Authors' objectives
To compare the efficacy of the newer atypical anti-psychotics with those of conventional agents and existing atypical agents.

Searching
MEDLINE was searched from July 1986 to June 1998. Bibliographies of review articles were searched for references. Indexing terms included: 'neuroleptics', 'atypical antipsychotics', 'clozapine', 'risperidone', 'olanzapine', 'sertindole', 'quetiapine', and 'ziprasidone'. Only studies published in English were included in the review.

Study selection
Study designs of evaluations included in the review
Comparative studies were selected when possible; placebo-controlled studies were included when data were limited on newer atypical antipsychotics.

Specific interventions included in the review
Clozapine, risperidone, olanzapine, sertindole, quetiapine, and ziprasidone. These were compared with each other, haloperidol and placebo.

Participants included in the review
Patients with schizophrenia and schizoaffective disorder, including treatment refractory patients.

Outcomes assessed in the review
Clinician rated outcome scales:
Clinical Global Impression Scale (CGI).
Efficacy index.
The Schedule of Affective Disorders and Schizophrenia-Change Version Nurses' Observational Scale for Inpatient Evaluation.
Brief Psychiatric Rating Scale (BPRS).
Positive and Negative Symptom Scale for Schizophrenia (PANS).
Scale for Assessment of Negative Symptoms (SANS).
Montgomery-Asberg Depression Rating Scale (MADRS).
Averse event rated on following scales:
Extrapyramidal Symptoms Rating Scale (ESRS).
Simpson-Angus Rating Scale (SARS).
Barnes Akathasia Scale (BAS).
Abnormal Involuntary movement Scale (AIMS).
Coding Symbol and Thesaurus for Adverse Effects (COSTART).

Association for Methodology and Documentation in Psychiatry Rating Scale (AMDP-5).

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 authors performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
Emphasis was placed on properly designed clinical trials that assessed dosage, expanded efficacy, enhanced adverse effect profile, and cost.

Methods of synthesis
How were the studies combined?
A narrative approach was used to combine studies.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
Twenty-eight studies were included, 18 controlled trial, 3 randomised controlled trials (RCTs) and 6 placebo controlled trials, 1 unknown design.

Clozapine - not discussed systematically (authors only report results of 1 RCT pivotal study, and a more recent study). Authors state that 20 years' experience has established clozapine as an effective treatment for acute and maintenance therapy of schizophrenia, including treatment-refractory schizophrenia. Authors state that numerous controlled studies have provided data corroborating that clozapine causes very few EPS.

Risperidone.
7 controlled studies (n=2305) compared the efficacy of risperidone with that of conventional antipsychotics. Studies ranged from 6-12 weeks, dose of risperidone and haloperidol ranged from 2 - 20 mg/day. Five of the studies investigated treatment-nonrefractory schizophrenia and 2 investigated treatment-refractory schizophrenia. Risperidone was generally as effective as haloperidol in treating positive symptoms, more effective in treating negative symptoms and faster in onset of action. EPS (extra-pyramidal side effects) were less frequent with risperidone compared with haloperidol at lower risperidone doses (<10mg/day) but equal at higher doses.

Risperidone was compared to clozapine in 3 studies (n=205) looking at treatment-refractory schizophrenics, the dose of risperidone ranged from 1-12 mg/day and clozapine from 100-400mg/day. Risperidone was as effective as clozapine in treating positive symptoms but negative symptoms were not evaluated. Incidence of EPS was similar for both agents (low).

Olanzapine.
2 controlled studies compared olanzapine with conventional antipsychotics (haloperidol) in non-refractory schizophrenics. Olanzapine and haloperidol doses ranged from 2.5-20mg/day and 5-20 mg/day respectively. In the first trial patients were randomised to 5 groups (low, moderate or high olanzapine, haloperidol or placebo) Moderate (7.5-12.5mg/day) and high (12.5-17.5 mg/day) doses of olanzapine and haloperidol produced a statistically significant reduction in BPRS scores compared with placebo, and high-dose was also superior to low dose (2.5-7.5mg/day).
high-dose olanzapine group was also statistically superior to the haloperidol and placebo treatment groups in reducing negative symptoms on SANS. The second study found that olanzapine was superior to the haloperidol group on most positive symptoms, negative symptoms and mood improvement. Olanzapine continued to be as effective as haloperidol on positive symptoms in the long term study but improvement in mood and negative symptoms was sustained only in schizoaffective groups. Olanzapine produced fewer EPS than haloperidol during both short (6 weeks) and long (12 months) parts of the study, for both trials.

One study compared olanzapine (mean dose 17.2mg/day) with risperidone (mean dose 7.2mg/day) in treatment refractory schizophrenics. Olanzapine was as effective as risperidone in treating positive symptoms, however olanzapine demonstrated greater efficacy than risperidone in treating negative symptoms as well as in overall response. A greater proportion of olanzapine patients maintained their response at 28 weeks. Significantly fewer EPS were reported by the olanzapine treated patients than by their risperidone-treated counterparts (p<0.05).

**Quetiapine.**

3 placebo controlled trials (n=1265) of inpatients with schizophrenia. In the first trial patients were given 1/5 fixed doses of quetiapine ranging from 75 to 750mg/day, the 4 highest doses (150, 300, 600, 750mg/day) produced superior results to placebo on BPRS and CGI, maximal effect was seen at 300mg/day, and other doses were generally indistinguishable, a dose of 300mg/day was also superior to placebo on the SANS. In the second trial quetiapine was given at either high (≤750mg/day) or low (≤250mg/day) dose, only the high dose group (mean = 500mg/day) showed results superior to placebo on BPRS, CGI and SANS. Quetiapine demonstrated EPS similar to placebo on SARS and BAS. In the third study involving 2 fixed doses of quetiapine (50 and 450 mg/day) only high dose-group was superior to placebo on BPRS, CGI and SANS, Quetiapine similar to placebo on SARS and on frequency of use of antiparkinsonian medication.

5 doses of quetiapine were compared with haloperidol (12mg) in a placebo controlled trial (n=361) of patients with acute exacerbation of chronic schizophrenia (not same as first trial above). Quetiapine 75-750mg/day and haloperidol 12mg were superior to placebo in treating positive symptoms, and quetiapine 300mg/day and haloperidol were superior to placebo in treating negative symptoms. All treatments were comparable in the incidence of EPS.

**Sertindole.**

3 controlled studies (n=1772) compared sertindole with conventional antipsychotics. Sertindole and haloperidol doses ranged from 12-24 and 4-16 mg/day. All 3 studies sertindole was as effective as haloperidol in treating positive symptoms and had significantly lower incidence of EPS (p<0.01). In the 2 studies that measured negative symptoms, sertindole 20mg/day was superior to all doses of haloperidol.

**Ziprasidone.**

3 placebo controlled studies (n=743) were conducted with ziprasidone in nonrefractory hospitalised schizophrenics. In the first study ziprasidone 80 or 160 mg/day was compared to placebo, both groups showed statistically significant changes from baseline BPRS, CGI and PANSS total scores (p<0.01) but did not differ from the placebo group. Scores on the PANSS negative sub-scale showed significant differences favouring the ziprasidone group over placebo. In the second study ziprasidone 40 and 120 mg/day were compared with placebo, there was a statistically significant improvement on BPRS and CGI with 120mg/day of ziprasidone compared with placebo (p<0.01) but not with the lower dose. The third study showed that ziprasidone may also reduce affective symptoms of schizophrenia, improvement in MADRS score was greater with ziprasidone 80 or 160 mg/day than with placebo. EPS were similar in all treatment groups in all studies. One study compared ziprasidone (160 mg/day) with haloperidol (15mg/day) in schizophrenic inpatients. This study found that ziprasidone (160 mg/day) was as effective as haloperidol in reducing BPRS scores, ziprasidone 4, 10 or 40mg/day was less effective. EPS was not reported.

**Authors’ conclusions**

Data from controlled trials on the efficacy and extrapyramidal side effects support risperidone or olanzapine as first-line agents for the treatment of schizophrenia.
CRD commentary
A reasonable review of the area. A literature search was conducted, however this search was limited to one database, published studies and English language studies, this could result in important studies being missed and the results may be susceptible to publication bias. No validity assessment was carried out and the authors do not always report any based study details, such as whether the studies used a randomised design and whether investigators and participants were blinded. The authors do not discuss the drop-out rates within the individual studies which is likely to be high due to the nature of the study population and the side effects of the drugs. Study details are clearly presented, however, there do not appear to be any details of the 3 sertindole studies. It is difficult to draw conclusions from the data presented without having more knowledge on the study designs used and validity of the included studies. Caution should be applied when interpreting the findings of this review.

Implications of the review for practice and research
The author states the following implications for each drug.

Quetiapine: because quetiapine's efficacy has been compared with that of conventional antipsychotics in only one study, and it has not been evaluated in refractory schizophrenia, more research is necessary before any treatment recommendations can be made.

Zisparidone: evidence is needed to evaluate its therapeutic effect. Although higher doses appear to be more effective, dose-response studies are needed to investigate its efficacy in treating positive and negative symptoms of schizophrenia.

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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.