**Authors' objectives**

To evaluate drug treatment for refractory schizophrenia, and to assess whether atypical antipsychotics are effective in schizophrenia unresponsive to prior antipsychotic treatment.

**Searching**

MEDLINE, PsycLIT and EMBASE were searched for English language reports that were published in full; the searches were conducted in October 1999. The search terms were 'schizophrenia-refractory', 'schizophrenia-resistant', 'amisulpride', 'clozapine', 'olanzapine', 'risperidone', 'sertindole', 'ziprasidone' and 'zotepine'. In addition, the references from retrieved articles were reviewed and the manufacturers of each of the drugs were contacted for reports of relevant trials.

**Study selection**

Study designs of evaluations included in the review

Eligible studies were not restricted by study design. The included studies were randomised double-blind controlled trials (RCTs), other prospective studies, retrospective analyses, case reports and switching studies. The duration of the RCTs ranged from 6 weeks to 1 year.

Specific interventions included in the review

Reports involving the use of amisulpride, clozapine, olanzapine, risperidone, sertindole, ziprasidone or zotepine were eligible. The actual active drugs and the maximum daily doses of drugs administered in the highest-quality trials were: clozapine (450 to 900 mg), haloperidol (15 to 30 mg), chlorpromazine (1,200 to 1,800 mg), fluphenazine (mean dose 29 mg), zotepine (450 mg), risperidone (6 to 15 mg) and olanzapine (20 to 25 mg).

Participants included in the review

Patients with schizophrenia said to be refractory, resistant or unresponsive to at least one drug given previously were eligible. The participants included children and adolescents.

Outcomes assessed in the review

Reports that formally evaluated outcomes were eligible. The measures used to assess the outcomes in the individual studies included the Brief Psychiatric Rating Scale Score (BPRS), Clinical Global Impression (CGI) and PANSS. Response rates were assessed in the review. The included studies used various definitions for response rate, for example: BPRS score of less than 35 and 20% improvement from baseline; 30% improvement in BPRS; much or very much improved on CGI score; CGI score 3 or less; 20% reduction in BPRS, with and without final BPRS score of less than 24; and 20% reduction in PANSS.

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 did not state that they assessed validity.

**Data extraction**

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

The information tabulated in the review were the author and year of publication, study duration, sample size, drugs...
compared, outcome and summary outcome. Studies were scored using a rating schedule for refractoriness (chronicity, severity and resistance to treatment) based on criteria suggested by Kane et al. (see Other Publications of Related Interest). In this schedule, one point is scored for meeting each of the following criteria (maximum 5 points): no period of good functioning in previous 5 years; BPRS score greater than 45; CGI score of 4 or more; pre-trial run-in exclusion using high-dose typical antipsychotics drugs; and prior nonresponse to at least three drugs from two chemical classes given for 6 weeks at doses of greater than 1,000 mg equivalent chlorpromazine.

Methods of synthesis
How were the studies combined?
The studies were grouped as follows and a narrative synthesis was undertaken: randomised double-blind comparisons; other prospective studies; retrospective analyses; case reports; and switching studies.

How were differences between studies investigated?
Differences were discussed within the text with particular emphasis on the refractory score of patients enrolled in studies.

Results of the review
Fourteen reports of 13 RCTs (1,664 patients) were included, in addition to 17 open prospective studies (480 patients) 11 retrospective studies (1,446 patients), 12 case reports and 5 reports of switching studies.

Methodological flaws included studies that lacked adequate statistical power to detect differences between the treatments, the inclusion of treatment intolerant patients, and the variable definition of refractoriness among the studies.

Randomised double-blind comparisons (14 reports). Clozapine was effective in clearly defined treatment resistance. Clozapine was of greater efficacy than chlorpromazine and, in less well-defined resistance, haloperidol. The evidence relating to risperidone and olanzapine was inconclusive.

Studies with a refractory score of 5 (2 RCTs): clozapine was associated with a significantly greater response rate (30%) than chlorpromazine (4%) in one RCT with 268 patients (P<0.01); the other RCT (18 patients) compared risperidone and haloperidol, but changes in BRPS and clinical outcomes were not stated clearly.

Studies with a refractory score of 4 (2 RCTs): risperidone was associated with a significantly increased number of patients with improved BPRS scores than haloperidol (1 RCT, 67 patients); there was no significant difference in the response rates between olanzapine and chlorpromazine in the other RCT (84 patients).

In other reports, refractoriness was much less well-defined. Trials with a refractory score of 1 or 2 (5 RCTs): 2 RCTs with 60 patients (one involving 21 children and adolescents) showed clozapine to be superior to haloperidol.

Trials with a refractory score of 0 (4 RCTs): clozapine was more effective than haloperidol (1 RCT, 423 patients) and olanzapine was more effective than haloperidol (1 RCT, 526 patients). There was no difference between clozapine and either risperidone (1 RCT, 86 patients) and zotepine (1 RCT, 26 patients).

Prospective open studies (17 studies, including 2 controlled studies).

Clozapine appeared overall to be more effective than risperidone in 2 controlled trials (121 patients). Neither study was adequately powered to detect important differences. All of the other studies were uncontrolled and the findings differed considerably.

Authors' conclusions
Overall, clozapine was consistently shown to be effective in refractory schizophrenia, even when this was stringently defined. Data relating to olanzapine and risperidone are equivocal at best, and there was evidence to suggest that they are less effective than clozapine. There is, essentially, no convincing evidence to support the use of any other atypical antipsychotic in refractory schizophrenia. Clozapine remains the drug of choice in this condition.
The aims were stated and the inclusion criteria were defined in terms of the intervention and participants. The inclusion criteria were not defined a priori in terms of the outcome, eligible studies were not restricted by study design, and there was no a priori definition of diagnostic criteria for schizophrenia. Three relevant databases were searched and drug manufacturers were contacted. By restricting eligible material to reports of studies published in full in English, other relevant studies may have been omitted. The methods used to select the studies were not described and different reports of at least one study were presented separately. Study validity was not formally assessed, although some aspects of validity were briefly mentioned in the text of the review. Relevant information was tabulated, but there were no details of the methods used to extract the data and allocate a refractory score. It was unclear whether the data were extracted on an intention-to-treat basis, and side-effects and drop-outs were not considered. In addition, 'response rate' was not defined in several of the primary RCTs and most of the studies were short term (less than 12 weeks).

Implications of the review for practice and research
Practice: The authors stated that clozapine is recommended for the treatment of refractory schizophrenia.

Research: The authors did not state any implications for further research.

Bibliographic details

PubMedID
11198061

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Antipsychotic Agents /therapeutic use; Double-Blind Method; Drug Resistance; Evidence-Based Medicine; Humans; Prospective Studies; Randomized Controlled Trials as Topic; Research Design; Retrospective Studies; Schizophrenia /drug therapy

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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.