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**File: ■ Ginkgo (*Ginkgo biloba*, Ginkgoaceae)**
**■ EGb 761®**
**■ Dementia**
**■ Systematic Review**

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**RE: Systematic Review of EGb 761® in Dementia with Behavioral and Psychological Symptoms**

von Gunten A, Schlaefke S, Überla K. Efficacy of *Ginkgo biloba* extract EGb 761® in dementia with behavioural and psychological symptoms: A systematic review. *World J Biol Psychiatry*. August 27, 2015; [epub ahead of print]. doi: 10.3109/15622975.2015.1066513.

Behavioral and psychological symptoms of dementia (BPSD), also known as neuropsychiatric symptoms, occur in 80-100% of patients with this condition. However, many studies evaluating dementia treatments exclude patients with BPSD. Meta-analyses evaluating the efficacy of EGb 761® (Dr. Willmar Schwabe GmbH & Co. KG; Karlsruhe, Germany), a proprietary ginkgo (*Ginkgo biloba*, Ginkgoaceae) leaf extract, for the treatment of dementia have produced equivocal conclusions. There are several new studies that assessed patients with BPSD that were not included in the meta-analyses. Hence, this systematic review was conducted to evaluate the safety and efficacy of EGb 761 for the treatment of dementia in patients who have clinically significant BPSD.

The following electronic databases were searched: PubMed (from inception through December 2013), EMBASE (January 2006 through December 2013), and PASCAL (inception through December 2013). Also, the reference sections of systematic reviews were screened and the manufacturer of EGb 761 was queried for unpublished research. The inclusion criteria were as follows: (1) randomized, placebo-controlled, double-blind, clinical trials assessing the effects of oral EGb 761 in patients with Alzheimer's disease (AD), vascular dementia (VaD), or mixed dementia, with a study duration of ≥ 22 weeks; (2) the patients enrolled were diagnosed with dementia according to the *Diagnostic and Statistical Manual of Mental Disorders* III-R and IV (DSM-III-R, DSM-IV), *International Statistical Classification of Diseases and Related Health Problems*, 10th revision (ICD-10), National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), or the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS/AIREN); (3) had clinically significant BPSD as defined by minimal scores on the Neuropsychiatric

Inventory (NPI) or other appropriate rating scales; (4) outcome measures were defined for BPSD and at least two of the three typical domains of assessment, namely, cognition, activities of daily living (ADL), and clinical global assessment (CGA); and (5) methodological quality was adequate (randomization, allocation concealment, and blinding; sample size estimation; numbers and disposition of patients who discontinued the trial prematurely; and statistical analyses were reported and judged adequate).

A total of four trials met the inclusion criteria. The manufacturer of EGb 761 provided the individual patient data from the studies so that the data could be pooled for analysis. The studies took place in Bulgaria (n = 1); Ukraine (n = 2); and Republic of Belarus, Republic of Moldova, and Russian Federation (multinational study, n = 1). In total, there were 1628 patients who were randomly assigned, and 1598 were included in the full analysis set (n = 796, EGb 761 and n = 802, placebo). Dropout rates were low (2-8%) and similar between groups. The mean age for the total population was 66 years. All studies evaluated 240 mg/day EGb 761 for 22-24 weeks. Baseline scores were similar between groups and across studies.

An analysis of covariance model was used to evaluate the effects of EGb 761 compared to placebo for the cognition, BPSD, ADL, and quality-of-life (QoL) domains; an analysis of variance model was used to assess CGA. In the case of the ADL and CGA domains where different outcome measures were used in different trials, the results were standardized within each individual trial to create a dimensionless measure. Treatment effects for the cognition, BPSD, ADL, and QoL domains were presented as standardized least mean squares differences (LMSD), and CGA was expressed as least mean squares. Standardized mean differences (Cohen's D) was used to compare overall effect sizes; standardized effect sizes of 0.2, 0.5, and 0.8 were classified as small, moderate, and large effects, respectively. Statistical significance was assumed with $P < 0.05$.

The short cognitive performance test (SKT) was used to evaluate cognition in all four trials. Three of the four studies demonstrated that EGb 761 was significantly superior to placebo; the numerical improvement in the fourth study did not reach statistical significance. In the pooled analysis, EGb 761 was significantly better than placebo ($P < 0.001$). The overall effect size was moderate.

All four of the studies demonstrated that EGb 761 was significantly better than placebo on the NPI total score assessing BPSD and the NPI caregiver distress score measuring BPSD-related caregiver distress. The pooled analysis indicated that EGb 761 was significantly better than placebo ($P < 0.001$). The overall effect size was moderate.

ADL assessments showed that in all four studies and in the pooled analysis, EGb 761 was significantly better than placebo ($P < 0.001$). The overall effect size was moderate.

CGAs showed that in three studies EGb 761 was significantly better than placebo; however, in one study there was no significant difference between groups. The pooled analysis revealed that EGb 761 was significantly better than placebo ($P < 0.001$). The overall effect size was moderate to large.

Only two of the four studies evaluated QoL. In both studies, and in the pooled analysis, EGb 761 was statistically superior to placebo ($P < 0.001$). The overall effect size was small.

Subgroup analysis of the three diagnostic subpopulations (AD, VaD, and mixed) revealed that EGb 761 was significantly better than placebo for all outcomes, except QoL for patients with VaD. The authors speculate that the lack of effect on QoL in the VaD group may be due to a lack of statistical power in this very small subsample or there may be different determinants of QoL for patients with VaD.

To evaluate whether the benefits were clinically meaningful, response rates and numbers needed to treat (NNTs) were calculated. NNTs of 6-9 are considered clinically meaningful in placebo-controlled trials of psychotropic drugs. In the present analysis, EGb 761 had NNTs of 4-5 for each outcome measure, indicating that it produced a clinically meaningful benefit.

The frequency of adverse events was similar between groups. "There was no clustering of any type of event in the EGb 761 treated patients."

Overall, the effect sizes were moderate for the domains of cognition, BPSD, ADL, and CGA, while the effect on QoL was small. The authors concluded that EGb 761 was statistically and clinically superior to placebo in improving cognitive performance, BPSD, functional abilities, and overall condition. Accordingly, caregiver distress decreased. Limitations are that none of the trials evaluated postponement of nursing home placement, and it is uncertain whether these results can be extrapolated to patients with severe BPSD. Although studies suggest that treatment benefits increase with increasing severity of BPSD, there are no published trials evaluating the efficacy of EGb 761 for the treatment of patients with severe BPSD.

This systematic review is unique and valuable because the authors conducted large-scale pooled analyses of individual patient data. This is opposed to the typical meta-analysis where authors evaluate mean data extracted from a published report. The pooled analyses support the conclusion that 240 mg/day EGb 761 is safe and moderately effective for the treatment of outpatients with dementia and mild to moderate BPSD.

Two of the authors (A. von Gunten and K. Überla) received consultant honoraria from Dr. Willmar Schwabe GmbH & Co. KG, and the third (S. Schlaefke) is a salaried employee of the company.

*—Heather S. Oliff, PhD*

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