Antipsychotic Combinations for Schizophrenia

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Background

Many people with schizophrenia do not achieve a satisfactory treatment response with their initial antipsychotic drug treatment. Sometimes a second antipsychotic, in combination with the first, is used in these situations.

Objectives

To examine whether:

1. treatment with antipsychotic combinations is effective for schizophrenia; and
2. treatment with antipsychotic combinations is safe for the same illness.

Search Methods

We searched the Cochrane Schizophrenia Group's register which is based on regular searches of CINAHL, BIOSIS, AMED, Embase, PubMed, MEDLINE, PsycINFO, and registries of clinical trials. There are no language, time, document type, or publication status limitations for inclusion of records in the register. We ran searches in September 2010, August 2012, and January 2016. We checked for additional trials in the reference lists of included trials.

Selection Criteria

We included all randomized and quasi-randomized controlled trials comparing antipsychotic combinations with antipsychotic monotherapy for the treatment of schizophrenia and/or schizophrenia-like psychoses.

Data Collection and Analysis

We independently extracted data from the included studies. We analyzed dichotomous data using risk ratios (RR) and the 95% CIs. We analyzed continuous data using mean difference (MD) with a 95% CIs. For the meta-analysis we used a random-effects model. We used GRADE to complete a "Summary of findings" table and assessed risk of bias for included studies.

Main Results

Sixty-two studies are included in the review, 31 of these compared clozapine monotherapy with clozapine combination. We considered the risk of bias in the included studies to be moderate to high. The majority of trials had unclear allocation concealment, method of randomization and blinding, and were not free of selective reporting.

There is some limited evidence that combination therapy may be superior to monotherapy in reducing the risk of no clinical response (RR 0.73 CI 0.64 to 0.83; participants = 2398; studies = 29; *very low-quality evidence*, [figure 1](#)), subgroup analyses show that the positive result was due to the studies with clozapine in both the monotherapy and combination groups (RR 0.66 CI 0.53 to 0.83; participants = 1127; studies = 17) and typical in both antipsychotics in both the monotherapy and combination groups (RR 0.64 CI 0.49 to 0.84; participants = 597; studies = 5). The subgroup with atypical antipsychotics in both groups did not show a difference between the 2 interventions (RR 0.95 CI 0.83 to 1.09; participants = 674; studies = 7). Few studies reported on rate of relapse, most likely due to the short length of the studies. Three studies provided data regarding relapse, the pooled data showed high heterogeneity ($I^2 = 82\%$).

Fig. 1. Comparison—antipsychotic combination versus antipsychotic monotherapy. Outcome—Clinical response: Not clinically improved. AP: Antipsychotic CPZ: chlorpromazine. Naming of the subgroups: The studies were arranged into 4 subgroups according to the type of antipsychotics used in both arms: clozapine, atypical antipsychotics other than clozapine, typical antipsychotics and any antipsychotics. Naming of the studies: The study tag starts with the duration category (A = long term [over 26 wk]; B = medium term [13 to 26 wk]; and C = short term [up to 12 wk]); the remainder of the tag is the additional drug in the combination antipsychotic group.

and therefore the results were not pooled. Two studies showed no difference between the interventions and one study showed that antipsychotics combination might decrease the risk of relapse. A combination of antipsychotics was not superior or inferior to antipsychotic monotherapy in reducing the number of participants discontinuing treatment early (RR 0.90 CI 0.76 to 1.07; participants = 3137; studies = 43, *low-quality evidence*).

No difference was found between treatment groups in the number of participants hospitalized (RR 0.96 CI 0.36 to 2.55; participants = 202; studies = 3, *very low-quality evidence*). We did not find evidence of a difference between treatment groups in serious adverse events or those requiring discontinuation (RR 1.05 CI 0.65 to 1.69; participants = 2398; studies = 30, *very low-quality evidence*). There is a lack of evidence on clinically

important change in quality of life, with only 4 studies reporting average endpoint or change data for this outcome on 3 different scales, none of which showed a difference between treatment groups.

Authors' Conclusions

Currently, most evidence regarding the use of antipsychotic combinations comes from short-term trials, limiting the assessment of long-term efficacy and safety. We found very low-quality evidence that a combination of antipsychotics may improve the clinical response. We also found low-quality evidence that a combination of antipsychotics may make no difference at preventing participants from leaving the study early, preventing relapse and/or causing more serious adverse events than monotherapy. Full details of the review are published on the Cochrane Library.¹

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Reference

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