Preventing the second episode: a systematic review and meta-analysis of psychosocial and pharmacological trials in first-episode psychosis
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CRD summary
The review found that specialist programmes were effective in preventing relapse in first episode psychosis. First- and second-generation antipsychotics may also reduce relapse rates. The review was generally well conducted. The authors’ conclusions about antipsychotics require cautious interpretation as they were based on trends that were not statistically significant. Their other conclusions appear reliable, although there were few studies.

Authors’ objectives
To evaluate the effectiveness of pharmacological and non-pharmacological interventions to prevent relapse in first-episode psychosis.

Searching
Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO, UMI ProQuest Digital Dissertations, Science Citation Index Expanded, Social Sciences Citation Index, Arts and Humanities Citation Index (inception to December 2008) and ISI Science & Technology Proceedings and Social Science and Humanities Proceedings were searched. There were no language restrictions. Search terms were available in an online appendix. Reference lists of studies retrieved, previous reviews and meeting abstracts were searched and unpublished studies were sought from trialists and other experts.

Study selection
Randomised controlled trials (RCTs) of pharmacological and non-pharmacological interventions for first-episode psychosis versus standard care, placebo or an active comparator were eligible for inclusion. Trials needed to last at least six months. It was required that least 75% of participants had first-episode psychosis (defined in the review). Participants could be either clinically remitted or responders from acute phase trials. The primary review outcome was relapse (as defined in the primary study). Secondary outcomes included hospital days, time to relapse, duration of second episode and treatment discontinuation due to adverse events.

The mean age of participants in the included studies ranged from 21 to 32 years. Psychosocial interventions included specialist first-episode psychosis programmes (various tailored pharmacological and non-pharmacological interventions), cognitive-behavioural therapy (CBT) that did not specifically target relapse, individual and family cognitive-based relapse prevention therapy (RPT) and family therapy; these were compared with each other or treatment as usual. Pharmacological interventions included first- and/or second-generation antipsychotics versus each other or placebo and treatment maintenance versus discontinuation therapy. Studies defined relapse with specific criteria or as admission to hospital. Follow-up ranged from seven months to two years. Studies were set in a wide range of countries.

Two reviewers independently selected the studies. Disagreements were resolved by discussion.

Assessment of study quality
The Cochrane Risk of Bias tool was used to assess sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other biases (baseline imbalance, pre-specified definition of relapse, prospective measure of relapse).

Three reviewers independently assessed study validity. Disagreements were resolved by discussion.

Data extraction
The reviewers calculated risk ratios (RRs) and number needed to treat (NNT) for dichotomous outcomes and weighted mean differences (WMDs) for continuous outcomes, with 95% confidence intervals (CIs). Authors of primary studies were contacted for more information where required.
Three reviewers independently extracted data. Disagreements were resolved by consensus.

**Methods of synthesis**
Studies were combined using random-effects models to calculate pooled risk ratios and weighted mean differences, with 95% CIs. Heterogeneity was assessed using $\chi^2$ and $I^2$. Publication bias was investigated with a funnel plot. Sensitivity analyses were used to assess the effect of alternative statistical methods (fixed-effect model, odds ratios).

**Results of the review**
Eighteen RCTs were included (2,707 participants). Eight trials described appropriate sequence generation and allocation concealment. Six trials used blinded outcomes assessors. Ten trials addressed incomplete data adequately. Seven trials measured relapse prospectively. Eleven trials predefined relapse.

**Psychosocial interventions (nine RCTs):** Specialist first-episode psychosis programmes were significantly more effective than treatment as usual at preventing relapse (OR 1.80, 95% CI 1.31 to 2.48, NNT=8, $I^2$=0%; three RCTs, 679 participants) and reducing hospital stay (WMD -26.2 days, 95% CI -7.35 to -45.06, $I^2$=0%; three RCTs, 679 participants).

There were no significant differences in relapse rates in comparisons of CBT versus supportive counselling or treatment as usual (one RCT), specialist first-episode psychosis programmes with CBT versus without (two RCTs), specialist first-episode psychosis programmes with relapse prevention therapy versus without (one RCT) and family therapy versus treatment as usual (two RCTs, some heterogeneity $I^2$=76%).

**Pharmacological interventions (nine RCTs):** There were no significant differences in relapse rates between antipsychotics and placebo (three RCTs, some heterogeneity $I^2$=50%) and between different types of first-generation antipsychotics (one RCT). However the relapse rate was significantly lower with second-generation antipsychotics than with first-generation antipsychotics (OR 1.47, 95% CI 1.07 to 2.01, NNT=10, $I^2$=0%; four RCTs). Treatment maintenance was significantly more effective for relapse prevention than guided discontinuation (OR 2.91, 95% CI 1.33 to 6.37, NNT=5; one RCT), but mean bed days did not differ significantly.

There was no clear evidence of any publication bias. Sensitivity analyses and other findings were reported.

**Authors' conclusions**
Specialist programmes were effective in preventing relapse in first-episode psychosis. First- and second-generation antipsychotics may also reduce relapse rates.

**CRD commentary**
The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies. There were no restrictions on language and publication status. The authors noted that there were too few studies to rule out publication bias. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer independently select studies, undertake validity assessment and extract data.

Appropriate statistical techniques were used to combine the studies and to assess and explore any heterogeneity between them. The authors noted that the review was limited by small sample sizes in the available studies, heterogeneity between studies and by possible selective reporting bias.

The review was generally well conducted. The authors’ conclusions about antipsychotics require cautious interpretation as they were based on trends that were not statistically significant. Their other conclusions appear reliable, although there were few studies.

**Implications of the review for practice and research**
**Practice:** The authors stated that targeted intensive CBT may be appropriate when clinically remitted patients show early warning signs of relapse, rather than using CBT strategies in the acute phase of illness. Cognitive-based programmes may need to specifically target relapse to improve on benefits provided by specialist first-episode psychosis programmes.

**Research:** The authors stated a need for larger and longer RCTs of all relapse prevention strategies for first-episode psychosis.
psychosis. Studies should compare placebo versus antipsychotics in combination with intensive psychosocial interventions in the early course of psychosis. Other implications for research were discussed in the review.

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