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Ginkgo biloba special extract EGb 761® in generalized anxiety disorder and adjustment disorder with anxious mood: A randomized, double-blind, placebo-controlled trial

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Abstract

Ginkgo biloba special extract EGb 761®, an anti-dementia drug, enhances cognitive functioning and stabilizes mood in cognitively impaired elderly subjects. Moreover, EGb 761® had been found to alleviate symptoms of anxiety in people with mental decline, therefore it was now tested for clinical efficacy in younger patients suffering from anxiety. One hundred and seven patients with generalized anxiety disorder (GAD, $n = 82$) or adjustment disorder with anxious mood (ADWAM, $n = 25$) according to the diagnostic and statistical manual of mental disorders, third edition – revised (DSM-III-R) were randomized to daily doses of 480 mg EGb 761®, 240 mg EGb 761® or placebo for 4 weeks. Intention-to-treat (ITT) analyses were performed on the primary outcome measure, the Hamilton rating scale for anxiety (HAMA), and the secondary variables, the clinical global impression of change (CGI-C), the Erlangen anxiety tension and aggression scale (EAAS), the list of complaints (B-L′), and the patient's global rating of change. The HAMA total scores decreased by −14.3 (±8.1), −12.1 (±9.0) and −7.8 (±9.2) in the high-dose EGb 761®, the low-dose EGb 761® and the placebo group, respectively. Changes were significantly different from placebo for both treatment groups with $p = 0.0003$ (high-dose group) and $p = 0.01$ (low-dose). Regression analyses revealed a dose–response trend ($p = 0.003$). EGb 761® was significantly superior to placebo on all secondary outcome measures. It was safe and well tolerated and may thus be of particular value in elderly patients with anxiety related to cognitive decline.

Keywords: Ginkgo biloba; EGb 761®; Randomized controlled trial; Anxiety; Generalized anxiety disorder; Adjustment disorder

1. Introduction

Symptoms of anxiety, usually not in appropriate response to a real threat, are among the frequent causes for seeking medical help. Estimated prevalence rates for anxiety disorders in primary care settings range from 2.5% to as much as 19% (Sansone et al., 2004; Ansseau et al., 2004). For generalized anxiety disorder (GAD) a prevalence of 10.3% was found in an adult primary care population (Ansseau et al., 2004), and a lifetime prevalence of 4–7% in the general population (Allgulander et al., 2003). From a survey in 88 outpatients of an internal medicine clinic Sansone et al. (2004) reported a 33% prevalence of generalized anxiety symptoms. Among the anxiety disorders classified by the diagnostic and statistical manual of mental disorders, third edition – revised (DSM-III-R, American Psychiatric Association, 1987) GAD is the second most frequent diagnosis found (Lépine and Lellouch, 1994).

Another disorder associated with symptoms of anxiety which are generalized rather than phobic in nature is adjustment disorder with anxious mood (ADWAM). Its

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prevalence was 7.8% as a sole diagnosis and a further 4.2% as comorbidity with other axis I and II diagnoses in a consultation-liaison psychiatry setting (Strain et al., 1998). In a primary care setting, the prevalence of ADWAM was 1% in the whole population of consecutive patients, 4.5% among the patients with psychological complaints and a further 9.2% in association with other psychiatric disorders (Semaan et al., 2001).

GAD is amenable to psychotherapy (primarily cognitive-behavioral therapy) as well as pharmacotherapy. Current recommendations include benzodiazepines, buspirone and antidepressants, above all serotonin and noradrenalin reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) (Allgulander et al., 2003). Benzodiazepines have the advantage of quick symptom relief, but side effects (sedation, psychomotor and cognitive impairment), physical dependence and withdrawal effects limit their long-term use. Buspirone is effective in the short-term treatment of GAD, but long-term studies are missing. All types of drugs currently recommended for treating GAD may adversely affect patients' functioning at work, car-driving and social life. Symptoms of anxiety, although often at a sub-syndromal level, are frequently found in subjects suffering cognitive decline (Lyketsos et al., 2002; Chan et al., 2003; Forsell et al., 2003). In such cases, anxiety may be a symptom of the underlying disease itself or a reaction to the perception of mental decline.

There appears to be a gap between the frequency of ADWAM and high-grade evidence for the effectiveness of treatments. In a cross-sectional study of a sample of ADWAM patients drawn from general practitioners in France (Semaan et al., 2001), 74% were prescribed drug treatments and 90% received non-pharmacological treatments. Anxiolytics were prescribed most frequently (60%), followed by antidepressants (11%) and hypnotics (8%). A Dutch group of experts issued a discussion paper suggesting practice guidelines based on "existing evidence, experience in adjacent fields and consensus procedures" (van der Klink and van Dijk, 2003) for the treatment of work-related adjustment disorders. While existing evidence was sparse, their proposed three-phase psychotherapeutic approach was based mainly on experience and consensus.

Ginkgo biloba special extract EGb 761® is registered in Germany and many other countries for the treatment of dementia disorders. In two large trials the drug has been shown to improve cognitive performance, activities of daily living and social functioning as well as the overall condition of patients with dementia (Kanowski et al., 1996; Le Bars et al., 1997). The efficacy of EGb 761® in the treatment of dementia and aging-related cognitive impairment has also been demonstrated in further studies, reviewed by Oken et al. (1998) and Birks et al. (2002). Cognition-enhancing effects in mentally healthy elderly subjects have been reported recently by Mix and Crews (2002) and Cieza et al. (2003). In one of the early studies enrolling patients with cognitive impairment due to cerebrovascular disease, anxiety was one of the non-cognitive symptoms relieved significantly by EGb 761® treatment (Eckmann and Schlag, 1982). Beneficial effects of EGb 761® on behavioral and psychological symptoms of dementia (BPSD), including anxiety, have been shown in a series of further studies (summarized in Hoerr, 2003), yet proof of efficacy in primary anxiety disorders or anxiety in response to stressful events has been lacking.

EGb 761® showed stress-alleviating and anxiolytic-like activity in pre-clinical studies. In a rat model EGb 761® significantly reduced the detrimental effects of learned helplessness on a subsequent conditioned avoidance task. It also increased the intake of novel food in a new environment in a mouse model of emotional hypophagia (Porsolt et al., 1992). On the elevated plus maze (EPM), senescent mice treated with EGb 761® spent significantly more time on the open ("unsafe") arms than those treated with drug-free vehicle only. In general, animals prefer the closed ("safe") arms. After a forced-swim task in cold water, anxiety was increased, i.e. the time spent on the open arms was decreased, in vehicle-treated, but not in EGb 761®-treated animals (Ward et al., 2002). Mice treated with a particular fraction of the special extract EGb 761® spent more time in the light part of a light-dark box than control animals. Similar effects were demonstrated for anxiolytic drugs, such as diazepam and buspirone (Nöldner and Chatterjee, personal communication). Anxiety-related hyperthermia as observed in the remaining animals after removing mice one by one from a cage and then replacing them, is also significantly attenuated by the same extract fraction (Nöldner and Chatterjee, personal communication).

Using a discrimination learning task in rats, Rapin and co-workers (1994) demonstrated that auditory perturbation ("stress") during the discriminative phase of learning decreased the percentage of correct responses and increased the number of errors. These changes were correlated with increases in plasma concentrations of epinephrine, norepinephrine and corticosterone. Both detrimental effects of auditory perturbation and rises in plasma hormones were suppressed by EGb 761®. The drug effects were present in both young and old animals. Long-term administration of EGb 761® to rats resulted in a decreased basal corticosterone secretion and an attenuation of the related increase in corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) gene expression (Marcilhac et al., 1998). Under intense surgical stress CRH, ACTH and corticosterone plasma concentrations were markedly elevated in control animals, but significantly less so in EGb 761® treated animals. These findings suggest that EGb 761® interferes with the regulation of the activity of the hypothalamic–pituitary–adrenocortical (HPA) axis.

In a randomized and placebo-controlled double-blind study in 70 healthy young volunteers, Jezova and co-workers (2002) used a stress model involving a combination of static exercise (handgrip) and mental stimuli. A single dose of 120 mg EGb 761® significantly attenuated the stress-induced rise in systolic and diastolic blood pressure without affecting the heart rate. A stress-related increase in salivary cortisol levels was observed in placebo-treated