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File: ■ Ginkgo (*Ginkgo biloba*)
■ Cognitive Decline
■ Long-term Effects

HC 031356-477

Date: July 31, 2013

RE: Ginkgo Use Reduces Long-term Cognitive Decline in Elderly without Dementia

Amieva H, Meillon C, Helmer C, Barberger-Gateau P, Dartigues JF. *Ginkgo biloba* extract and long-term cognitive decline: A 20-year follow-up population-based study. *PLoS One*. 2013;8(1):e52755. doi: 10.1371/journal.pone.0052755.

Ginkgo (*Ginkgo biloba*) is used to treat patients with mild cognitive impairment or dementia. Reviews and meta-analyses conclude that the ginkgo leaf extract EGb 761® (Dr. Willmar Schwabe Pharmaceuticals; Karlsruhe, Germany) is effective in the symptomatic treatment of patients with dementia. A couple of large-scale clinical trials (> 2800 participants) failed to show efficacy in preventing the development of dementia in healthy, elderly people. This exploratory retrospective analyses of data from a prospective study evaluates the efficacy of ginkgo in a study of 3612 subjects who were followed for 20 years.

This paper reports on a retrospective analysis of data collected prospectively over 20 years as part of the PAQUID (personnes âgées quid) cohort. The PAQUID study is a population-based study conducted in Gironde and Dordogne, France, which has completed 20 years of follow-up. This makes it one of the largest and longest-running prospective studies evaluating the natural history of cognitive decline and incidence of dementia. The PAQUID study originally enrolled 3777 people aged ≥ 65 years representing the community. Data were collected by means of a questionnaire administered at home by trained psychologists at inclusion and after 1, 3, 5, 8, 10, 13, 15, 17, and 20 years. The questionnaire included an evaluation of mental status via the mini-mental state exam (MMSE), the Benton Visual Retention Test (BVRT), the Isaacs Set Test (IST), and an assessment of dementia according to the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-III-R*) criteria. Participants in PAQUID who were diagnosed with dementia at study inclusion (n = 102) were not included in this retrospective analysis. The included subjects were separated into the 3 following groups: (1) subjects reporting use of EGb 761 (e.g., Tanakan®; Ipsen; Paris, France; Tebonin®; Dr. Willmar Schwabe Pharmaceuticals) at any visit (n = 589), (2) subjects reporting use of piracetam at any visit (n = 149), and (3) subjects not reporting use of either EGb 761

or piracetam (n = 2874). Those using both EGb 761 and piracetam at any time (n = 63) were also excluded from the analysis.

At baseline, the groups did not differ in age or number of medications consumed. Also at baseline, subjects taking "neither treatment" were more frequently men, less educated, and had fewer memory complaints. Subjects using EGb 761 were more frequently women and less frequently reported depressive symptoms or memory complaints compared to subjects taking piracetam. Baseline MMSE scores were slightly higher in the EGb 761 group. At 20 years, 73.3% of the EGb 761 group, 86.6% of the piracetam group, and 81.3% of the control group had died.

Subjects using EGb 761 had a rate of MMSE decline that was significantly less rapid than the "neither treatment" group ($P < 0.0001$). The mean difference in the MMSE score at 20 years was 5 points, which is considered clinically relevant. The piracetam group declined more rapidly than the "neither treatment" group. On the IST and BVRT, there was no significant difference in the rate of decline between the EGb 761 and "neither treatment" groups, whereas the piracetam group declined more rapidly. The differences in cognitive decline between groups did not change after controlling for psychotropic drug use (antidepressants, benzodiazepines, and antipsychotics).

The authors conclude that non-demented subjects who used EGb 761 had a slower rate of cognitive decline as measured with the MMSE than untreated subjects or subjects treated with piracetam. The clinical benefit of EGb 761 was only apparent after several years. The study shows that cognitive decline in elderly, non-demented subjects is a slow process. Therefore, it is possible that other studies that have reported that ginkgo was not beneficial for the prevention of cognitive decline did not have a duration of sufficient length (they were 3.5 to 6 years in duration). The authors state that firm conclusions should not be drawn from the piracetam results because the population size was too small.

The limitations of this study are that the dose and duration of EGb 761 treatment were not controlled. In addition, treatments were self-selected and had differing characteristics at baseline. Therefore, conclusions cannot be drawn regarding optimal dosage or when to initiate treatment. Nonetheless, the study suggests a possible effect of ginkgo in a real-world setting.

—Heather S. Oliff, PhD

Referenced article can be accessed at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3543404.