Oral versus depot antipsychotic drugs for schizophrenia: a critical systematic review and meta-analysis of randomised long-term trials

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CRD summary
This largely well-conducted review concluded that available evidence suggested a clinically meaningful superiority of intramuscular depot injection compared with oral administration of antipsychotic drugs in outpatients with schizophrenia, but that further research is needed. The authors' conclusions are appropriately cautious given the suboptimal quality of included trials and limited evidence available.

Authors' objectives
To compare intramuscular depot injections with oral formulations of antipsychotic drugs in people with schizophrenia or related disorders.

Searching
Published trials in any language were identified through an initial search of Cochrane reviews on single depot antipsychotics which had already been undertaken. Update searches in the Cochrane Schizophrenia Group Register were conducted (which was compiled from BIOSIS Previews, CINAHL, ClinicalTrials.gov, Dissertation Abstracts, EMBASE, LILACS, MEDLINE, PSYNDEX, PsycINFO, RUSSMED and Sociofile) from 2009. Search terms were reported. Reference lists of included studies were searched. Relevant journals and conference proceedings were handsearched. Manufacturers of second generation antipsychotic depots were contacted for details of further trials.

Study selection
Randomised controlled trials of intramuscular depot compared with oral formulations of antipsychotic drugs in outpatients with schizophrenia or related disorders (including schizophreniform, schizoaffective, or delusional disorder) were eligible for inclusion. Outpatients were eligible for inclusion regardless of age, gender, or diagnostic system used. Trials with fewer than 25% inpatients or with an initial inpatient phase were also eligible. Follow-up time was required to be one year or longer.

The primary outcome was the number of participants who relapsed. Secondary outcomes included rehospitalisation due to worsening of psychopathology, non-adherence and drop-outs due to inefficacy of treatment, adverse events, or any other reason.

Most participants had schizophrenia diagnosed by standardised or clinical criteria. The average age of participants was 35.89 (±7.36) years (where reported). Mean illness duration ranged from 4.4 to 16.7 years. In included trials, the most frequently used intervention was fluphenazine depot; other interventions included risperidone long-acting-injectable, haloperidol-decanoate, and zuclopenthixol depot. Oral comparators were fluphenazine, pimozide, zuclopenthixol, quetiapine, and olanzapine. Some trials used different antipsychotics in the depot compared with the oral administration group. Doses varied and were higher in the older trials. Relapse was variably defined. Included trials were conducted in the USA, Europe, Russia, and China.

One reviewer selected studies for inclusion; a second reviewer verified the selection in a random sample of 20%.

Assessment of study quality
Methodological quality was assessed by two independent reviewers using the Cochrane risk of bias tool. This covered randomisation, allocation concealment, blinding, data completeness, selective reporting, and other biases.

Data extraction
Two independent reviewers extracted outcome data. Relative risks (RRs) and 95% confidence intervals (CIs) were derived from the data in each trial. Analyses were conducted by intention-to-treat (ITT) where possible. Absolute risk differences and numbers needed to treat/harm (NNT/NNH) were also reported. Trial authors and manufacturers were contacted for missing information or corrections. Disagreements were resolved by discussion or by involving a third
reviewer.

**Methods of synthesis**

Pooled relative risks and corresponding 95% confidence intervals were calculated using the Mantel-Haenszel random-effects model by DerSimonian and Laird. A fixed-effect model was used as part of the sensitivity analysis. Heterogeneity was assessed using $X^2$ and $I^2$; $I^2$ of 50% or higher was considered substantial heterogeneity.

Subgroup analysis investigated the influence of single blind, double blind, and open trials. Sensitivity analyses were conducted to test the influence of Chinese studies and of different depot and oral drugs.

Publication bias was assessed using funnel plots.

**Results of the review**

Ten trials (n=1,700 participants) were included in the review; sample sizes ranged from 36 to 710. Overall trial quality was average; three studies were open, two were single-blind, and five were double blind. Only three trials described the randomisation method. Drop-out rates ranged from 11 to 69% (median 38%). Eight trials followed the intention-to-treat principle. Follow-up ranged from one to two years.

**Relapse**: Intramuscular depot injection significantly reduced relapse rates compared with oral administration of antipsychotics (RR 0.70, 95% CI 0.57 to 0.87) in ten trials (n=1,672). No significant heterogeneity was observed. The number needed to treat with depot administration of antipsychotics to prevent one relapse was 10 (95% CI 6 to 25).

**Rehospitalisation**: The analyses showed no significant difference in rehospitalisation between participants who received antipsychotics by depot or orally (RR 0.78, 95% CI 0.57 to 1.05) in seven trials (n=1,476). When trials using different drugs in the depot compared with oral administration groups were excluded, depot was significantly more likely to reduce rehospitalisation.

**Drop-outs**: Significantly fewer patients in the depot group dropped out due to inefficacy of treatment (RR 0.71, 95% CI 0.57, 0.89) in nine trials (n=1,380), but there were no differences between groups for dropouts for any reason, or dropouts due to adverse events.

**Non-adherence**: The analyses showed no significant difference between participants who received antipsychotics by depot or orally (RR 0.76, 95% CI 0.37 to 1.56) in five studies (n=1,141).

Sensitivity analysis confirmed the superiority of depot administration for drop-outs and rehospitalisation when a fixed meta-analysis was conducted.

Heterogeneity was investigated as reported for relapse ($I^2=41\%$), rehospitalisation ($I^2=42\%$) and non-adherence ($I^2=58\%$). Heterogeneity was attributed to differences in blinding, outliers, and limited amount of outcome data available.

Funnel plots did not indicate publication bias.

**Authors’ conclusions**

Available evidence suggested a clinically meaningful superiority of depot medication compared to oral antipsychotic drugs in outpatients with schizophrenia, but further research is needed.

**CRD commentary**

This review addressed a clear question. Inclusion criteria were adequately specified to enable replication. Relevant databases were searched with no language restrictions. Attempts were made to identify unpublished data. Publication bias was assessed. Language and publication biases appeared to have been minimised. Suitable methods to minimise risk of reviewer error and bias were reported for data extraction and validity assessment, but the process was less robust for study selection.

The decision to pool trials using meta-analysis was appropriate; heterogeneity was assessed. The authors acknowledged some of the methodological difficulties with the review, specifically the relatively poor reporting in the included trials.
and the differences in the type of drug offered in depot compared with oral administrations.

This was a largely well-conducted review. The authors’ conclusions are appropriately cautious given the suboptimal quality of included trials and limited evidence available.

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

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

**Research:** The authors stated that future studies should compare the same substances in the oral and depot groups, always investigate hospitalisation and adherence, and possibly use single-blind design with blind raters.

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