Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials
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CRD summary
This review concluded that in certain clinical situations, anti-psychotic co-treatment could be superior to monotherapy for people with schizophrenia. Due to possible publication bias and heterogeneous findings, firm clinical recommendations could not be made. It is appropriate that the authors were cautious in their conclusions as the analysis had some limitations and its generalisability was unclear.

Authors' objectives
To assess the therapeutic and adverse effects of anti-psychotic co-treatment compared with monotherapy in schizophrenia.

Searching
The Cochrane Schizophrenia Group trial register was searched up to March 2007. Search terms were reported and there were no language restrictions. The reference lists of included trials were also scanned and first authors contacted to enquire whether they were aware of additional trials.

Study selection
Randomised controlled trials (RCTs) were eligible for inclusion if they compared antipsychotic monotherapy with combination treatment of the same antipsychotic plus a second antipsychotic, in patients with schizophrenia or a related disorder. The primary outcomes were a clinically significant response, dropout rate, and relapse rate. A clinically significant response was defined as at least a 50% reduction in score on the Positive and Negative Syndrome Scale or the Brief Psychiatric Rating Scale, or a categorisation of "much better" on the Clinical Global Impressions scale. Several secondary outcomes including adverse effects were also of interest.

The mean age of participants in the included trials was 33.4 years (range 16 to 65), the majority were male (62.3%) and had schizophrenia. The majority of participants were in-patients in the chronic illness phase; there were a small number of trials of patients with acute illness. The primary outcomes were a clinically significant response, dropout rate, and relapse rate. A clinically significant response was defined as at least a 50% reduction in score on the Positive and Negative Syndrome Scale or the Brief Psychiatric Rating Scale, or a categorisation of "much better" on the Clinical Global Impressions scale. Several secondary outcomes including adverse effects were also of interest.

The RCTs were most commonly conducted in China and the USA. The monotherapy was either a first-generation antipsychotic or a second-generation antipsychotic. Combination treatments consisted of two first-generation antipsychotics, a first- in combination with a second-generation antipsychotic, and two second-generation antipsychotics. The majority of trials used clozapine. Other antipsychotics used in more than one RCT were chlorpromazine, risperidone, and sulpiride. There were a few trials in which the combination arm dose of one or both antipsychotics was lower than in the monotherapy arm. Treatment duration ranged from four to 52 weeks. In some trials, the combination treatments were started together at initiation and, in some, the second antipsychotic was added following non-response to monotherapy.

Two authors independently selected trials.

Assessment of study quality
The authors reported whether trials were double-blinded. Further details were not provided.

Data extraction
For dichotomous outcomes, such as clinically significant response, the number of participants with the event were extracted and the relative risk (RR) and 95% confidence interval (CI), based on intention-to-treat, were calculated. For continuous data the effect size was calculated using Hedges' g.

Two researchers independently extracted data.
Methods of synthesis
Trials were pooled using a random-effects meta-analysis. Statistical heterogeneity was assessed using the $I^2$ statistic ($I^2$ of 50% or higher showed considerable heterogeneity). For the nine trials with more than one monotherapy arm, the combination group was entered twice into the meta-analysis.

Nine sensitivity analyses were undertaken and these variables were entered into a meta-regression: double-blind versus other trials, Chinese versus other trials, acutely exacerbated versus chronically ill patients, combined treatment at initiation versus after no response to monotherapy, comparable versus reduced antipsychotic dose in the combination treatment, less than ten weeks treatment duration versus ten weeks or more, clozapine versus non-clozapine combinations, the different combinations of first- and second-generation antipsychotics, and for trials with multiple arms they investigated whether entering the combination only once (by combining the multiple monotherapy groups) altered the results.

An additional subgroup analysis was conducted investigating the variation in antipsychotic dose (in chlorpromazine equivalents) between monotherapy and combination therapy in those trials that reported superior efficacy with combination treatment compared with those reporting no difference. The possibility of publication bias was assessed using a funnel plot.

Results of the review
Nineteen RCTs were included (n=1,216) and sample sizes ranged from 17 to 233. Fifteen studies were double-blind, one single-blind, two were not blind, and one was not reported.

Combination therapy was associated with a significant increase in positive clinical response compared with monotherapy (RR 0.76, 95% CI 0.63 to 0.90). There was considerable heterogeneity in this group of studies ($I^2=79\%$).

Compared with combination therapy, monotherapy was associated with an increase in drop-out due to any reason (RR 0.65, 95% CI 0.54 to 0.78) and drop-out related to treatment inefficacy, but there was no difference in adverse events. Data on other outcomes were not reported due to the sparse data available.

Based on the sensitivity analysis, combination therapy was not superior to monotherapy in five of the subgroups. Based on the meta-regression, there were three statistically significant moderators of superior efficacy with combination treatment: a similar dose in the monotherapy and combination therapy arms, second- plus first-generation combinations, and concurrent initiation of the combination therapy.

There was statistically significant asymmetry in the funnel plot suggesting that trials with negative results were not published and were missing from the review.

Authors’ conclusions
In certain clinical situations, anti-psychotic co-treatment might have been superior to monotherapy for people with schizophrenia. The data was subject to possible publication bias and was too heterogeneous for firm clinical recommendations, emphasising the need for future research.

CRD commentary
This review had a clearly stated review question. The authors stated that the register they searched for RCTs used multiple sources for published and unpublished trials up until June 2006, but only MEDLINE thereafter, which means that relevant trials may have been missed. Appropriate methods were used to minimise error and bias in trial selection and data extraction. The assessment of trial quality was limited as it only included blinding, but quality was considered in the synthesis. Statistical heterogeneity was high in the analysis of one of the primary outcomes. The authors investigated relevant sources of heterogeneity in the main analysis, but the extent of heterogeneity in the subgroups was unclear. There were also a large number of moderator variables, in the subgroup and regression analyses, relative to the number of trials, which makes the usefulness of the findings unclear.

It was appropriate that the authors were tentative in their conclusions. The results of the analysis cannot be considered to be a precise estimate of the difference between anti-psychotic monotherapy and combination therapy, due to the
limitations outlined above and the large number of trials in which the control groups were used more than once.

Implications of the review for practice and research

Practice: The authors stated that the results from their meta-analysis were insufficient to derive conclusive clinical recommendations. Until further research is available, combination antipsychotic treatment should be reserved for severely ill patients with a documented lack of response to monotherapy during the acute or chronic phase of illness.

Research: The authors stated that large scale trials are required comparing monotherapy with combination therapy of antipsychotics other than clozapine, and comparing combination treatment at initiation with waiting until monotherapy treatment failure. These trials should last longer than ten weeks and be conducted in non-Asian as well as Asian countries.

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