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File: ■ Ginkgo (*Ginkgo biloba*, Ginkgoaceae)
■ EGb 761®
■ Cognitive Function

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RE: EGb 761® Ginkgo Extract Improves Cognitive Flexibility in Elderly Adults

Beck SM, Ruge H, Schindler C, et al. Effects of *Ginkgo biloba* extract EGb 761® on cognitive control functions, mental activity of the prefrontal cortex and stress reactivity in elderly adults with subjective memory impairment – a randomized double-blind placebo-controlled trial. *Hum Psychopharmacol*. 2016;31(3):227-242.

Studies indicate that the dopaminergic system in the prefrontal cortex of the brain modulates attention, impulse inhibition, prospective memory, and cognitive flexibility. It plays a key role in cognitive control and stress reactivity, and both of these functions decline with age. The proprietary ginkgo (*Ginkgo biloba*, Ginkgoaceae) leaf extract EGb 761® (Dr. Willmar Schwabe Pharmaceuticals; Karlsruhe, Germany) is a registered drug in Europe for the treatment of age-related cognitive decline. Evidence from animal studies and clinical trials indicates that in addition to improving memory, EGb 761 may also enhance dopaminergic function in the prefrontal cortex. Hence, the objective of this randomized, double-blind, placebo-controlled, parallel-group study was to evaluate the effect of EGb 761 on prefrontal dopaminergic function in non-demented elderly people.

Healthy subjects (n = 62; aged 50-65 years) with subjective memory impairment participated in this study conducted at the Technische Universität in Dresden, Germany, from October 2010 to April 2012. Included subjects had (1) subjective memory impairment as indicated by ≥ 1 question answered with "rather often" or "very often" or ≥ 5 questions answered "sometimes" on the Prospective and Retrospective Memory Questionnaire, and (2) had average or slightly below average cognitive performance on the Wechsler Abbreviated Scale of Intelligence and the Consortium to Establish a Registry for Alzheimer's Disease-Neuropsychological Battery, revised German edition. Excluded subjects had (1) depression requiring antidepressive drug treatment within the last 12 months, (2) Beck-Depression-Inventory revised edition 1996 (BDI-II) score of > 18, (3) other psychotherapeutic/psychiatric treatment within the 12 months before study commencement, (4) cerebrovascular disease including stroke, Alzheimer's disease, or other dementia, or (5) were taking concomitant central nervous system-affecting medication.

Subjects received either placebo or 240 mg/day EGb 761 for 56 days. EGb 761 is a 35-67:1 ginkgo leaf extract "adjusted to 22.0-27.0% ginkgo flavonoids, calculated as ginkgo flavone glycosides and 5.0-7.0% terpene lactones consisting of 2.8-3.4% ginkgolides A, B, C and 2.6-3.2% bilobalide and contains less than 5-ppm ginkgolic acids. … Placebo tablets were identical in taste, form, size and appearance of coating and tablet core."

Stress reactivity was evaluated with the Trier Social Stress Test (TSST) at baseline and day 56. Salivary cortisol was measured at baseline and 1, 10, 20, 30, 45, and 60 min after the TSST. At baseline and day 56, reaction times (RT) and error rates during the following cognitive tests were assessed: Task-set Switching, Delayed-Response Task, nonverbal Spatial Stroop Task, daily prospective memory task, and Go–NoGo Task. All of the cognitive tests were conducted while the subject was in a functional magnetic resonance imaging (fMRI) scanner to measure the blood oxygenation level dependent (BOLD) response to the task; BOLD response is an indirect indicator of neuronal activity. The primary efficacy endpoints were the TSST, cognitive task performance, and BOLD response. Safety and tolerability also were evaluated.

Of the 211 subjects screened, 75 met the study criteria and were randomly assigned (43 to EGb 761 and 32 to placebo). A total of 13 subjects were excluded from the per protocol (PP) analysis; 8 subjects (7, EGb 761; 1, placebo) were not suited for fMRI testing, 3 (2, EGb 761; 1, placebo) were excluded because of upcoming surgery, and 2 subjects in the EGb 761 group were excluded for unspecified reasons. One subject taking EGb 761 dropped out because of poor compliance; therefore, the safety analysis evaluated 32 EGb 761 and 30 placebo subjects. The efficacy PP analysis included 31 EGb 761 and 30 placebo subjects. Based on pill counts, compliance amongst the intent-to-treat population was excellent (99%). The gender ratio was balanced in the EGb 761 group (15 females and 16 males) but not in the placebo group (18 females and 12 males). There were no significant differences between groups in other sociodemographic characteristics; however, mean BDI-II score was significantly higher ($P < 0.02$) for the EGb 761 group compared to placebo.

EGb 761 significantly improved task-set switching performance (a measure of cognitive flexibility) compared with placebo ($P < 0.02$). This effect was maintained when the analysis was adjusted for baseline differences in BDI-II score and gender. On the Go–NoGo Task, the EGb 761 group had a decrease in RT, while the placebo group had an increase; however, the difference was not statistically significant even after correcting for BDI-II score and gender. The EGb 761 group also had significantly less false alarms on the Go–NoGo Task ($P < 0.05$); however, after controlling for the covariates BDI-II score and gender, the significance of the effect was decreased ($P < 0.052$). The EGb 761 group performed better than the placebo group on the daily prospective memory task; however, the number of subjects in each group who failed the task was not large enough for statistical comparison. There were no significant treatment effects on the Delayed-Response Task, prospective memory task, or BOLD response. The effect of EGb 761 on salivary cortisol levels was not statistically significant but there was a numerically superior response, suggesting endocrine stress recovery may have been improved with EGb 761 treatment.

The frequency of adverse events (AEs) was higher in the EGb 761 group (n = 19; 54%) compared with the placebo group (n = 12; 40%). There were no severe or serious AEs – 2 AEs in each group were moderately severe, and all other AEs were mild; no subjects terminated treatment due to AEs. The most frequently reported AE was headache (n = 8;

6, EGb 761 and 2, placebo), which is a listed adverse reaction of EGb 761; all were mild except for 1 subject who reported headache of moderate severity. There were no relevant changes in laboratory tests or vital signs. The authors conclude that 240 mg EGb 761 administered daily in healthy adults for 8 weeks was safe and well tolerated.

In summary, EGb 761 improved cognitive flexibility without changing brain activation (BOLD response), suggesting that EGb 761 improved processing efficiency. There were nonsignificant trends for improved response inhibition and endocrine stress recovery. These results are compatible with the hypothesis that EGb 761 enhances prefrontal dopamine. However, the authors point out that this small pilot study had a number of limitations and that the results cannot be extrapolated to ginkgo products that do not conform to the EGb 761 quality specifications. They conclude that these findings must be replicated "before improvement of cognitive flexibility and stress reactivity in the healthy elderly by EGb 761® can definitely be concluded." They recommend that future studies should confirm the effects of EGb 761 on dopaminergic systems by direct measurements.

The manufacturer of EGb 761, Dr. Willmar Schwabe GmbH & Co. KG (Karlsruhe, Germany), was the sponsor of this trial; 1 author (Burkart) is an employee of the company and another author (Goschke) is a consultant for the company. "Funding of the project by Dr. Willmar Schwabe GmbH & Co. KG included consumables, participant payment, salaries for student assistance and PhD students."

—Heather S. Oliff, PhD

Referenced article can be accessed at http://onlinelibrary.wiley.com/doi/10.1002/hup.2534/epdf.