Review and meta-analysis of usage of ginkgo as an adjunct therapy in chronic schizophrenia
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CRD summary
Ginkgo as an adjunct therapy ameliorated the symptoms of chronic schizophrenia. The authors’ conclusions should be viewed with caution given the potential for publication bias, the small number of included trials with small sample sizes and of poor quality, and the combining of data from trials using different antipsychotic drugs.

Authors' objectives
To evaluate the effectiveness of ginkgo as an adjunct therapy for chronic schizophrenia.

Searching
PubMed, the Cochrane Library, EMBASE, CINAHL, PsycINFO, AMED, Chinese Clinical Trials Register, ilib.cn, Traditional Chinese Medicine Literature Analysis and Retrieval System (TCMLARS), the China National Knowledge Infrastructure database and the Chinese Biomedical databases were searched for published studies. Search terms were reported, but search dates were not. Reference lists of retrieved articles were scanned for additional studies.

Study selection
Randomised controlled trials (RCTs) of drug interventions for schizophrenia that also used ginkgo as an adjunct therapy were eligible for inclusion. Trials were excluded if they used electroconvulsive therapy and transcranial magnetic stimulation, or rapid tranquilisation as part of the intervention. Trials were also excluded if duration of treatment was less than two weeks. The primary outcome was response to treatment monitored using a standardised symptom rating scale.

All the included trials used a standardised extract of ginkgo in the form of EGb (a compound derived from dried ginkgo leaves); dosage ranged from 120 to 360mg/day. Antipsychotic drugs also included were chlorpromazine, clozapine, haloperidol, olanzapine or combined regimens. Most included trials were compared with placebo. Total symptoms were measured using either the Scale for the Assessment of Positive symptoms (SAPS) or the Brief Psychiatric Rating scale (BPRS). Negative symptoms were measured using the Scale for the Assessment of Negative Symptoms (SANS).

Diagnosis of schizophrenia varied between trials, but all participants were considered to have chronic schizophrenia. The age of participants ranged from 28 years to 46 years; the proportion of men ranged from 50 to 82%. Most trials reported illness duration of between six and eleven years, but one trial reported illness duration of patients of 21 years. Trial duration ranged from eight to 16 weeks. Most trials were conducted in China, with the remainder conducted in Turkey.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Quality was assessed using the Jadad scale, including the assessment of randomisation, blinding and withdrawals and drop-outs, with a maximum possible score of 5 points.

The authors did not state how many reviewers assessed validity.

Data extraction
Data on the difference of mean and standard deviation (SD) of response scores from baseline to end of intervention were extracted for the intervention and control groups. These were used to calculate standardised mean differences (SMDs) and corresponding 95% confidence intervals (CIs). Missing data were imputed where possible.

The authors did not state how many reviewers extracted the data.
Methods of synthesis
Standardised mean differences (SMDs) from individual trials were pooled using a fixed-effect model or, in the presence of heterogeneity, a random-effects model. Heterogeneity was assessed using the Q statistic.

Subgroup analyses by drug (typical and atypical) and regional variance were also conducted. Stepwise regression was used to estimate the association of underlying variables with therapeutic outcome.

Publication bias was assessed using the trim-and-fill method.

Results of the review
Six trials (n=828 participants) were included in the review. The sample sizes ranged from 36 to 512. Three RCTs scored 3 points on the Jadad scale and three scored 2 points. Only three trials reported being double blinded.

Ginkgo (EGb) was effective as an adjunct therapy for the treatment of negative symptoms of chronic schizophrenia (SMD -0.5, 95% CI -0.81 to -0.18; random-effects model; six trials). EGB was also effective as an adjunct therapy for the treatment of the total symptoms of chronic schizophrenia (SMD -0.5, 95% CI -0.64 to -0.36; fixed-effect model; six trials). There was evidence of significant statistical heterogeneity for the analysis of negative symptoms (p<0.05).

Subgroup analysis reported that EGb was effective when added to typical antipsychotic medications such as chlorpromazine and haloperidol (p<0.05), but not when added to atypical antipsychotics such as clozapine and olanzapine. Trials of EGb appeared to be effective for both negative and total symptoms of chronic schizophrenia when conducted in China; however, trials conducted in Turkey reported no significant differences between intervention and placebo groups.

Regression analysis was not possible due to the small number of trials.

There was some evidence of publication bias for the outcome of total symptoms.

Authors' conclusions
Ginkgo as an adjunct therapy ameliorated the symptoms of chronic schizophrenia.

CRD commentary
The review question was broadly defined with similarly broad inclusion criteria. Several relevant sources were searched, although only published studies were eligible for inclusion, so there was the potential for publication bias. The authors did not report the search dates, so it was unclear how up-to-date the search was; although the latest trial was conducted in 2008. Formal analysis of publication bias reported some evidence for one outcome. Attempts were made to reduce reviewer error and bias for the selection of studies, but it was unclear whether similar steps were taken for data extraction or the assessment of quality.

Quality was assessed using an appropriate tool; some results were reported. The data were pooled in a meta analysis; sources of heterogeneity were explored. However, given the differences between trials in the antipsychotics used and the varying doses, a meta analysis may not have been appropriate. All the included trials were conducted in China or Turkey, so the results of the review may not be generalisable to other cultural settings. The authors appropriately reported a number of limitations of the review, including the small number of included trials with small sample sizes. In addition, the trials were of poor quality.

Consequently, the authors' conclusions should be viewed with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further RCTs are required to investigate the role of antioxidants in the pathophysiology of schizophrenia. Further research is also required in the area of phytochemistry and for the

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