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**File: ■ Ginkgo (*Ginkgo biloba*, Ginkgoaceae)
■ Schizophrenia
■ Systematic Review/Meta-analysis**

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RE: Systematic Review of Ginkgo Extract Studies with Patients with Chronic Schizophrenia on Antipsychotic Medication Demonstrates Its Efficacy as an Adjunct Therapy

Chen X, Hong Y, Zheng P. Efficacy and safety of extract of *Ginkgo biloba* as an adjunct therapy in chronic schizophrenia: A systematic review of randomized, double-blind, placebo-controlled studies with meta-analysis. *Psychiatry Res.* 2015;228(1):121-127.

The exact etiology of schizophrenia is unknown. One theory is that excessive free radical production, oxidative stress, and an increase in lipid peroxides may be involved in the pathogenesis. Therefore, free radical scavengers may be useful as a treatment for schizophrenia. Ginkgo (*Ginkgo biloba*, Ginkgoaceae) leaf extract is a free radical scavenger and has been evaluated as a treatment for schizophrenia. The results have been variable. According to the authors, two published meta-analyses failed to include the vast published Chinese literature because of lack of access or Chinese language barrier. Hence, the purpose of this study was to conduct a meta-analysis that would include English and Chinese published studies evaluating the efficacy and safety of ginkgo as adjuvant therapy in schizophrenia.

The following electronic databases were searched from inception through August 28, 2014: PubMed/Medline, Embase, PsycINFO, the Cochrane Library, China National Knowledge Infrastructure, Wanfang Data Digital Periodicals, and Chinese Scientific Journals Database. The following search strategies were used for article titles and/or abstracts: (EGb 761 OR Ginkgo biloba OR ginkgo leaf OR ginkgo OR ginkgo OR ginko OR bilobalid* OR gintonin OR shuxuening) and (schizophrenia OR mental illness OR psychosis OR psychotic disorder OR delusion) in non-Chinese databases, and (yinxing OR yinxingye OR yinxingneizhi OR baiguoneizhi OR shuxuening OR nao'en [trade name] OR sitailong [trade name]) AND (jingshen-fenlie OR jingshenzhang'ai OR jingshenbing OR jingshenjibing OR wangxiang) in Chinese databases.

Included studies met the following inclusion criteria: randomized, double-blind, placebo-controlled study with complete data analysis; patients had chronic schizophrenia; used ginkgo extract as an adjunct therapy to treat schizophrenia; did not restrict race or nationality; the primary outcome variables were the Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Negative Symptoms (SANS), and/or Positive and Negative Syndrome Scale (PANSS); the secondary outcome variables were adverse reactions

(including the Treatment Emergent Symptom Scale [TESS]) and a Rating Scale for Extrapyramidal Side Effects (RSESE); and any language. The methodological quality of the studies was evaluated according to the *Cochrane Handbook for Systematic Reviews of Interventions*. Repeated data articles and duplicate studies were excluded.

A total of 339 studies (84 from non-Chinese journals and 254 from Chinese journals) were retrieved with the initial search; however, only eight articles (all Chinese) met all of the inclusion criteria. [Note: The top box of Fig. 1 indicates that the number of studies is 338; however, the next three box totals equal 339.] Together, the studies included 1033 patients (n = 571 treated with ginkgo extract and n = 462 treated with placebo), with an average onset age range of 30-50 years. One study had n = 512, while the other studies had n = 29, 36, 40, 60, 90, 109, and 157 patients. Duration of disease was ≥ 3 years. Patients were treated with 240 mg/day ginkgo extract (n = 4 studies) or 360 mg/day ginkgo extract (n = 4 studies) for eight weeks (n = 1 study), 12 weeks (n = 3 studies), or 16 weeks (n = 4 studies) while being maintained on their original antipsychotic medication. All studies claimed to have used products containing the standardized ginkgo extract EGb 761[®] (Dr. Willmar Schwabe GmbH & Co. KG; Karlsruhe, Germany).

The pooled studies had a low overall risk of bias, and there was no evidence of publication bias. Seven of the eight studies were combined into a meta-analysis to determine the effect of ginkgo as an adjunct therapy for total symptoms of chronic schizophrenia (e.g., delusion, disorganized thinking, and hallucinations) and all eight studies were included in the meta-analysis of negative symptoms of schizophrenia (e.g., avolition and psychomotor poverty). There was no statistical heterogeneity among the studies for either endpoint, meaning that the clinical or methodological diversity among the studies was not variable (heterogeneous). The ginkgo group had significantly more improvement in total symptoms and negative symptoms than placebo (P < 0.01 for both); however, one study with the largest sample size (n = 512) contributed more heavily to these outcomes (28.5% and 48.5%, respectively) and this study reported a benefit of ginkgo.

Five of the studies reported adverse events (AEs). The AE scores were similar among groups. The AEs were scored lower in the ginkgo group, but the difference among groups was not significantly different. One study reported that two placebo-treated patients received 480 mg/day ginkgo (after the end of the study) as an adjunct to their psychiatric treatment in an attempt to improve negative symptoms, which were not responding to therapy. Both patients had severe persecutory delusions after 12 and 14 days of ginkgo, a symptom that resolved after removing ginkgo and adding antipsychotic drugs. The authors conclude that the safety of ginkgo as adjunct therapy for schizophrenia may be related to its dose, and additional research is needed.

The authors conclude that ginkgo adjunct therapy may be more beneficial than antipsychotics alone in people with schizophrenia. The severity of adverse side effects associated with ginkgo or the herb-drug interaction may be related to the dose of ginkgo. The authors acknowledge that limitations of the meta-analysis are that all patients were Chinese and that there were only eight studies included. This study is valuable – oftentimes, Chinese language studies are excluded from meta-analyses or reviews because the author cannot read Chinese or does not have the resources to translate the article – and thus this article fills a gap in Western-based publications.

—Heather S. Oliff, PhD

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