Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis

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CRD summary

The authors concluded that amisulpride, clozapine, olanzapine and risperidone can be effective in treating schizophrenia patients. Second-generation antipsychotic drugs can also result in fewer extrapyramidal side effects, but can induce weight gain. The authors' conclusions reflected the evidence presented, but some potential methodological flaws in the review process meant that the extent to which those conclusions were reliable was unclear.

Authors' objectives

To compare the effects of first and second-generation antipsychotic drugs in schizophrenia patients.

Searching

The search for eligible studies was started in 2005, including MEDLINE to October 2006, Cochrane Schizophrenia Group's Specialised Register and the US Food and Drugs Administration website. Search terms were reported and there were no language restrictions. Previous reviews were searched for additional relevant studies.

Study selection

Randomised controlled trials (RCTs) of oral second-generation antipsychotic drugs (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone and zotepine) compared with first-generation drugs in patients with schizophrenia or related disorders (schizoaffective, schizophreniform or delusional disorders) irrespective of diagnostic criteria were eligible for inclusion in the review. The optimum doses of second-generation drugs were selected in fixed-dose studies. Studies were included where switching of medications between groups was allowed. Comparator drugs included haloperidol, chlorpromazine, perphenazine, fluphenazine, flupenthixol, perazine, thioridazine, levomepromazine, chlopenthixol, zuclopenthixol, mosapramine, tiothixene, clocapramine, trifluoperazine, periciacine and any first-generation drugs. Outcomes of interest included overall efficacy; positive, negative and depressive symptoms; and relapse, quality of life, extrapyramidial side-effects, weight gain and sedation. Outcome measurements included the positive and negative syndrome scale (PANSS), the brief psychiatric rating scale (BPRS) and the clinical global impression scale (CGIS). The majority of included studies had a duration of 12 weeks or less. The mean age of patients was 36.2 years. The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality

Studies were included if they met quality criteria A (adequate randomisation) and B (randomisation without details) according to the Cochrane Handbook, but the authors did not state how the validity assessment was performed. Only double-blinded studies were included in the meta-analysis.

Data extraction

Continuous data were extracted to calculate the standardised mean difference (SMD). Dichotomous data were extracted to calculate the relative risk (RR) and risk differences, with corresponding 95% confidence intervals (CI). The number needed to treat (NNT) or number needed to harm (NNH) were reported, and intention to treat data were used where possible. Authors were contacted for missing data where necessary. Two independent reviewers extracted the data for the review.

Methods of synthesis

A random effects meta-analysis (DerSimonian and Laird) was used to pool the results using the inverse of the variance weighting method. The I^2 statistic was used to assess heterogeneity. Meta-regression or sensitivity analyses were conducted to explore the potential moderating effects of industry sponsorship, chronicity, study duration, western versus Oriental (mainly Chinese) studies, comparator dose, differences in extrapyramidal side-effects, prophylactic antiparkinsonian medication and haloperidol versus low-potency comparator drug. Publication bias was assessed using funnel plots.

Results of the review

One hundred and fifty double-blind studies (n=21,533 patients) were included in the review. The majority of analyses suggested no publication bias.

Pooled results showed that overall efficacy was statistically greater in four second-generation drugs (amisulpride, clozapine, olanzapine, and risperidone) with SMDs ranging from -0.52 to -0.13 , p<0.002. The NNT for one additional responder was between six (95% CI: 4,10) for amisulpride and 15 (95% CI: 9, 36) for risperidone. The four drugs were also more effective in terms of treating positive and negative symptoms (SMD range: -0.36, -0.13, p<0.005). Amisulpride, clozapine, olanzapine, aripiprazole and quetiapine were statistically more efficacious that first-generation drugs in treating depression (SMD range: -0.51, -0.12, p<0.04).

Relapse was improved in four studies (n=1,008) of olanzapine, RR 0.67 (95% CI: 0.49, 0.92; NNT 17), five studies (n=1,174) of risperidone, RR 0.74 (95% CI: 0.63, 0.87; NNT 11) and one study (n=282) of sertindole, RR 0.17 (95% CI: 0.04, 0.73; NNT 14) when compared with first-generation drugs. Quality of life was improved in three of 17 studies following treatment with amisulpride, clozapine, and sertindole (SMD range: -0.44, -0.24, p<0.039).

There were statistically significant reductions in extrapyramidal side effects in all second-generation drugs when compared to haloperidol (p<0.037; NNT varied between two for clozapine and five for zotepine), and this remained using a low comparator dose. However, this was not the case for the majority of drugs when compared with low-potency first generation drugs. Amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole and zotepine were associated with significant weight gain when compared to haloperidol (mean weight gain difference range: 0.9 to 3.4, p<0.04). Increased sedation was reported with clozapine (NNH 5), quetiapine (NNH 13) and zotepine (NNH not significant) (RR range: 1.50 to 2.07, p<0.047) and aripiprazole was significantly less sedating RR 0.65 (95% CI: 0.45, 0.95; p=0.024; no NNH reported). Only clozapine was significantly more sedating than low-potency first generation drugs, p=0.003.

Results for the moderating effects of comparator doses and prophylactic antiparkinsonian medications were inconsistent. The efficacy of clozapine on overall symptoms remained significant, but the effect size was reduced when industry sponsored studies were removed in the sensitivity analysis.

Authors' conclusions

There is substantial variation in the properties of second-generation antipsychotic drugs. Small to medium effects are possible following treatment with amisulpride, clozapine, olanzapine and risperidone in terms of overall efficacy and positive and negative symptoms. Second generation drugs can also result in fewer extrapyramidal side effects, but can induce weight gain.

CRD commentary

The research question was clear and supported by well-defined inclusion criteria. The search strategy appeared to include some relevant sources, and included appropriate steps to minimise publication and language biases. Limited validity assessment beyond the selection of double-blind studies for the meta-analysis means that a full interpretation of the quality of included studies was not possible. The absence of reporting on how studies were selected for inclusion means that errors and bias in the review process could not be fully ruled out. Details of the primary studies were summarised in terms of outcomes arising from the individual drugs. Scant detail was provided on the patient population, making it difficult to interpret the external generalisability of the review findings. Given that heterogeneity was reported to be considerable (although no results of this analysis were apparent), the chosen method of synthesis appeared to be appropriate. The authors' conclusions reflect the evidence presented, but some potential methodological limitations noted above means that the extent to which these are reliable is unclear.

Implications of the review for practice and research

Practice: the authors stated that the results of this review could be used by clinicians for the individualised treatment of patients with schizophrenia.

Research: the authors did not state any implications for research.

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