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[Intervention Review]

Antipsychotic combinations for schizophrenia

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ABSTRACT

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 randomised and quasi-randomised 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 analysed dichotomous data using risk ratios (RR) and the 95% confidence intervals (CI). We analysed 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 randomisation 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*), 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 groups (RR 0.64 CI 0.49 to 0.84; participants = 597; studies = 5). The subgroup with atypical antipsychotics in both groups did not showed a difference between the two interventions (RR 0.95 CI 0.83 to 1.09; participants = 674; studies = 7). Three studies provided data regarding relapse, the pooled data showed high heterogeneity (I^2 = 82%) 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 hospitalised (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 four studies reporting average endpoint or change data for this outcome on three 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 very 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.

PLAIN LANGUAGE SUMMARY

Combining antipsychotic medication for the treatment of schizophrenia

Background

Antipsychotic medication was introduced in the 1950s to reduce or alleviate the symptoms of schizophrenia, such as the psychotic states of hearing voices, visual hallucinations and strange thoughts such as paranoia (feeling singled-out or put upon by others). Medication for mental illness also helped to establish care in the community, because people could take medication in their homes or by regularly visiting the hospital. But this also led to new issues such as the effectiveness of different medication (taken alone or in combination) and compliance (the willingness of service users to take their medication without being supervised).

The range of antipsychotic medication available is wide and their effectiveness can also vary from individual to individual. In addition, not all patients fully respond to a single antipsychotic, and in these situations, a combination of antipsychotics are often prescribed. The evidence for the benefits of taking one or more antipsychotics in combination is often unclear. There are also differing profiles of typical (first generation) and atypical (second generation) antipsychotics adding to a confusing array of terminology and dilemma of what is the best medication for service users.

Searches

This review investigates the effects of different antipsychotic combinations compared with single antipsychotics for people with schizophrenia. Searches for randomised controlled trials have now been run by the Information Specialist of the Cochrane Schizophenia Group in 2010, 2012 and 2016. Sixty-two trials, reporting useable data, are included in the review.

Main results

The review of available evidence found that combinations of antipsychotics may be more effective in treating symptoms of schizophrenia compared with taking one antipsychotic. In particular, combination treatments that included clozapine and typical antipsychotic in both groups were found to be effective. Few studies reported on this central issue of relapse rates (service users becoming unwell again), but this was because most of the studies were of short length (whereas schizophrenia is a long-term health problem that requires studies of an equally long duration). No real differences were found between combinations of antipsychotics and single antipsychotics for preventing relapse and roughly equal numbers of people discontinued their treatment. There was also no difference between combination therapy and monotherapy regarding hospital admission and/or occurrence of serious adverse events. Numbers leaving the studies early were similar. Clinically meaningful data for quality of life were not reported.

Conclusions

These results show that there may be some clinical benefit for combination therapy in that more people receiving a combination of antipsychotic showed an improvement in symptoms. For other important outcomes such as relapse, hospitalisation, adverse events, discontinuing treatment or leaving the study early, no clear differences between the two treatment options were observed. However, these results are based on very low or low-quality evidence and more research providing high-quality evidence is needed before firm conclusions can be made.

This plain language summary has been adapted from an original summary by Benjamin Gray, Service User and Service User Expert, Rethink Mental Illness. Email: ben.gray@rethink.org