that clinicians need to weigh up the medical seriousness and reversibility of rare but serious adverse effects versus the frequency and seriousness of more common adverse effects in the context of long-term use. Advantages in terms of efficacy and extrapyramidal symptoms necessitate the consideration of olanzapine, risperidone and amisulpride as first-line drugs.

Research: The authors stated that trials independent of the pharmaceutical industry are needed to reduce the potential for bias.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.