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File: ■ Ginkgo (*Ginkgo biloba*, Ginkgoaceae)
■ EGb 761®
■ Attention Deficit Hyperactivity Disorder

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RE: Ginkgo Extract Pilot Study Suggests Potential for Application in Childhood Attention Deficit Hyperactivity Disorder

Uebel-von Sandersleben H, Rothenberger A, Albrecht B, Rothenberger LG, Klement S, Bock N. *Ginkgo biloba* extract EGb 761® in children with ADHD. *Z Kinder Jugendpsychiatr Psychother*. September 2014;42(5):337-347.

Attention deficit hyperactivity disorder (ADHD) affects children and is characterized by inattention or lack of focus, disruptive behavior, and hyperactivity. Adverse side effects or nonresponse associated with standard treatments have increased the use of alternative therapies; however, knowledge on safety and efficacy of botanical treatments for ADHD in children is important to assess any potential herb-drug interactions and to enable physicians to make the best informed decisions about patient care. Ginkgo (*Ginkgo biloba*, Ginkgoaceae) has shown efficacy in treating cognitive impairment in certain adult populations[1] as well as tolerance and significant improvements in children and adolescents with ADHD.[2] This observational study tested ginkgo leaf extract (EGb 761®; Dr. Willmar Schwabe GmbH & Co. KG; Karlsruhe, Germany) for appropriate dosage and efficacy in treating ADHD symptoms in children.

Patients (24) with ADHD were enrolled from the Department of Child and Adolescent Psychiatry at the University of Göttingen, Göttingen, Germany. From these, 4 patients did not participate due to consent problems or other disorders. Included patients (20) ranged in age from 6-13 years (mean age 8.2 ± 1.6 years) and were not taking methylphenidate (a standard medicine for ADHD) due to preference or tolerance issues. Patients also attended "regular" school and had an IQ of over 80. Those that had received standard medication in the 2 weeks prior to the study, had seizures or other health problems causing symptoms similar to ADHD, or suffered from other medical conditions were excluded.

EGb 761 is a dry acetone extract of ginkgo leaves standardized to 22.0-27.0% flavonoids, 5.0-7.0% terpene lactones (2.8-3.4% ginkgolides A, B, and C, and 2.6-3.2% bilobalide), and less than 5 ppm ginkgolic acids. Patients initially took 40 mg twice daily for 1 week and increased their dosage successively to 60 mg and, after another week, 120 mg twice daily, if scores on an attention problem assessment were indicative of

continued relevant difficulties. The highest achieved dose was taken for 3 additional weeks. Adverse side effects were documented by both parents and patients with the Side Effects Rating Scale (SERS-D, mild effects are rated as 1 and most severe effects are rated as 9).

The primary outcome was change in the item "severity of attentive problems" of the FBB-HKS questionnaire (this German rating scale contains 20 aspects of ADHD symptoms, assessed by parents) as an assessment of attentiveness. Secondary outcomes included assessment of hyperactivity, impulsiveness, and aggression as measured by the FBB-HKS and FBB-SSV (an assessment of behavioral problems where parents rate symptoms according to "strongly agree" or "strongly disagree") tests. The FaBel assessment was used to gauge family life disruptions (a lower score indicates less strains on family life). The KINDL and SDQ-D questionnaires (higher scores indicate improvement) were used to assess quality of life and psychopathological problems, respectively. A behavioral attention test known as the Continuous Performance Test was also conducted; patients were instructed to act when they detected a specific combination of letters. Electrophysiological recordings were also used to assess cue-onset performance amplitudes.

The dose of 120 mg daily was sufficient for 2 patients, while the other 18 patients were administered 240 mg per day of EGb 761 for 3 weeks, after having taken 120 mg daily for 1 week. Three adverse side effects observed were considered "mild," and while 2 were described as unrelated to the medication, 1 case of prolonged thrombin time was termed "unlikely related" to the ginkgo extract. For all patients, the total FBB-HKS score was significantly improved from baseline to endpoint of the study (1.9 ± 0.4 vs. 1.5 ± 0.7, $P<0.01$). Individual categories of the assessment, including attention problems, hyperactivity, and impulsiveness, were also significantly improved ($P<0.01$, $P=0.02$, $P<0.01$, respectively). The total score for the FBB-SSV was also significantly improved from baseline to endpoint (0.7 ± 0.3 vs. 0.6 ± 0.3, $P<0.01$).

The SDQ-D score for prosocial behavior was improved from baseline to endpoint (6.5 ± 2.4 vs. 7.6 ± 2.2, $P<0.01$), but no changes were seen in peer problems, hyperactivity, or the emotion and conduct problem categories of the assessment. A significant decrease in FaBel score, indicating improved quality of family life, was observed from baseline to endpoint (11.7 ± 1.2 vs. 11.2 ± 1.2, $P<0.01$), and an improvement in SERS-D scores of the patient-reported adverse effects assessment was observed (33.1 ± 20.7 vs. 25.3 ± 22.4, $P=0.02$). Elevated error with this assessment brings the significance between the SERS-D score changes into question. The Continuous Performance Test suffered from experimental errors, resulting in 35% of results being dropped from the final analysis. Improvements in ADHD symptoms were positively related to changes in electrophysiological recordings.

In summary, significant changes were seen in attention and quality-of-life assessments in patients with ADHD taking EGb 761. Although significant improvements were noted in several of the assessments used in this study, it is mentioned that additional assessments done in the patients' school settings would be important additions in future studies. Other mentioned limitations include a small sample size and short treatment duration, and no use of placebo or randomization. Despite this, EGb 761 was well tolerated in patients that did not use methylphenidate, suggesting its usage as an alternative or adjuvant to this standard treatment. Future clinical trials will ideally incorporate the randomized, double-blind, placebo-controlled format with a larger patient

group and further confirm dose-dependent efficacy of ginkgo for the treatment of ADHD in children. This study was sponsored by Dr. Willmar Schwabe GmbH & Co. KG; one of the authors (Klement) is an employee of the company.

—Amy C. Keller, PhD

References

[1]Blumenthal M, Goldberg A, Brinckmann J, eds. *Herbal Medicine: Expanded Commission E Monographs*. Austin, TX: American Botanical Council; Newton, MA: Integrative Medicine Communications; 2000.

[2]Salehi B, Imani R, Mohammadi MR, et al. *Ginkgo biloba* for attention-deficit/hyperactivity disorder in children and adolescents: a double blind, randomized controlled trial. *Prog Neuropsychopharmacol Biol Psychiatry*. February 2010;34(1):76-80.

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