Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials
Chakos M, Lieberman J, Hoffman E, Bradford D, Sheitman B

Authors' objectives
To compare the efficacy and tolerability of typical and second-generation antipsychotics for patients with treatment-resistant schizophrenia.

Searching
MEDLINE was searched from 1966 to August 1999, and Current Contents from 1996 to August 1999. In addition, the authors examined the references of the identified studies and obtained information from studies presented at scientific meetings that were pending publication.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies which compared the effectiveness of typical and second-generation antipsychotics were eligible for inclusion. The included studies compared a typical antipsychotic, i.e. chlorpromazine (1,163 to 1,386 mg/day) or haloperidol (10 to 28 mg/day), with a second-generation antipsychotic, i.e. clozapine (176 to 600 mg/day), olanzapine (11 to 25 mg/day), or risperidone (7.5 mg/day). Some studies compared risperidone (6 to 6.4 mg/day) with clozapine (291 to 403 mg/day). The duration of the trials ranged from 6 weeks to 2 years.

Participants included in the review
Schizophrenia. Studies that included patients with chronic refractory schizophrenia were eligible for inclusion. All patients met American Psychiatric Association DSM-III-R criteria for chronic schizophrenia, with the exception of one study in which the patients met the criteria for chronic schizoaffective disorder. The majority of the patients in the included studies were classified as treatment resistant (partial responders with residual symptoms were included), although the definition varied across the studies. The mean age of the patients ranged from 13.7 to 43.2 years.

Outcomes assessed in the review
The inclusion criteria were not defined in terms of the outcomes. The primary outcomes of interest were the Brief Psychiatric Rating Scale (BPRS) total and positive symptom scores. In cases where the BPRS scores were unavailable, the total and positive symptom scores from the Positive and Negative Syndrome Scale were converted. Other outcomes of interest were scores on the Clinical Global Impression, Scale for the Assessment of Negative Symptoms (SANS), Simpson-Angus Rating Scale, and the Abnormal Involuntary Movement Scale.

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

Assessment of study quality
No formal method of validity assessment was reported. However, the authors addressed the following factors relating to study quality: reliable diagnostic criteria; well-defined inclusion and exclusion criteria; well-established scales for the measurement of outcome; and use of an intention-to-treat, last-observation-carried-forward analysis.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. The data were extracted into tables under the following headings: the number of participants; the mean age of the participants; the mean age at onset of illness; the proportion of male patients; medication regimen; study design; improvement in BPRS total score; categorical response rate; and study completion rate. The corrected effect size (Cohen's d) was calculated for each of the included studies (see Other Publications of Related Interest no.1).

**Methods of synthesis**

**How were the studies combined?**

Four approaches were undertaken.

1. A meta-analysis with an analysis of covariance (ANCOVA) model, which used end point scores, was used to examine the score improvement for studies comparing clozapine with typical antipsychotics.

2. The weighted least-squares analysis used the change score as the outcome measure.

3. A categorical data analysis using the Cochran-Mantel-Haenszel approach (see Other Publications of Related Interest no.2) was used to examine the treatment response in patients who met an a priori definition of response.

4. The effect size of treatment was explored by combining the values of the corrected effect sizes across the individual studies that compared clozapine with typical antipsychotics. The values were weighted according to their variance.

**How were differences between studies investigated?**

The authors do not report a formal method for assessing heterogeneity.

**Results of the review**

Twelve RCTs were eligible for inclusion. Ten studies (n=1,801) compared a second-generation antipsychotic with a typical antipsychotic, while 2 studies (n=115) compared risperidone with clozapine.

Clinical outcome: 6 of the 10 studies comparing second-generation antipsychotics with typical antipsychotics reported a significant difference that favoured the second-generation antipsychotics on measures of treatment efficacy; 4 studies found no significant difference. Five of the 7 studies that compared clozapine with typical antipsychotics found a significant difference in favour of clozapine.

Overall psychopathology: results of the ANCOVA analysis showed there was a main effect of treatment, with a greater reduction in psychopathology in the clozapine-treated groups than in those treated with a typical antipsychotic (ANCOVA F=8.51, d.f.=1, 8, p<0.05). The weighted least-squares analysis revealed a non significant effect of treatment, with clozapine-treated patients having greater reductions in total BPRS scores than patients treated with typical antipsychotics (weight least-squares F=3.78, d.f.=1, 14, p=0.07). In 5 studies where there was sufficient data to calculate the effect sizes, the overall estimate of effect was 0.48 (moderate). There were no significant treatment effects for clozapine over all typical antipsychotics on scores for the BPRS positive symptoms subscale or the SANS in the ANCOVA model.

Categorical response to treatment: the pooled data from 5 studies (n=1,028) that categorically compared patients treated with clozapine to those treated with a typical antipsychotic, showed that clozapine-treated patients were 2.45 times more likely to meet the treatment response criteria: 20 to 30% decrease from baseline BPRS total score (chi-squared 45.41, d.f.=1, p<0.001). The pooled data from 2 studies (n=610) that compared treatment with olanzapine to treatment with a typical antipsychotic, showed that olanzapine-treated patients were 1.71 times more likely to meet the categorical response criteria (chi-squared 7.96, d.f.=1, p=0.005). The categorical comparison of 115 patients treated with clozapine to those treated with risperidone was not significant (chi-squared 0.08, d.f.=1, p=0.79).

Extrapyramidal symptoms: 6 studies comparing olanzapine or clozapine with typical antipsychotics showed a significant treatment effect, with patients treated with clozapine or olanzapine exhibiting fewer extrapyramidal symptoms in terms of the score on the Simpson-Angus Rating Scale (ANCOVA F=54.95, d.f.=1, 10, p<0.002).
Tardive dyskinesia: 4 studies comparing olanzapine or clozapine with typical antipsychotics showed no significant treatment effect (ANCOVA $F=6.60$, d.f.=1,7, $p=0.13$).

Adverse events: non-motor adverse events were reported in 6 studies. Hypotension was observed in patients treated with chlorpromazine (42%), clozapine (11%), olanzapine (10%) and risperidone (12%). Sedation was reported by patients administered haloperidol (33.3%), chlorpromazine (21.8%), clozapine (37.4%), olanzapine (35.7%) and risperidone (30.2%). Weight gain was observed for patients treated with chlorpromazine (1%), clozapine (7.1%) and risperidone (23.3%). Concentration problems were reported by patients receiving chlorpromazine (3.4%), clozapine (2.9%) and risperidone (25.6%). Other adverse events reported in patients receiving clozapine included neutropenia, enuresis, and seizures. Neuroleptic malignant syndrome developed in 0.5% of the patients treated with chlorpromazine.

Study completion rates: patients treated with risperidone had the highest completion rates (84.8%; $n=78$) while those treated with antipsychotics had the lowest completion rate (56.1%; $n=398$). In 7 studies that compared treatment with clozapine to treatment with typical antipsychotics, clozapine-treated patients were significantly more likely to complete the clinical trial (odds ratio 1.49; chi-squared 8.95, d.f.=1, $p=0.003$). In 2 studies that compared treatment with olanzapine to treatment with typical antipsychotics, olanzapine-treated patients were also more likely to complete the trial (odds ratio 1.81; chi-squared 11.73, d.f.=1, $p=0.001$). In 2 studies that compared treatment with clozapine to treatment with risperidone, there was no significant difference in completion (chi-squared=0.00, d.f.=1, $p=1.00$).

Authors’ conclusions
The results of this meta-analysis indicated that clozapine exhibits superiority over typical antipsychotics in terms of both efficacy (as measured by improvement in overall psychopathology) and safety (in terms of reduced extrapyramidal side-effects). However, the magnitude of the clozapine treatment effect was not consistently robust. The efficacy data for other second-generation antipsychotics in the treatment of refractory schizophrenia were inconclusive. There is, therefore, a growing need to consider new and different treatment strategies, whether they be adjunctive or monotherapeutic, for schizophrenia that continues to be resistant or only partially responsive to treatment.

CRD commentary
The authors set out a clear review question and reported sufficient inclusion criteria. The search was fairly comprehensive, though the authors could have undertaken an assessment of publication bias. The authors did not report the process of, or the number of reviewers who carried out the study selection and data extraction. However, sufficient details of the included studies were adequately presented in tabular format. Study validity was not formally assessed, but the authors investigated some factors relating to study quality as part of the study selection process. The method of pooling seemed to be appropriate but the authors did not adequately investigate heterogeneity. A formal, statistical test of heterogeneity should have been performed since the included studies differed with regards to the treatment regimen and study duration.

The authors’ conclusions should be treated with caution given the methodological problems outlined, particularly with respect to heterogeneity.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors state that there is a growing need to consider new and different treatment strategies, whether they be adjunctive or monotherapeutic, for schizophrenia that continues to be resistant or only partially responsive to treatment.

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