Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo: a meta-analysis of randomized controlled trials
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Authors' objectives
To summarise the efficacy and tolerability of the new antipsychotics risperidone, olanzapine, sertindole and quetiapine in schizophrenia compared to placebo and conventional antipsychotics.

Searching
MEDLINE (1966-January 1998) and Current Contents (1966-March 1998) were searched using the following search terms (detailed strategy available from authors): 'olanzapine or quetiapine or seroquel or risperidone or sertindole'. Additional studies were located by searching the bibliographies of retrieved articles and earlier reviews, and by contacting the respective pharmaceutical companies. No language restrictions were reported.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs). The duration of studies included in the review ranged from 3-12 weeks

Specific interventions included in the review
Risperidone (1-20mg/day), olanzapine (1-20mg/day), sertindole (8-24mg/day), and quetiapine (75-800mg/day). Comparison groups included placebo and conventional antipsychotics (haloperidol 1-20mg/day, chlorpromazine 50-750mg/day, zuclopenthixol 20-100mg/day, perphenazine 16-48mg/day).

Participants included in the review
Individuals with schizophrenia or schizophrenia-like psychoses (schizoaffective disorder). The diagnosis of schizophrenia was made according to American Psychiatric Association DSM-III-R criteria in all trials with the exception of one study that used ICD-9. Approximately 70% of the participants included in the review were male, and they typically showed a chronic disease course with moderate to severe schizophrenic symptoms and were in their mid to late 30's.

Outcomes assessed in the review
The mean change of the Brief Psychiatric Rating Scale (BPRS) total score was used to assess the global improvement in schizophrenic symptoms. Where this was not available the mean change of the total score on the Positive and Negative Syndrome Scale (PANSS) was used. Further outcome measures included the mean change as measured by the Scale for the Assessment of Negative Symptoms (SANS) or the PANSS negative subscore; the number of patients requiring at least one dose of antiparkinson medication; drop-outs due to treatment failure; and drop-outs due to adverse events.

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 reviews performed the selection.

Assessment of study quality
The authors do not appear to have assessed the quality of the studies.

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. Data tables reported in the review include information about the intervention and control groups, sample size, study duration, baseline BPRS, mean illness duration and selected entry criteria.

Methods of synthesis
How were the studies combined?
Pearson's correlation coefficients (r) were calculated according to the method described by Rosenthal (see Other Publications of Related Interest no.1). These effect sizes were then converted into Fisher's 'z' values. Where appropriate (i.e. not where significant heterogeneity was identified) the weighted mean effect sizes of the 'z' values, with 95% confidence intervals (CIs), was calculated. Two-tailed significant tests were used with p values less than 0.05 considered significant.

How were differences between studies investigated?
A chi-squared test was used. Sensitivity analyses were also carried on sub- and supra-therapeutic doses of the new antipsychotics. If a dose regimen of a new antipsychotic was not statistically significantly more effective in terms of BPRS reduction than placebo in one of the studies analysed, this dose was considered to be potentially subtherapeutic and was excluded from the analysis. Doses that induced more EPS without resulting in higher efficacy were also excluded as potentially supratherapeutic.

Results of the review
Twenty-one double-blind RCTs were included with a total of 7245 participants. All except one of the studies used an intention to treat last observation carried forward analysis.

1. Global efficacy:
All new antipsychotics and haloperidol reduced the BPRS global score more effectively than placebo.
Pooled mean BPRS changes were (all results were significant but 95% CI not reported):

- Olanzapine vs placebo r=0.23 (n=574 participants, 2 studies).
- Quetiapine vs placebo r=0.23 (n=991 participants, 4 studies).
- Risperidone vs placebo r=0.28 (n=686 participants, 2 studies).
- Sertindole vs placebo r=0.20 (n=649 participants, 2 studies).
- Haloperidol vs placebo r=0.28 (n=814 participants, 5 studies).

All antipsychotics vs placebo r=0.25, 95% CI: 0.22, 0.28.
Risperidone and olanzapine produced statistically significant but modest effects that were superior to haloperidol, but the olanzapine studies showed significant heterogeneity.
Pooled mean BPRS changes were (95% CI not reported):

- Olanzapine vs haloperidol r=0.07, statistically significant, but significant heterogeneity chi-squared=9.84, p<0.01 (n=2994 participants, 3 studies).
- Quetiapine vs haloperidol r=-0.05 (n=953 participants, 2 studies).
- Risperidone vs haloperidol r=0.06, statistically significant (n=2926 participants, 2 studies).
- Sertindole vs haloperidol r=-0.03 (n=1218 participants, 1 study).

The heterogeneity for olanzapine disappeared in the sensitivity analysis of optimum doses (see 'Sensitivity analysis after
exclusion of subtherapeutic and supratherapeutic doses’).

2. Negative symptoms:

All antipsychotics (atypicals and haloperidol) induced significantly higher reductions from baseline to end point than placebo.

Pooled mean changes in negative symptoms were (all results were significant but 95% CI not reported):

- Olanzapine vs placebo r=0.21 (n=582 participants, 2 studies).
- Quetiapine vs placebo r=0.19 (n=823 participants, 4 studies).
- Risperidone vs placebo r=0.20 (n=686 participants, 2 studies).
- Sertindole vs placebo r=0.21 (n=392 participants, 1 study).
- Haloperidol vs placebo r=0.17 (n=796 participants, 5 studies).

Olanzapine and risperidone were both superior to haloperidol whereas sertindole and haloperidol were equally effective.

Pooled mean changes in negative symptoms were (95% CI not reported):

- Olanzapine vs haloperidol r=0.08, statistically significant (n=2993 participants, 3 studies).
- Quetiapine vs haloperidol r=-0.12, statistically significant (n=487 participants, 2 studies).
- Risperidone vs haloperidol r=0.04, statistically significant (n=3000 participants, 5 studies).
- Sertindole vs haloperidol r=-0.01 (n=1125 participants, 1 study).

3. Use of antiparkinson medication:

All four new antipsychotics were associated with a similar use of antiparkinson medication as placebo and all were clearly superior to haloperidol in this respect.

The use of antiparkinson medication (95% CI not reported):

- Olanzapine vs placebo r=-0.02 (n=418 participants, 2 studies).
- Quetiapine vs placebo r=0.06 (n=716 participants, 4 studies).
- Risperidone vs placebo r=-0.09, 95% CI: -0.18, 0.00 (n=436 participants, 2 studies).
- Sertindole vs placebo r=0.07 (n=494 participants, 2 studies).
- Haloperidol vs placebo r=-0.36 statistically significant, p<0.05 (n=696 participants, 5 studies).

The use of antiparkinson medication (all statistically significant, but 95% CI not reported):

- Olanzapine vs haloperidol r=0.35, but significant heterogeneity chi-squared=5.46, p<0.05 (n=2694 participants, 3 studies).
- Quetiapine vs haloperidol r=0.38 (n=758 participants, 2 studies).
- Risperidone vs haloperidol r=0.12, 95% CI: 0.07, 0.16, p<0.000001 (n=1938 participants, 5 studies).
Sertindole vs haloperidol $r=0.34$ (n=424 participants, 1 study).

The heterogeneity for olanzapine disappeared in the sensitivity analysis of optimum doses (see 'Sensitivity analysis after exclusion of subtherapeutic and supratherapeutic doses'). Three studies chose comparators other than haloperidol (risperidone vs zuclopenthixol; risperidone vs perphenazine; quetiapine vs chlorpromazine). In the latter two studies conventional antipsychotics were not associated with statistically significantly greater use of antiparkinson medication than their newer counterparts ($p=0.54$ and 0.27 respectively).

4. Analysis of dropout rates:

Only the smaller of the sertindole studies provided exact drop-out rates. With the exception of sertindole all antipsychotics showed fewer drop-outs than placebo due to the lack of efficacy of the placebo. No antipsychotic had any significantly different number of drop-outs due to adverse events compared to placebo.

Olanzapine vs placebo $r=0.00$, $95\%$ CI: -0.09, 0.10, $p>0.5$.

Quetiapine vs placebo $r=0.02$, $95\%$ CI: -0.06, 0.09, $p>0.5$.

Risperidone vs placebo $r=0.03$, $95\%$ CI: -0.15, 0.21, $p>0.5$.

Sertindole vs placebo $r=-0.01$, $95\%$ CI: -0.15, 0.13, $p>0.5$.

Haloperidol vs placebo $r=-0.02$, $95\%$ CI: -0.13, 0.10, $p>0.5$.

Only the following were found to be statistically significant for comparisons with haloperidol:

Olanzapine vs haloperidol. Drop-outs due to treatment failure $r=0.09$, $95\%$ CI: 0.05, 0.13, $p<0.0001$.

Drop-outs due to adverse events $r=0.06$, $95\%$ CI: 0.02, 0.10, $p<0.005$.

Quetiapine vs haloperidol.

Drop-outs due to adverse events $r=0.17$, $95\%$ CI: 0.10, 0.24, $p<0.0001$.

5. Sensitivity analysis after exclusion of subtherapeutic and supratherapeutic doses:

Several of the studies were designed as dose finding studies for new compounds and so a sensitivity analysis was conducted to exclude doses now thought to be subtherapeutic or supratherapeutic. The sensitivity analyses did not change the overall results, but quetiapine was no longer statistically significantly inferior to haloperidol in the treatment of negative symptoms and risperidone showed a tendency to be more effective and to be associated with less EPS.

Authors' conclusions

This meta-analysis suggests that patients treated with olanzapine and risperidone showed a greater overall improvement than patients treated with haloperidol or other conventional antipsychotics. Both quetiapine and sertindole turned out to be as effective as haloperidol and all compounds analysed were superior to placebo with regards to antipsychotic efficacy. In addition, all new antipsychotics were associated with less frequent use of antiparkinson medications than haloperidol, with risperidone appearing to have slightly less favourable EPS-profile than the other new antipsychotics. This meta-analysis confirms that not only atypical but also conventional antipsychotics such as haloperidol are effective against negative symptoms in general.

CRD commentary

This is a clearly presented review based around a well-defined review question. The literature search is based around a reasonable search of the literature, which does not limit the language of publication and also seeks unpublished data in an attempt to reduce the chance of publication bias. However, the authors do not give details of how studies were
The methods used to pool and analyse the data would appear to be appropriate and the level of heterogeneity between studies was taken into account using the chi-squared test. However, although the authors state that they calculated the 95% CI very few of the effect sizes were accompanied by confidence intervals in the text. 95% CIs were represented graphically in the accompanying figures, but the exact values were not reported. The results otherwise appear to be comprehensive and the important issue of drop-outs is considered in detail. The very nature of the patient population and the side-effects of the drugs means that drop-outs in these types of trials are often very common. In view of the data presented the authors’ findings would appear to be valid and their suggestions for future research would seem reasonable. However, the above comments should be borne in mind when interpreting the findings.

95% CI are often not reported for individual studies and pooled effect sizes.

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

Research: The authors state 'more studies comparing the other new compounds with clozapine are needed. Future studies should also compare the efficacy and safety of the new compounds taking their optimum doses into account; use other (preferably less EPS-associated) conventional antipsychotics than haloperidol as control agents; evaluate the new antipsychotics in maintenance treatment; and specifically assess patients with predominant persistent negative symptoms, antipsychotic naive patients, first-episode patients and in particular treatment-resistant patients'. Also 'further studies with other low-potency conventional antipsychotics and studies on patients with predominant primary negative symptoms are necessary'.

Bibliographic details

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Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

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