Early interventions to prevent psychosis: systematic review and meta-analysis
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CRD summary
This review assessed interventions to prevent or delay transition to psychosis in high-risk individuals, and concluded that psychological interventions might be effective, but the evidence for specific interventions was not conclusive. This conclusion was based on the quantity and quality of the available evidence and, with their recommendation for further research, is likely to be reliable.

Authors' objectives
To determine whether psychological, pharmacological or nutritional interventions could prevent or delay transition to psychosis, in individuals at a high risk of psychotic disorders.

Searching
MEDLINE, EMBASE, PsycINFO and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for articles from their inception to November 2011. The search strategy was reported in an online appendix. There were no restrictions on publication status. References were checked and study authors and experts on psychotic disorders were contacted.

Study selection
Randomised controlled trials (RCTs) of patients at risk of psychotic disorders, or with schizotypal disorders, were eligible. Risk was defined as those with early symptoms, identified at clinical assessment. Trials had to assess any pharmacological, psychological or nutritional intervention, or a combination of these. Trials of patients with a diagnosis of schizophrenia, bipolar disorder or first-episode psychosis were excluded. The primary outcome was the transition to psychosis and secondary outcomes were the symptoms of psychosis, depression and mania, quality of life, weight, and treatment discontinuation.

The included trials assessed cognitive-behavioural therapy (CBT) with or without risperidone, or supportive counselling versus supportive counselling; olanzapine versus placebo; integrated therapies versus supportive counselling or standard treatment; omega-3 fatty acids versus placebo; and a needs-based intervention, with or without amisulpride. Treatment duration ranged from 12 weeks to two years. The median of the mean age of participants in included trials was 21 years, with ranges from 12 to 36, where reported, and 57% of participants were male. Most trials included participants in one of three groups: attenuated psychotic symptoms; transient psychotic symptoms; or trait and state risk factors. Participants in the other trials met the criteria for schizotypal disorder or were identified as being at risk using the early recognition inventory (ERIraos).

The authors did not state how many reviewers assessed the studies for inclusion.

Assessment of study quality
The trials were independently assessed for quality by two reviewers, using the Cochrane Collaboration risk of bias tool, which assessed sequence generation; allocation concealment; blinding of participants, providers and outcome assessors; selective outcome reporting; and incomplete data. The risk of bias was rated as high, unclear or low. Disagreements were resolved by discussion with a third reviewer.

The evidence for each comparison and outcome was graded as high, moderate, low or very low quality, using the GRADE system.

Data extraction
The data were extracted to permit the calculation of risk ratios, with 95% confidence intervals, for dichotomous outcomes, and mean differences, with 95% confidence intervals, for continuous outcomes. The authors did not state how many reviewers extracted the data.

Methods of synthesis
For dichotomous outcomes the pooled risk ratios, with 95% confidence intervals, were calculated using random-effects Mantel-Haenszel meta-analyses. Risk differences were also calculated. Continuous data were combined by calculating the standardised mean difference, with 95% confidence interval. Where possible, data that controlled for dropouts were used. Statistical heterogeneity was assessed using $X^2$ and $I^2$.

For the primary outcome, a sensitivity analysis was used to assess the impact of trials that only reported data for patients who completed the trial. A trial with three treatment arms was included in three pairwise comparisons. Publication bias was not formally assessed.

**Results of the review**
Eleven RCTs, with 1,246 participants, were included in the review; eight comparisons were assessed. The median sample size was 81; range 51 to 288. Follow-up ranged from one to four years, except one 12-week trial had no follow-up. All the included trials had a high risk of bias from incomplete outcome data, reflecting the high rates of attrition. All trials had a high or unclear risk of bias for at least one other criterion and four were at a high risk for three or more criteria.

For CBT, compared with supportive counselling, moderate-quality evidence from five trials found a benefit. In the CBT group, of those who completed treatment, fewer patients developed psychosis at six to 12 months (RR 0.54, 95% CI 0.34 to 0.86). Low-quality evidence from four trials found a benefit after 12 months (RR 0.63, 95% CI 0.40 to 0.99), which was not statistically significant in the sensitivity analysis. The outcomes for individual symptoms were reported. There was no evidence of significant heterogeneity between trials.

The evidence for CBT plus risperidone (two RCTs), integrated psychotherapy versus supportive counselling (one RCT), olanzapine (one RCT), and amisulpride (one RCT) was very low quality; details were reported. Low-quality evidence from one trial found a benefit from integrated psychotherapy, compared with standard treatment, with fewer patients transitioning to psychosis by six to 12 months (RR 0.24, 95% CI 0.07 to 0.81).

Low-quality evidence from one trial found a benefit from omega-3 fatty acids, compared with placebo, at six to 12 months, with a lower rate of transition to psychosis (RR 0.18, 95% CI 0.04 to 0.75). Benefits were found for total and individual symptoms.

**Authors’ conclusions**
The evidence for any specific intervention was not conclusive, but it might be possible to delay or prevent transition to psychosis and further research was required.

**CRD commentary**
The review question was clear, but broad for the interventions, and it was supported by clear inclusion criteria. The search was thorough, making it less likely that relevant studies were missed. An appropriate assessment of trial quality was conducted, using methods designed to reduce reviewer error and bias. But the authors did not report using such methods for the selection of studies and the data extraction.

An appropriate statistical synthesis was conducted and methods were used to incorporate and control for the impact of missing data, which could be the most significant source of bias. Some of the review methods were not reported, but this was a robust assessment of the evidence, which took into consideration the key limitations of the included trials.

The conclusions, with the recommendation for further research, are likely to be reliable.

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

**Practice:** The authors stated that in the absence of further research, family and individual CBT were the most appropriate choices to avert the onset of psychosis in those at a high risk.

**Research:** The authors stated that a large multicentre trial of combined family and individual CBT should be undertaken, with groups of people at a high risk of psychosis. This trial should evaluate the benefits and potential harms of treatment. They also recommended that a large RCT of omega-3 fatty acids should be undertaken, with high-risk people.
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