Review: new generation antipsychotics do not induce fewer extrapyramidal side effects than low potency antipsychotics

Leucht S, Wahlbeck K, Hamann J, et al. *New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. Lancet* 2003;**361**:1581–9.

QUESTION: In patients with schizophrenia, do new generation antipsychotics (NGAs) cause fewer extrapyramidal side effects (EPSs) than low potency antipsychotics (LPAs)?

Data sources

Studies were identified by searching the Cochrane Schizophrenia Group's register of randomised trials (up to March 2002) and hand searching relevant journals and conference proceedings. Bibliographies of relevant articles were reviewed and manufacturers of new generation antipsychotics and authors of primary research articles were contacted for further studies and data verification.

Study selection

Studies were selected if they were randomised controlled trials (RCTs) that compared NGAs (eg, clozapine) with LPAs (eg, chlorpromazine) in patients with schizophrenia or other disorders with psychotic features.

Data extraction

2 reviewers independently extracted data on sample size, patient characteristics, details of the intervention, study duration and quality, and outcomes. The primary outcome was the number of patients who had ≥ 1 EPS. The major secondary outcome was the number of patients who achieved a clinically important improvement.

Main results

31 RCTs (2320 patients) met the selection criteria. 95% of patients had schizophrenia. Other conditions included schizoaffective, schizophreniform, or delusional disorders; or an unclear diagnosis. Comparisons of antipsychotic medications included amisulpride with perazine (1 RCT), clozapine with chlorpromazine (13 RCTs) or thioridazine (1 RCT) or chlorpromazine plus benztropine (1 RCT), olanzapine with chlorpromazine (3 RCTs) or chlorpromazine plus benztropine (1 RCT), quetiapine with chlorpromazine (1 RCT), remoxipride with chlorpromazine (1 RCT) or thioridazine (3 RCTs), risperidone with methotrimeprazine (1 RCT), and zotepine with perazine (2 RCTs) or chlorpromazine (2 RCTs) or thioridazine (1 RCT). Meta-analyses were done using a random effects model.

Fewer patients treated with clozapine than those treated with chlorpromazine developed EPSs (11 RCTs) (table). For all other comparisons, the groups did not differ for number of patients with EPSs. A clinically significant improvement was more frequent in patients treated with clozapine (number needed to treat [NNT] 7, 95% CI 4 to 33) (7 RCTs) or olanzapine (NNT 5, CI 2 to 50) (4 RCTs) or quetiapine ($p=0.05$, 1 RCT) than with chlorpromazine, and more frequent in those treated with risperidone compared with methotrimeprazine (NNT 3, CI 2 to 100) (1 RCT).

Conclusion

In patients with schizophrenia, clozapine induces fewer extrapyramidal side effects than chlorpromazine.

*Clozapine v chlorpromazine in schizophrenia at 4–12 weeks**

Outcomes	Number of RCTs (n)	Weighted event rates		RRR (95% CI)	NNT (CI)
		Clozapine	Chlorpromazine		
Number of patients with ≥ 1 EPS	11 (755)	11%	26%	44% (15 to 62)	7 (4 to 25)

*EPS = extrapyramidal side effect; RCTs = randomised controlled trials. Abbreviations defined in glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

The review by Leucht *et al* addresses the possibility that some or even all of the apparent benefits of the NGAs in schizophrenia may be attributable to the dose of the comparator drug—usually haloperidol. These new drugs have been promoted by their manufacturers as generally having an increased efficacy, favourable adverse effect profile, and a tendency to improve compliance when compared with the older much cheaper drugs. 2 previous systematic reviews have specifically addressed the issue of the effects of comparative dose.^{1–2} The first of these found insufficient data to reliably answer the question.¹ The second review suggested that controlling for the dose of comparator drug removed at least the apparent efficacy benefits, and generated heated debate.²

Unfortunately, the results from this review do not take us a great deal further forward. Leucht *et al* adopted the promising strategy of including any RCT that compared any LPA (usually chlorpromazine) with an NGA (usually clozapine), but the results vary depending on which drugs were compared and whether the dose of comparator was $>$ or < 600 mg chlorpromazine equivalents—making interpretation of their results far from straightforward. The clearest result is that clozapine reduces EPSs. As a group, NGAs may have improved efficacy, but this improvement could be attributable to the known benefits of clozapine in treatment resistant schizophrenia. In further distinction from the previous review,² the NGAs did not reduce EPSs compared with low doses of LPAs.

Thus, when reviewing the apparent benefits of NGAs, the results vary depending on the studies and the particular data included. Overall, the only confident conclusion is that more RCTs are needed. Thus far, almost all have been organised and/or funded by the drugs' manufacturers and designed to obtain Food and Drug Administration approval in the US. There remains a need for large scale, pragmatic, longer clinical trials with more clinically useful outcomes in this area, as in most of psychiatry. Given the genuine uncertainty in this field, and the fact that many of the NGAs have other unpleasant adverse effects—such as weight gain, and possibly diabetes—any prescriptive clinical guidelines would be premature. Continuing uncertainty makes further trials an ethical imperative.

Stephen Lawrie, MRCPsych, MPhil
University of Edinburgh
Edinburgh, UK

- Kennedy E, Song F, Hunter R, *et al*. Risperidone versus typical antipsychotic medication for schizophrenia. *Cochrane Database Syst Rev* 2000;(2):CD00040.
- Geddes J, Freemantle N, Harrison P, *et al*. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *BMJ* 2000;**321**:1371–6.