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File: ■ Ginkgo (*Ginkgo biloba*)
■ Neuropsychiatric Symptoms
■ Mild Cognitive Impairment

HC 051451-497

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RE: Ginkgo Extract Found Safe and Effective in Treating Amnestic Mild Cognitive Impairment in Exploratory Trial

Gavrilova SI, Preuss UW, Wong JWM, et al. Efficacy and safety of *Ginkgo biloba* extract EGb 761® in mild cognitive impairment with neuropsychiatric symptoms: a randomized, placebo-controlled, double-blind, multi-center trial. *Int J Geriatr Psychiatry*. March 16, 2014; [epub ahead of print]. doi: 10.1002/gps.4103.

Mild cognitive impairment (MCI) is a condition associated with an elevated risk of developing dementia; however, it is not necessarily a transitional stage of dementia. MCI is often accompanied by neuropsychiatric symptoms, which are an indicator of an increased risk for dementia. An indicator of a high risk for dementia is amnestic MCI (aMCI), which is characterized by impaired short-term memory as the main symptom. Many studies demonstrate the efficacy of ginkgo (*Ginkgo biloba*) extract EGb 761® (Dr. Willmar Schwabe GmbH; Karlsruhe, Germany) in improving cognition and neuropsychiatric symptoms associated with dementia. The purpose of this randomized, placebo-controlled, double-blind, multicenter trial was to evaluate EGb 761 in patients with aMCI and at least one type of neuropsychiatric symptoms.

Patients (n = 160, aged ≥ 55 years) diagnosed with aMCI according to international consensus criteria were enrolled at psychiatric or neurologic outpatient departments of 7 academic hospitals in Russia. Inclusion criteria (in part according to the international consensus criteria) were as follows: cognitive complaints expressed by the patient were corroborated by an informant; the total score on the revised version of the cognitive part of the Cambridge Mental Disorders of the Elderly Examination (CAMCOG) was below the 10th percentile for age, sex, and educational level; the CAMCOG combined memory score was ≤ 20 for patients < 80 years old and ≤ 17 for patients ≥ 80 years old; a decline from a former level of functioning was demonstrated either by informant report or by cognitive testing; basic activities of daily living were preserved with a mean score < 4 on the short form of the Informant Questionnaire on Cognitive Decline in the Elderly; overall cognition was not severely impaired as evidenced by a score of ≥ 24 on the mini-mental state examination; *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) criteria for dementia were not fulfilled; cognitive complaints were present for ≥ 6 months; a total score of ≥ 6 on the 12-item Neuropsychiatric Inventory (NPI); on the NPI, at least 1 of the item scores for "depression/dysphoria," "anxiety," "apathy/indifference," "agitation," or "irritability/lability" were ≥ 4; a magnetic resonance imaging (MRI) scan taken ≤ 1 year prior to screening had to

be consistent with the diagnosis of MCI; major depression was ruled out; and adequate Russian language skills were required. Also, an informant who was frequently in contact with the patient was required to provide information about the patient's history of cognitive problems, functional abilities, and behavioral symptoms.

The exclusion criteria were as follows: any type of neurological disorder, stroke with sequelae within the last 3 months, hemorrhagic stroke within the last 12 months before enrollment, or dementia; current or recurrent psychiatric disorder; severe or insufficiently controlled cardiovascular disorder or insulin-dependent diabetes mellitus; severe hepatic or renal dysfunction, clinically significant anemia, thyroid dysfunction, or vitamin deficiency; gastrointestinal disorders with uncertain absorption; alcohol or substance abuse; active malignant disease; severe and insufficiently corrected impairment in vision or hearing; previous participation in any trial of a ginkgo product; female patients of child-bearing age and no contraception; or intake of any medication that could interfere with the efficacy assessment.

Patients received either 240 mg/day EGb 761 or placebo for 24 weeks. The following battery of cognitive tests was conducted at baseline, week 12, and week 24: NPI, Geriatric Depression Scale (GDS), the state subscale of the State-Trait Anxiety Inventory (STAI-X1), the Clinical Global Impression (CGI), the Trail-Making Test (TMT), and CAMCOG. In general, both groups of patients improved; however, patients in the EGb 761 group had a greater improvement. On the NPI composite score, the EGb 761 group had a statistically significantly greater improvement than the placebo group ($P = 0.001$). Also, according to the NPI composite score, statistically more patients in the EGb 761 group had a clinically significant improvement than in the placebo group (78.8% vs. 55.7%, respectively; $P = 0.002$). Similarly, the EGb 761 group was significantly more improved than the placebo group on the STAI-X1 ($P = 0.027$), the informants' global impression of change ($P = 0.014$), and both TMT scores ($P = 0.045$ and $P = 0.011$). Symptoms of depression on GDS total score were not significantly altered by EGb 761, though there was a trend ($P = 0.066$); the authors attribute this to the low baseline depression scores (i.e., the patients were close to "normal"). Adverse events (AEs) were reported by 37 patients taking EGb 761 and 36 patients receiving placebo, and all were non-serious. Eighteen AEs in the EGb 761 group and 16 in the placebo group had a potential causal relationship with treatment (the specific AEs were not noted), though none were serious. AEs reported included headache, increased blood pressure, respiratory infections, and gastric discomfort.

According to the authors, this is the first study of EGb 761 in patients with aMCI diagnosed according to the international consensus criteria. The authors point out that the conclusions may not apply to aMCI diagnosed by other criteria since there is dissimilarity among the different MCI diagnostic criteria. The authors conclude that EGb 761 treatment improved performance in cognitive tests, tapping attention, working memory, visuospatial orientation, and executive function. Patients with MCI do not have significant impairment at work or in social life, so it is difficult to gauge the relevance of the observed improvements. However, low executive function is associated with a shorter time to progression to dementia and Alzheimer's disease. There is the potential that EGb 761 would delay the progression. Also, the improvement in TMTs may indicate a better ability to deal with demands at work. The conclusions of this study are supported by the excellent methodological design.

—Heather S. Oliff, PhD

The American Botanical Council has chosen not to include the original article.