Augmentation of clozapine with a second antipsychotic: a meta-analysis of randomized, placebo-controlled studies

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CRD summary
The authors found that augmentation of clozapine with an antipsychotic for up to 16 weeks was of marginal therapeutic benefit. The meta-analysis was well-conducted, but lack of detail about review methods suggests that a degree of caution may be advisable in interpreting the authors’ conclusions.

Authors’ objectives
To evaluate the effectiveness of augmenting clozapine with a second antipsychotic drug.

Searching
PubMed, EMBASE, PsycLIT, Cochrane Central Register of Controlled Trials (CENTRAL) databases and Google Scholar (including the citation function) were searched in April 2008. Search terms were reported. Reference lists of articles retrieved were handsearched. The search was restricted to studies in English.

Study selection
Randomised placebo-controlled trials of the addition of a second antipsychotic to treatment with clozapine were eligible for inclusion. Included studies needed to use accepted symptom-rating scales at baseline and endpoint and conduct blinded outcome assessment.

The studies in the review included outpatients and/or inpatients who in most cases met psychiatric diagnostic criteria for schizophrenia. Mean age ranged from 30 years to 43 years. Trial entry criteria varied: in most cases, participants had been taking clozapine for periods that ranged from at least six weeks to one year (where stated), had poor response to other antipsychotics and experienced inadequate response to clozapine. Second antipsychotics used were chlorpromazine, sulpiride, risperidone, haloperidol, aripiprazole and amisulpride. Doses varied across studies, but in most cases recognised therapeutic drug doses were used. In most study groups more than 90% of participants completed treatment (range 50% to 100%). All studies used either Positive and Negative Symptom Scale (PANSS) or Brief Psychiatric Rating Scale (BPRS) to measure outcomes. Other outcomes measured included Clinical Global Impression (CGI) scores and risk of withdrawal for any reason. Duration of follow up ranged from six to 16 weeks.

The authors stated neither how papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
The following aspects of study validity were reported: allocation concealment, blinding, use of intention-to-treat analysis and withdrawal rate. The authors did not state how the assessment was performed.

Data extraction
Standardised mean differences (SMDs) were calculated for continuous outcomes and risk ratios (RRs) for dichotomous outcomes, with 95% confidence intervals (CIs).

The authors stated neither how data were extracted for the review nor how many reviewers performed the data extraction, but noted that study authors were contacted for more information as necessary.

Methods of synthesis
Studies were combined using a fixed-effect model. Heterogeneity was assessed with the $I^2$ statistic. If heterogeneity was detected ($I^2 \geq 50\%$), a random-effects model was used. Publication bias was assessed with a funnel plot. Subgroup analysis was conducted by study duration (under 10 weeks versus longer). Meta-regression was used to examine the effect of study duration. Studies in which the participants differed in clozapine exposure or response were excluded in a
sensitivity analysis.

**Results of the review**

Ten randomised controlled trials (RCTs) were included (n=522, range 10 to 207). Three reported adequate allocation concealment, nine were double blinded and eight used intention-to-treat analysis.

There was a significantly greater reduction in PANSS/BPRS scores in the intervention group (SMD -0.180, 95% CI -0.356 to -0.004, $I^2=33.5%$; 10 RCTs).

Subgroup and meta-regression analyses showed that study duration had no statistically significant impact on effect size. There was no statistically significant difference between the groups in CGI scores (WMD -0.661, 95% CI -1.475 to 0.151, $I^2=78%$; four RCTs) or in risk of withdrawal (RR 1.261, 95% CI 0.679 to 2.345, $I^2=0%$; seven RCTs).

No evidence of obvious publication bias was detected.

**Authors' conclusions**

Augmentation of clozapine with an antipsychotic for up to 16 weeks was of marginal therapeutic benefit.

**CRD commentary**

The objectives and inclusion criteria of the review were clear and relevant sources were searched for studies. The restriction to studies in English made the review prone to language bias. It was unclear whether steps were taken to minimise the risk of reviewer bias and error (such as having more than one reviewer independently select the studies, assess validity and extract the data). Appropriate statistical techniques were used to combine the data, check for heterogeneity and publication bias and investigate differences between the studies. Differences between the studies (such as dosage variation) were suggested that might plausibly account for variability in study findings. The meta-analysis was well-conducted, but a lack of detail about review methods suggests that a degree of caution may be advisable in interpreting the authors' conclusions.

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

**Practice:** The authors stated that antipsychotic augmentation in those who did not respond to clozapine appeared to confer only a small benefit; augmentation may be worthwhile in some patients (such as those with a long history of treatment-resistant illness). Treatment response may not be evident for at least 10 weeks.

**Research:** The authors stated that future studies in this area should be powered to reveal small differences and should have at least 10 weeks' follow-up.

**Funding**

Not stated.

**Bibliographic details**


PubMedID

19245679

DOI

10.1111/j.1600-0447.2009.01367.x

**Original Paper URL**


**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Antipsychotic Agents /therapeutic use; Brief Psychiatric Rating Scale /statistics & numerical data; Clozapine /therapeutic use; Drug Therapy, Combination; Female; Humans; Male; Placebos; Psychiatric Status Rating Scales /statistics & numerical data; Psychotic Disorders /diagnosis /drug therapy /psychology; Randomized Controlled Trials as Topic /statistics & numerical data; Schizophrenia /diagnosis /drug therapy; Schizophrenic Psychology; Treatment Outcome

**AccessionNumber**
12009105847

**Date bibliographic record published**
09/09/2009

**Date abstract record published**
20/01/2010

**Record Status**
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.