Low dose vs standard dose of antipsychotics for relapse prevention in schizophrenia: meta-analysis

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CRD summary
This review concluded that efficacy of low dose and standard dose antipsychotic medication may be comparable in preventing relapse in schizophrenia and schizoaffective disorders. Less than half the standard dose may increase the risk of overall treatment failure. The authors’ conclusions reflect the evidence presented but the conclusions should be interpreted with caution because of a lack of details on quality assessment and the small number of included studies for each pooled outcome.

Authors’ objectives
To compare the efficacy between standard dose versus low dose or very low dose of antipsychotics for relapse prevention in schizophrenia.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Current Contents, E-Journals Database and Science Citation Index Expanded were searched up to August 2009. Search terms were reported. There were no language restrictions. Reference lists of relevant reviews and studies were screened. Pharmaceutical companies were contacted for any additional trials. ClinicalTrials.gov and the United States Food and Drug Administration website were searched for unpublished trials.

Study selection
Double-blind randomised controlled trials (RCTs) that compared standard dose versus low dose of antipsychotics for relapse prevention with a minimum follow-up duration of 24 weeks in patients with schizophrenia or schizoaffective disorder (defined using recognised criteria) were eligible for inclusion. Only trials of patients with stable psychopathology at baseline were included. Eligible trials had to involve a standard dose group with a mean dose ≥1 DDD (defined daily dose) unit and less than the upper limit of locally approved dose range. This was compared against either a very low dose group with a mean dose of <0.5 DDD unit or a low dose group with a mean dose of ≥0.5 and <1 DDD unit. The primary outcome was the rate of overall treatment failure (defined as discontinuation of assigned treatment for any reason). Secondary outcomes were the rate of hospitalisation, relapse and drop-outs due to side effects.

Most of the included studies evaluated first-generation antipsychotics; some studies evaluated second-generation antipsychotics. Definition of relapse varied between included studies. Study duration ranged between 24 and 104 weeks. The mean age of patients ranged from 28.3 to 50.1 years. Most studies included clinically stable ambulatory patients.

Two reviewers independently assessed studies for inclusion.

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

Data extraction
Data were extracted on event rates to enable calculation of risk differences (RDs) with 95% confidence intervals (CIs) on an intention-to-treat basis. Study authors were contacted for missing data.

Two reviewers independently performed data extraction.

Methods of synthesis
The studies were combined in a meta-analysis. Pooled risk differences with 95% CIs were calculated with a random-effects model. Where there were significant differences between treatment groups, the number needed to harm (NNH)
was calculated. Statistical heterogeneity was assessed using visual inspection of forest plots and $\chi^2$ and $I^2$ statistics. Publication bias was assessed using funnel plots. Subgroup analyses were conducted on the basis of patients receiving depot antipsychotics.

**Results of the review**

Thirteen studies were included in the review (1,395 patients: 739 in standard dose groups, 457 in low dose groups and 199 in very low dose groups). Most studies had follow-up of at least one year.

There was no significant difference in the rate of overall treatment failure, relapse or hospitalisation between standard dose and low dose groups.

Compared with standard dose treatment, very low dose treatment was associated with a significant increase in the rate of overall treatment failure (RD 0.14, 95% CI 0.02 to 0.26, NNH=8, 95% CI 4 to 50; six RCTs), hospitalisation (RD 0.11, 95% CI 0.04 to 0.17, NNH=9, 95% CI 6 to 25; five RCTs) and relapse (RD=0.26, 95% CI 0.12 to 0.41, NNH=4, 95% CI 3 to 8; six RCTs).

No significant difference was found between standard dose group and low dose group or very low dose group in the rate of drop-outs due to side effects.

Significant heterogeneity was observed only in the outcome of relapse for the comparison between very low dose and standard dose groups ($I^2$=59%). Subgroup analyses on patients who received depot antipsychotics showed similar results. No evidence of publication bias was found for efficacy outcomes.

**Authors' conclusions**

The efficacy of low dose and standard dose antipsychotic medication may be comparable in the prevention of relapse in schizophrenia and schizoaffective disorders. Less than half the standard dose may increase the risk of overall treatment failure.

**CRD commentary**

This review's inclusion criteria were clear. Several relevant sources were searched for published and unpublished studies without language restrictions, which reduced risks of publication and language biases. Sufficient attempts were made to minimise reviewer bias and errors during study selection and data extraction. Double-blind RCTs were included in the analysis, but no formal quality assessment was performed. Heterogeneity was assessed and appropriate methods were used to pool the results.

The authors' conclusions reflect the evidence presented but the conclusions should be interpreted with caution because of a lack of details on quality assessment and the small number of included studies for each pooled outcome.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further well-designed clinical trials were required to assess the impact of different dosing of antipsychotics in patients with schizophrenia.

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