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INSIDE

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The Use of *Ginkgo biloba* for Alzheimer Dementia

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PART 1 OF A SERIES ON ALZHEIMER'S DISEASE

THE GERIATRIC (PERSONS OLDER THAN 65 YEARS OF AGE) SEGMENT of the U.S. population, which numbered 36.3 million or 12.4% of the total population in 2004, is projected to increase to 71.5 million or 20% of the population by 2030.[1] As this demographic increases, Alzheimer's disease (AD) and other dementing illnesses will become greater sources of morbidity, mortality, and increasing health care costs.

Although some risk factors for Alzheimer's disease *(see table 1)* cannot be altered,[2] certain strategies (such as regular physical exercise and increased dietary consumption of plant-based flavonoids) can improve quality of life and prolong independent life expectancy, thereby reducing economic costs and social burdens. Additionally, phytomedicines like *Ginkgo biloba* that target specific degenerative processes, such as free radical formation and lipid membrane peroxidation, that impair brain and other bodily functions may provide additional benefits when used judiciously.

Botanical History of *Ginkgo biloba*

The ginkgo tree is the last surviving species on earth of the Ginkgoaceae family of trees whose origins date back 200 million years. Although the ginkgo became extinct in Europe and North America during the Ice Age, one species, *Ginkgo biloba* survived in China. The leaves, fruit, and seed of this tree have been part of Chinese herbal medicine since 2800 BC, employed for the treatment of asthma and as a wound dressing and memory enhancer. It has been reintroduced to other countries worldwide. Darwin called this tree a "living fossil" and its resilience has sparked the interest of Western medicine in the last half of the 20th century with regard to the biologic and pharmacologic utility of extracts of the ginkgo leaf.[3,4]

VOLUME 9 • NUMBER 6 • JUNE 2006 • PAGES 61-72

Standardization of *Ginkgo biloba* Products

The standardization of ginkgo leaf extract is important in reducing variability in results of clinical research studies. EGb 761 is a patented extract developed from the leaves of the *Ginkgo biloba* tree in 1964 by Dr. Willmar Schwabe GmbH & Co., a phytopharmaceutical company in Karlsruhe, Germany. The bulk of scientific research, including most of the European and U.S. clinical trials, has used this extract.

This product contains 24% flavonoids (including quercetin, isorhamnetins, and kaempferol) and 6% terpenes (including the diterpenes ginkgolide A, B, and C, and the sesquiterpene bilobalide) with less than 5 ppm of ginkgolic acids. The standardization process systematically verifies 70% of the total constituents of EGb 761, regardless of the origin of the raw material and in particular aims to maintain the low concentration of ginkgolic acids because they are allergenic.[5]

EGb 761 has been marketed in Europe under various brand names such as Tebonin forte, Kaveri, Rokan, and Tanakan. In the United States, ginkgo is classified as a dietary supplement; the American brand that is comparable to EGb 761 is Ginkgold.[6]

Mechanism of Action

The rationale behind testing EGb 761 in Alzheimer dementia derives from its polyvalent mode of action as a free radical scavenger, an antioxidant, and a platelet-activating factor antagonist (PAF), an effect mediated primarily by the constituent ginkgolide B. EGb 761 also has pharmacologic effects as a vasomodulator and an energy enhancer.

Animal studies have shown that EGb 761 decreases lipid peroxidation,[7] protects hippocampal neurons against cell death by amyloid beta peptide,[8] and restores the age-related loss of neurotransmitter receptor density, especially increasing the number of hippocampal muscarinic acetylcholine and alpha adrenoceptors and cortical 5-hydroxytryptamine 1A receptors. Restoration of these receptors is important because they exist in areas of the brain that regulate cognitive functioning.[6,9] EGb 761 also protects energy metabolism of neurons under conditions of oxygen and glucose deficiency and maintains Na/K ATPase activity, which ensures normal membrane functioning.[10]

In vitro studies by Ramassamy et al examined the effect of EGb 761 on stimulated oxidation of phospholipids in hippocampal and frontal cortical samples from AD patients with different apolipoprotein E genotypes (ApoE is a glycoprotein involved in cholesterol homeostasis and lipid turnover).[11] Inheritance of the e4 allele of apolipoprotein E is considered a major risk factor for late-onset familial and sporadic forms of AD.[2]

In this study, EGb 761 prevented oxidation of phospholipids in control tissues and tissues in AD patients with the e3/e3 or e3/e4 genotype of the apolipoprotein E, whereas this protective effect was less potent in tissues of the AD patients with the e4/e4 genotype. Such results indicate that patients who possess the e4 allele show more aberrant lipid homeostasis and that, although treatment with EGb 761 can mitigate these disturbances, it may be less effective for people with AD who are homozygous for e4.[11]

Domains for Evaluating Efficacy of Antidementia Drugs

Because dementia is a multifaceted chronic medical problem with numerous interrelated symptoms, standardization of outcome measures is necessary to evaluate whether a specific treatment intervention beneficially alters the natural history of the disease. To achieve this effect, the Committee for Proprietary Medicinal Products has published guidelines for the assessment of pharmacotherapy in dementia. Significant improvement must be demonstrated in at least two of three primary variables covering the domains of cognition, activities of daily living, and overall clinical response.[12]

Although many psychometric tests have been developed and used for each of the domains, the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) has been generally accepted as the

Alternative Medicine Alert, ISSN 1096-942X, is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/PUBLISHER: Brenda L. Mooney.
EDITORIAL GROUP HEAD: Lee Landenberger.
MANAGING EDITOR: Paula L. Cousins.
GST Registration Number: R128870672.

Periodical postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Alternative Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back Issues: $58 per issue. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Table 1

Risk factors for developing Alzheimer dementia[2]

- Inheritance of e4 allele of apolipoprotein E (ApoE)
- Family history of dementia
- Low educational level
- Advanced age

primary outcome measure. The scores range from 1 to 70, with lower scores consistent with better cognitive functioning. Psychologists, physicians, and study staff perform this assessment, which evaluates memory, concentration, and speech and motor ability. The annual increase in untreated Alzheimer patients is from 2 to 10 points. In several studies, "responders" were classified as patients whose scores decreased by 4 points or greater during the course of a minimum of 24 weeks of therapy.[13]

For the second domain of overall assessment of social functioning, one validated test used as an outcome measure is the Geriatric Evaluation by Relatives Rating Instrument (GERRI). The instrument assesses the ability of the patient to perform daily activities associated with personal care and social behavior such as washing, dressing, eating, mobility, etc. The observers are relatives, nursing staff, and caregivers. The score ranges from 1 to 5; higher scores indicate increasing functional impairment.

An example of an assessment of the third domain is the Clinical Global Impression of Change (CGI-C).[13] This instrument evaluates the patient's overall treatment response compared to baseline status in terms of cognitive functioning, behavior, and daily activities. It is scored by the physician after consultation with the patient and caregivers. The measurement is given as a number on a 7-point scale with a range of very much improved to very much worse.

Clinical Studies

A Cochrane systematic analysis of 33 trials conducted by Birks et al overall showed no significant adverse effects of treatment with EGb 761 compared to placebo.[14] Although the authors concluded that the studies showed evidence of improvement in cognition and social functioning measures in patients with dementia after ginkgo treatment of 12-24 weeks duration with dosages of up to 240 mg daily, they recommended larger studies to confirm these findings because some recent trials showed conflicting results despite similar, good quality study designs.

One such trial analyzed in the Cochrane review was that of LeBars et al in the North American EGb 761 Study Group.[5] This was a placebo-controlled, double-blind, randomized trial of EGb 761 for dementia that enrolled 327 outpatients with AD or Multi-Infarct Dementia. The treatment group received a daily dose of 120 mg of EGb 761 over 52 weeks. The authors reported less impairment for the ginkgo-treated group compared to the placebo group on the ADAS-Cog score (-0.1 vs. +1.5, respectively, $P = 0.04$) and a small beneficial effect on the GERRI score (-0.06 vs. +0.08, respectively), which resulted in a statistically significant mean treatment effect ($P = 0.004$). There was no difference on the CGI-C (4.2 vs. 4.2).

Problems with this study include the fact that only 137 patients completed it (50% for ginkgo and 38% for placebo), which clearly could have affected the study outcome. There was a wide range of impairment as assessed by Mini-Mental Status Examination (MMSE), with scores ranging from 9 to 26. Subsequently, the data were reanalyzed using MMSE cutoffs of 23 and 14 for an additional six months. This intention-to-treat analysis showed a favorable treatment effect of EGb 761 with respect to cognitive performance ($P = 0.02$) and social functioning ($P = 0.001$) regardless of the stage of dementia. However, the relative changes from baseline measured at endpoint depended upon the baseline dementia severity. The MMSE cutoff scores segregated out two different patterns of response. While patients with mild cognitive impairment showed improvement on the EGb 761, the group of more severely demented patients stabilized in their cognitive decline compared to the deterioration noted in the placebo-treated group.[5,15]

Another trial reviewed in the Cochrane meta-analysis was conducted by van Dongen et al.[16] This trial evaluated 214 retirement home residents over a 24-week period using three arms: two treatment groups of EGb 761, 160 mg daily (medium dose) and 240 mg daily (high dose), and placebo in a randomized, controlled, double-blind, crossover study design. This study also included patients with a broad range of baseline MMSE scores (range, 7-29) and failed to show statistically significant improvement in age-associated memory impairment and mild and moderate dementia between treatment and placebo patients in several neuropsychological and behavior outcome measures. The study's statistical power may have been limited, however, by the inclusion of patients with age-associated memory impairment.

Currently, a multicenter, randomized, double-blind, placebo-controlled trial, the Ginkgo Evaluation of Memory (GEM) Study, is ongoing.[17] This trial is sponsored

by the National Institutes of Health and includes 3,000 non-demented participants older than age 75. One of the endpoints is an evaluation of the efficacy and safety of EGb 761 (240 mg/d) for the prevention of dementia and age-related cognitive decline. The study is scheduled to continue through 2009.

Dosage

For patients with memory problems and dementia, the dosage used safely and effectively in many clinical studies is 120-240 mg/d taken in 2-3 divided doses. An initial period of 6-12 weeks is generally recommended to assess effectiveness, although results in individual patients may be observed within four weeks.

Name brands using the same extract (EGb 761) as used in clinical research studies are to be recommended as the most reliable in the current herbal market in the United States.[18]

Effects of Discontinuing Medication

An interesting comparative outpatient study of persons with AD by Rainer et al showed that average increases in ADAS-Cog scores within six weeks of ending the acetylcholinesterase inhibitors (ChE) donepezil, rivastigmine, and galantamine was 3.41 points compared with only a 1.17 point increase after stopping common nootropics (agents that enhance cognitive ability), particularly EGb.[19] This effect was not modified by gender, apolipoprotein E genotype, or extent of ventricular enlargement on computer tomography scans. Such findings have practical clinical relevance because even for initial drug responders, antidementia drugs, in many cases, cannot be continued for the duration of a patient's life due to side effects, cost, increasing debility, or a combination of these effects.[13,19]

Adverse Effects and Drug Interactions

Although clinical studies with EGb 761 have not revealed significant side effects, it does have a potent antiplatelet effect. Therefore, it should not be used in patients on antiplatelet or anticoagulant therapy and should be used cautiously in patients on nonsteroidal anti-inflammatory therapy due to potential synergistic effects that could result in bleeding complications.[20] Certain herbal medications *(see Table 2)* may also increase the risk of bleeding if used in conjunction with ginkgo.[21] Although there is no clear consensus,[22] ginkgo should be discontinued at least 36 hours prior to surgery and ideally two weeks prior to surgery. Case reports of bleeding complications associated with *Ginkgo biloba* use include subdural hematoma,[23] hyphema,[24] intracerebral hemorrhage,[25] and subarachnoid hemorrhage.[26]

Table 2

Herbal medications that may increase risk of bleeding if used with ginkgo[21]

- Ginger
- Garlic
- Ginseng
- Feverfew
- Red clover
- Dong quai

The side effects reported in studies using EGb 761 are rare and usually mild and may include nausea, vomiting, diarrhea, headaches, dizziness, palpitations, restlessness, and weakness. Hypersensitivity to ginkgo is a contraindication to its use and persons allergic to urushiols such as mango rind, poison ivy, poison oak, sumac, and cashews may be cross-reactive to ginkgo products.

Uncooked ginkgo seeds, and to a lesser extent unprocessed ginkgo leaves, contain ginkgotoxin, a chemical that can cause seizures and ultimately death if large quantities are ingested over time.[21]

Because ginkgo may affect insulin and blood sugar levels, patients with diabetes who choose to take ginkgo leaf extract preparations should monitor sugar levels carefully as adjustments to diabetic medications may be necessary.

The use of ginkgo is not recommended during pregnancy and breastfeeding due to a lack of scientific study. Ginkgo use may result in significant bleeding complications during labor and delivery.[18,21]

Conclusion

There have been several well designed clinical trials showing that the *Ginkgo biloba* extract EGb 761 has efficacy in the treatment of Alzheimer's disease. Only products with this formulation should be used as it has been shown to be safe and reliable in two to three divided daily doses of 120-240 mg and has efficacy that is nearly equivalent to that of acetylcholinerase inhibitors with less adverse side effects and cost.

Current ongoing multicenter trials such as the GEM study endeavor to demonstrate whether EGb 761 is effective as a preventive measure for dementia.

Patients on anticoagulant medications should not be treated with ginkgo products due to the possibility of serious bleeding sequelae. Patients undergoing dental or surgical procedures should stop taking ginkgo preoperatively according to the advice of their physicians. Patients with known hypersensitivities to ginkgo or urushiols should avoid its use. Ginkgo products should not be given to pregnant or breastfeeding women.

Recommendation

Ginkgo biloba in the form of EGb 761 is a safe, effective treatment for dementia, which although statistically less effective than ChE inhibitors, has a lower cost, better side effect profile, and less rebound effect, as measured in one study. The choice of ginkgo product should be restricted to brands such as Ginkgold, which contain the standardized extract EGb 761 that has been used in all of the clinical trials. ❖

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Treatment of Premenstrual Syndrome with Vitamin B_6

By Felise B. Milan, MD

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THE LARGE MAJORITY OF WOMEN EXPERIENCE UNpleasant premenstrual symptoms at some times during their lives. A full 75-80% of women report some emotional or physical changes during the luteal phase of their menstrual cycle,[1,2] 40-50% experience these symptoms as annoying and 3-8% have symptoms severe enough to produce dysfunction in some aspect of their lives.[3-5] The characteristic symptoms of premenstrual syndrome (PMS) include a mix of emotional (i.e., irritability, affective lability, depression, anxiety), physical (i.e., fatigue, bloating, weight gain, breast tenderness, change in appetite), and cognitive (i.e., confusion, difficulty concentrating) changes. The hallmark of PMS is that these symptoms occur within the two weeks before menses, remit within two days of menstruation, and are absent until ovulation.[4] Women typically begin to experience PMS symptoms in their 20s but usually do not seek care until their 30s.[4,5] It is not clear whether PMS symptoms worsen with age or whether older women are more likely to seek help for the problem.[4] Of the women who report bothersome premenstrual symptoms, 30-40% will seek help from their primary care provider.[6]

PMS Etiology/Theories

The exact pathophysiology of PMS is not entirely clear. *(See sidebar for more information on diagnosing PMS.)* It is clear that for PMS to occur, a woman must ovulate in that cycle.[7] There is an obvious link between the symptoms of PMS/premenstrual dysphoric disorder (PMDD) and the rise and fall of sex steroids associated with ovulation. Cyclical PMS symptoms do not occur with pregnancy and resolve after menopause.[8] Although suppression of ovulation with a synthetic androgen (danazol) and gonadotropin-releasing hormone agonists seems to be an effective therapy for PMS,[9-13] suppression of ovulation with oral contraceptives (OCPs) has not been shown to be as reliably effective.[7,8] There is, however, some evidence that an OCP formulated with drospirenone (a progestin and spironolactone analog) may be effective in reducing PMS symptoms.[8,14] One theory, espoused by Katarina Dalton, was that progesterone deficiency is the underlying cause of PMS.[15] Although some early evidence also suggested that PMS could be treated effectively with micronized progesterone,[16] a subsequent large randomized controlled trial was negative.[17] It has been shown that progesterone levels are not altered in women with PMS.[18] There is ample evidence to suggest alterations in serotonergic functioning during the luteal phase in women with PMS/PMDD. In addition, selective serotonin reuptake inhibitors that have been studied for treating PMS have produced an average response rate of approximately 60%.[8]

CAM for PMS

In the 1970s and 1980s, many investigators focused on supplementation with a variety of vitamins and minerals, both singly and in combination, to treat PMS. Although calcium and magnesium both have been shown to have some potential as effective therapies for PMS/PMDD, their mechanism of action remains unclear.[19-21] Vitamin E has been studied in the treatment of premenstrual mastalgia with highly variable results.[7,19] Vitamin B_6 as a cofactor in the synthesis of neurotransmitters was studied as a treatment for depression related to OCP use.[22] These data produced interest in vitamin B_6 as a treatment for PMS. Vitamin B_6 has been studied both alone and in combination with other vitamins and minerals.

Mechanism of Action

Pyridoxine HCl is the standard form of vitamin B_6 available as a supplement and is the least expensive form to produce commercially. Pyridoxine HCl is absorbed in the upper small intestine but is not metabolically active until it is phosphorylated in the liver into pyridoxal 5'phosphate (P5P). P5P is exported from the liver bound to albumin and is the most relevant measure of vitamin B_6 status.[23] Vitamin B_6 nutritional status has a significant and selective modulatory impact on central production of both serotonin and gamma-aminobutyric acid,[24] as P5P is a cofactor in the synthesis of these neurotransmitters. It is this biochemical activity that is behind the rationale for the use of vitamin B_6 in PMS/PMDD.

Prevalence of Use

Several studies conducted in the United Kingdom (UK) before 1997 found that vitamin B_6 was the most commonly used therapy for PMS,[25] with one survey finding 68% of general practitioners prescribing it for this indication. A similar survey of primary care providers in the United States and Canada, however,

found the most prescribed treatment for PMS was progesterone.[26] In 1997, the UK Department of Health proposed to limit the sales of vitamin B_6 because of possible neurotoxic side effects at higher doses. A UK study that measured prescribing practices for PMS from 1993 to 1998 found a sudden 50% decrease (from 22% to 11%) in prescriptions for vitamin B_6 for PMS from 1997 to 1998.[27]

Clinical Evidence for PMS/PMDD

Many of the studies evaluating vitamin B_6 as a therapy for PMS were done before there were well-outlined

Definitions and Diagnosis of Premenstrual Syndrome

By Felise B. Milan, MD

While aspects of premenstrual mood changes were described by Hippocrates, premenstrual tension syndrome was first delineated as a disorder in the 1930s and the term premenstrual syndrome (PMS) was first defined in the 1950s.[1] Although many recognized that a subset of the population suffered from a particularly severe form of PMS resulting in a significant level of dysfunction, clear clinical definitions were not outlined until recently. The American College of Obstetrics and Gynecology (ACOG) established clinical guidelines for PMS in 2000[2] and criteria for Premenstrual Dysphoric Disorder (PMDD) were included in DSM-IV.[3] Both the ACOG criteria for PMS and the DSM-IV criteria for PMDD require confirmation of the luteal nature of the problem through the use of prospective symptom charts or a daily rating instrument for a minimum of two menstrual cycles.

A number of valid and reliable diagnostic instruments are available to document symptoms including the Calendar of Premenstrual Experiences,[4] the Premenstrual Syndrome Diary,[5] and the Daily Record of Severity of Problems.[6] One expert recommends that women record daily the presence and severity of five of their most bothersome symptoms.[7] The use of prospective symptom recording is important in both clinical and research settings as the literature shows that more than half of the women who present with complaints of "severe PMS" are found not to have a pure luteal phase pattern based on prospective charts.[3,7]

It is necessary to establish a diagnosis of either PMS or PMDD and rule out other psychiatric disorders. One study found that of 426 women recruited from primary care obstetrics and gynecology practices who reported having PMS, 22% (93) were found to have major depressive disorder and 14% (61) had panic disorder.[8] Of the women in that study who charted their symptoms for a cycle, only 22% were confirmed to have PMS.[8] The symptom diaries also can identify women who present with complaints of PMS but are found to have psychological symptoms present throughout their cycle that worsen between ovulation and menstruation. This phenomenon is referred to as "menstrual magnification."[7] Many women find the information gleaned from charting their symptoms helpful in identifying potential triggers or lifestyle habits that may exacerbate them. Lastly, several experts[7,9] have recommended that women try certain lifestyle changes or nutritional interventions during the cycles when they are recording their symptoms.

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clinical criteria emphasizing the need to distinguish PMS from PMDD, a more severe form of the syndrome. Therefore, studies have somewhat heterogeneous inclusion criteria and outcome measures. In addition, studies on PMS, similar to those evaluating therapies for depression, have notoriously high placebo response rates. Not surprisingly, the results of these studies have been quite variable.

A 1990 review by Kleijnen of 12 controlled trials found four trials with negative results, three with positive results, and five with ambiguous results.[28] All of the studies were small (n < 50) and had some important methodological problems.

A more recent review and meta-analysis identified 25 trials: Nine of these trials were placebo-controlled and had data that could be pooled for meta-analysis.[29] The methodological quality of the trials was evaluated by Jadad[30] score as well as by a second quality scale developed by the authors. The overall quality of the trials was poor with only three of the trials achieving the recommended Jadad score of 3.[31-33] Of the nine trials included in the meta-analysis, three[31,34,35] used a high-dose multivitamin product (Optivite) which, at the recommended dose of 6-12 tablets per day, provides 300-600 mg/d vitamin B_6, 12,500-25,000 IU/d vitamin A, and 250-500 mg/d magnesium in addition to a long list of other vitamins and minerals in amounts in excess of the recommended daily allowance.[7,19] These multivitamin studies also divided patients into four symptomatic subgroups, so their analyses were done differently than the other studies. The other six studies used vitamin B_6 alone in doses of 500 mg/d[36] or 50-200 mg/d.[32,33,37-39] In one study subjects took the vitamin supplement during the luteal phase only,[32] while subjects in the other trials received the supplement throughout the menstrual cycle. Two of the studies evaluated only mastalgia,[33,35] while the others measured effects on a variety of physical, emotional, and cognitive symptoms.

The outcome measures of the nine studies were too disparate to compare directly, so the authors of this meta-analysis calculated odds ratios (OR) by dichotomizing patients into "better" or "not better" groups. After excluding one trial for failing the homogeneity test, the overall OR was 2.32 (95% confidence interval [CI] 1.95-2.54) in favor of vitamin B_6 over placebo and 1.57 (95% CI 1.40-1.77) when that trial was included.[29] The authors also extracted data from five trials with outcome measures looking specifically at depressive symptoms[31,32,35,37,38] and calculated an OR of 1.69 (95% CI 1.80-2.48) in favor of vitamin B_6. No dose-response relationship was found among the nine studies. An additional problem with the meta-analysis is that four of the nine trials used doses of vitamin B_6 that are higher than what is currently considered safe (see below). One of the larger (n = 617) and better quality studies (Jadad score of 3) randomized women with PMS to receive placebo or vitamin B_6 at doses of either 50 mg/d, 100 mg/d, or 200 mg/d for three cycles.[32] Improvement as measured by global assessment was significantly greater in the treatment group ($P < 0.02$).

Another double-blind, randomized controlled trial that was not included in the review by Wyatt et al treated women with PMS with either 300 mg/d vitamin B_6, alprazolam, propranolol, fluoxetine, or placebo.[40] Although the other groups did better than placebo, the group receiving B_6 did worse than those receiving placebo. A recent systematic review looking at the use of vitamin B_6 as a treatment for depression concluded that while the literature reviewed did not show vitamin B_6 to be valuable in the treatment of depression in general, there did seem to be a consistent indication for its use to treat depression in premenopausal women.[41]

Safety

The Institute of Medicine of the National Academy of Sciences has set the upper limit of vitamin B_6 at 100 mg/d after reports of neuropathy with doses as low as 200 mg/d.[42] Vitamin B_6 can cause nausea, vomiting, abdominal pain, loss of appetite, headache, paresthesia, somnolence, increased serum AST, decreased serum folic acid levels, allergic reactions, breast tenderness and enlargement, and photosensitivity. Large doses (1-6 g/d) can be neurotoxic. Symptoms can include tingling in the hands and feet, decreased muscle coordination, and stumbling gait.[43]

Conclusion

The diagnosis of PMS/PMDD has been aided in recent years by the establishment of clinical criteria for both the milder (PMS) and more severe (PMDD) versions of the disorder. The literature shows very clearly that women who complain of PMS symptoms often are inaccurate in their assessment of the problem. It is therefore essential to screen for other psychiatric comorbidities as well as use laboratory tests to rule out other possible diagnoses. The literature on vitamin B_6 is methodologically very poor and quite equivocal as to its efficacy as a therapy for PMS.

Recommendation

The recommended approach to the treatment of women who have a history consistent with premenstrual symptoms is to use one of the validated instruments for symptom charting. During the cycles when she is

charting, a woman can try to identify and then alter lifestyle habits that may improve her symptoms. It is also a time when a trial of vitamin B_6 at 100 mg/d could be tried and assessed for efficacy. After the symptom charts are reviewed, if a diagnosis of PMS is made or if the patient with PMDD does not choose to use a psychotropic medication, a trial of vitamin B_6 could also be considered. ❖

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CME Questions

CME Instructions: Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

After completing the program, physicians will be able to:

a. present evidence-based clinical analyses of commonly used alternative therapies;
b. make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
c. describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

18. Which of the following increases the risk of developing Alzheimer dementia?
a. inheritance of the e4 allele of apolipoprotein E (ApoE).
b. family history of dementia.
c. low education level.
d. advanced age.
e. All of the above

19. The use of *Ginkgo biloba* should be avoided in persons taking any type of anticoagulant medications.
a. True
b. False

20. Which of the following statements is *false*?
a. *Ginkgo biloba* has a better side effect profile than ChE inhibitors.
b. *Ginkgo biloba* is less expensive than ChE inhibitors.
c. *Ginkgo biloba* is as effective as ChE inhibitors.
d. *Ginkgo biloba* has less rebound effect than ChE inhibitors.

21. Although 75-80% of women report some emotional or physical changes during the luteal phase of their menstrual cycle, only 30-40% seek help from their primary care provider.
a. True
b. False

22. To make an accurate diagnosis of PMS or PMDD, the luteal nature of the problem must be confirmed through the use of prospective symptom charts or a daily rating instrument for a minimum of:
a. one menstrual cycle.
b. two menstrual cycles.
c. three menstrual cycles.
d. four menstrual cycles.

Answers: 18. e, 19. a, 20. c, 21. a, 22. b.

With Comments from Russell H. Greenfield, MD

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Astragalus and Chemotherapy

Source: McCulloch M, et al. Astragalus-based Chinese herbs and platinum-based chemotherapy for advanced non-small cell lung cancer: Meta-analysis of randomized trials. *J Clin Oncol* 2006;24:419-430.

Goal: To assess evidence from published studies and determine whether astragalus-based Chinese herbal medicine offers therapeutic benefit in the setting of lung cancer when combined with platinum-based chemotherapy.

Design: Meta-analysis of randomized trials (n = 34).

Subjects: More than 2,800 subjects with non-small cell lung cancer were assessed in the 34 studies.

Methods: A systematic search of multiple databases without restriction based on language of publication was performed. Out of an initial 1,305 potentially relevant articles identified a total of 34 studies were included in the analysis. Data were assessed for survival outcome, objective tumor response, decreased chemotherapy toxicity, and improved/stabilized performance status.

Results: Twelve trials reported a decreased risk of death at 12 months, while 30 studies reported improved tumor response. A small number of studies also suggested stabilized or improved Karnofsky performance status. No significant data were identified having to do with hematologic toxicity.

Conclusion: Astragalus-based herbal therapy may increase the effectiveness of platinum-based chemotherapy for the treatment of non-small cell lung cancer.

Study strengths: Use of Jadad scale (validated 5-point scale used to evaluate the quality of randomized trials in meta-analysis); conservative nature of assessment of treatment impact; use of Begg test to assess existence of publication bias (none found).

Study weaknesses: Weaknesses inherent in a meta-analysis (for example, some trials employed various combinations of herbs together with astragalus, while others used specific herbal formulas).

Of note: In China, herbal therapies are commonly combined with chemotherapy for the treatment of cancer; *Astragalus membranaceus* may augment immunity through improved recognition of lung cancer cells (lessened immunologic tolerance to tumor progression) and by stimulating both macrophage and natural killer cell activity; in Chinese medicine, astragalus is almost always used in combination with other Chinese medicinal herbs; though treatment advances continue to be developed, new therapies for non-small cell lung cancer are limited by both significant toxicity and low efficacy; addition of platinum-based drugs to standard chemotherapy has been shown to increase 12-month survival by 5% and tumor response by 62%, but at the expense of significant side effects (nausea and vomiting, renal and hematologic toxicity); only three of 34 studies had a Jadad score of 2 or more (suggesting very poor quality of the studies); there exists no published evidence of interaction between platinum-based chemotherapy and astragalus.

We knew that: Lung cancer is the leading cause of cancer death in the United States; adjuvant chemotherapy reduces risk of death at two years from non-small cell lung cancer by only 13% when compared with treatment by surgery alone, adjuvant chemoradiotherapy reduces the risk by only 14%, and adjuvant radiotherapy alone actually increases the risk of death by 21%; quality of life for people with advanced non-small cell lung cancer is often poor; in a study published in 2003 platinum-based chemotherapy combined with astragalus significantly decreased risk of death at 12 and 24 months (RR = 0.62 and 0.75, respectively).

Clinical import: Astragalus, also known as Huang Qi, has a rich tradition of use in Chinese medicine, especially as an immunostimulant. The data presented in this meta-analysis are far from definitive, especially considering the poor quality of trials assessed, but they are nonetheless compelling in light of the significant therapeutic challenge posed by non-small cell lung cancer. This work does, however, underscore the apparent safety of astragalus, and supports future performance of methodologically sound study of astragalus in combination with chemotherapy. Should practitioners recommend astragalus to their patients who are receiving platinum-based chemotherapy? It is still too early to say with authority. For patients inclined to use herbs or supplements during treatment it is best to include their oncologist in the decision, else the patient could wind up in the middle of divergent medical opinions, adding stress to an already difficult situation.

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Ginseng and Hypertension

Source: Stavro PM, et al. Long-term intake of North American ginseng has no effect on 24-hour blood pressure and renal function. *Hypertension* 2006;47:791-796. Epub 2006 Mar 6.

Goal: To evaluate the effect of North American ginseng (NAG) on mean

24-hour ambulatory blood pressure (ABP) and renal function after 12 weeks use in hypertensive subjects.

Design: Randomized, controlled, double-blind crossover trial.

Subjects: Fifty-two people from Toronto with hypertension (data from 37 subjects, 30 men, were included in the main analysis).

Methods: Subjects recruited through newspaper advertisements were randomized to receive, following a four-week open label placebo run-in, 3 g NAG followed by cornstarch placebo, or cornstarch placebo followed by 3 g NAG (identical capsules). Participants ingested the capsules orally in divided doses (bid) during the first 12 weeks (between 7-9 am and again between 7-9 pm). Following an eight-week washout period subjects took the crossover treatment for 12 weeks in the same manner. ABP monitors were fitted, weight was recorded, and blood samples were drawn at the beginning of the run-in and at study's end after a 10-12 hour fast overnight and discontinuation of blood pressure medications (8 hours). During the two days that the ABP monitor was worn (activated between 9-10 am) no NAG or placebo was ingested. Participants also filled out a 24-hour diary of activity, sleep, and drug schedules. Primary outcome measure was mean 24-hour ambulatory systolic blood pressure at 12 weeks. Additional blood pressure measures, body weight, and serum cystatin C levels were secondary outcome measures.

Results: No significant treatment effect was found for mean 24-hour systolic blood pressure or most other blood pressure parameters (including day and nighttime readings). At week 12, diastolic blood pressure readings for the NAG group were higher at 1 pm than in the placebo group, but this was considered insignificant since mean daytime and 24-hour diastolic blood pressure readings did not differ between the groups. No significant change was noted in body weight or serum cystatin C between the two groups at the end of the study.

Conclusion: In hypertensive individuals, 12 weeks of NAG has no effect on ambulatory blood pressure or renal function.

Study strengths: Use of 24-hour ambulatory blood pressure monitoring rather than office blood pressure; intention-to-treat analysis included.

Study weaknesses: Significant dropout rate with small sample (15/52, or 29%); compliance estimated by pill count; the authors state that ginsenosides remain in human plasma for approximately 12 hours, while 12-week ABP monitor readings were initiated at least 12 hours after the last ingestion of NAG.

Of note: While there are many species of ginseng, *Panax quinquefolius* (NAG) and *Panax ginseng* (Asian or Korean ginseng) comprise the majority of ginseng consumed worldwide; ginseng is used by 10-20% of adult Asians and by up to 5% of adults in Western countries, while estimates are that 20-40% of people in these same regions have hypertension; concerns about ginseng causing elevated blood pressure come primarily from a 1979 observational study noting development of hypertension in 14 subjects after three months of use; a single batch of NAG, reportedly representative of NAG on the world market, was used in the current trial; subjects were permitted to take their antihypertensive agents during the study; a previous trial by the same study group showed that even NAG batches differing in quality and ginsenoside content had no acute effect on blood pressure.

We knew that: Though data are conflicting, ginseng has been reported to improve cognitive function, immune system activity, and glycemic control, and is widely perceived to be a tonic that enhances overall vitality; serum cystatin C is a marker of glomerular filtration rate and cardiovascular mortality; the 3 g dosage employed in this study is the same dosage typically used in traditional Chinese medicine and matches the average intake reported to cause hypertension in the 1979 study that gave rise to cautions; NAG contains a three- to five-fold higher ginsenoside content than do both forms of *Panax ginseng*; early data on *Panax ginseng* suggest that it might actually lower blood pressure.

Clinical import: Concern about using ginseng in people with hypertension was raised more than two decades ago and has made its way into the general mindset of practitioners under the heading "contraindication." The current study suggests that long-term ingestion of NAG does not have a lasting effect on blood pressure in hypertensive patients, but the trial is flawed. Aside from the significant dropout rate, the 12-hour lag time between measurement of 24-hour ABP and last ingestion of NAG is at least puzzling, making firm conclusions elusive. As the authors point out, it would be interesting to determine the effect of NAG on blood pressure in people with untreated mild hypertension or pre-hypertension. Likewise, a larger trial involving hypertensive patients with fewer dropouts and improved methodology would be welcome. Practitioners should keep in mind that this trial only addressed North American ginseng, so results do not apply to all forms of ginseng in therapeutic use. It is possible that NAG may be safely employed in hypertensive patients where indicated, but the current study does not prove this true. Monitoring of blood pressure in this setting remains the prudent course until more definitive data become available.

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Supplement to *Alternative Medicine Alert*
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ALTERNATIVE MEDICINE ALERT™

A Clinician's Evidence-Based Guide to Alternative Therapies

Alzheimer's Disease: A Caregiver's Guide, Part 1

CARING FOR A PERSON WITH ALZHEIMER'S DISEASE (AD) AT HOME IS A DIFFICULT TASK AND can become overwhelming at times. One of the biggest struggles caregivers face is dealing with the difficult behaviors of the person they are caring for. Many caregivers have found it helpful to use strategies for dealing with difficult behaviors and stressful situations. Following are some suggestions to consider when faced with difficult aspects of caring for a person with AD.

Dealing with the Diagnosis

Finding out that a loved one has Alzheimer's disease can be stressful, frightening, and overwhelming. As you begin to take stock of the situation, here are some tips that may help:

- Ask the doctor any questions you have about AD. Find out what treatments might work best to alleviate symptoms or address behavior problems.
- Contact organizations such as the Alzheimer's Association for more information about the disease, treatment options, and caregiving resources. Some community groups may offer classes to teach caregiving, problem-solving, and management skills.
- Find a support group where you can share your feelings and concerns. Members of support groups often have helpful ideas or know of useful resources based on their own experiences. On-line support groups make it possible for caregivers to receive support without having to leave home.
- Study your day to see if you can develop a routine that makes things go more smoothly. If there are times of day when the person with AD is less confused or more cooperative, plan your routine to make the most of those moments. The way the person functions may change from day to day, so try to be flexible and adapt your routine as needed.
- Consider using adult day care or respite services to ease the day-to-day demands of caregiving. These services allow you to have a break while knowing that the person with AD is being well cared for.
- Begin to plan for the future. This may include getting financial and legal documents in order, investigating long-term care options, and determining what services are covered by health insurance and Medicare.

Communication

Trying to communicate with a person who has AD can be a challenge. Both understanding and being understood may be difficult.

- Choose simple words and short sentences and use a gentle, calm tone of voice.
- Avoid talking to the person with AD like a baby or talking about the person as if he or she weren't there.
- Minimize distractions and noise—such as the television or radio—to help the person focus on what you are saying.
- Call the person by name, making sure you have his or her attention before speaking.
- Allow enough time for a response. Try not to interrupt.

- If the person with AD is struggling to find a word or communicate a thought, gently try to provide the word he or she is looking for.
- Frame questions and instructions in a positive way.

Driving

Making the decision that a person with AD is no longer safe to drive is difficult, and it needs to be communicated carefully and sensitively. Even though the person may be upset by the loss of independence, safety must be the priority.

- Look for clues that safe driving is no longer possible, including getting lost in familiar places, driving too fast or too slow, disregarding traffic signs, or getting angry or confused.
- Be sensitive to the person's feelings about losing the ability to drive, but be firm in your request that he or she no longer do so. Be consistent—don't allow the person to drive on "good days" but forbid it on "bad days."
- Ask the doctor to help. The person may view the doctor as an "authority" and be willing to stop driving. The doctor also can contact the Department of Motor Vehicles and request that the person be reevaluated.
- If necessary, take the car keys. If just having keys is important to the person, substitute a different set of keys.
- If all else fails, disable the car or move it to a location where the person cannot see it or gain access to it.

Visiting the Doctor

It is important that the person with AD receive regular medical care. Advance planning can help the trip to the doctor's office go more smoothly.

- Try to schedule the appointment for the person's best time of day. Also, ask the office staff what time of day the office is least crowded.
- Let the office staff know in advance that this person is confused. If there is something they might be able to do to make the visit go more smoothly, ask.
- Don't tell the person about the appointment until the day of the visit or even shortly before it is time to go. Be positive and matter-of-fact.
- Bring along something for the person to eat and drink and any activity that he or she may enjoy.
- Have a friend or another family member go with you on the trip, so that one of you can be with the person while the other speaks with the doctor.

Visiting a Person with AD

Visitors are important to people with AD. They may not always remember who the visitors are, but just the human connection has value. Here are some ideas to share with someone who is planning to visit a person with AD.

- Plan the visit at the time of the day when the person is at his or her best. Consider bringing along some kind of activity, such as something familiar to read or photo albums to look at, but be prepared to skip it if necessary.
- Be calm and quiet. Avoid using a loud tone of voice or talking to the person as if he or she were a child.
- Respect the person's personal space and don't get too close.
- Try to establish eye contact and call the person by name to get his or her attention. Remind the person who you are if he or she doesn't seem to recognize you.
- If the person is confused, don't argue. Respond to the feelings you hear being communicated, and distract the person to a different topic if necessary.
- If the person doesn't recognize you, is unkind, or responds angrily, remember not to take it personally. He or she is reacting out of confusion.

Coping with Holidays

Holidays are bittersweet for many AD caregivers. The happy memories of the past contrast with the difficulties of the present, and extra demands on time and energy can seem overwhelming. Finding a balance between rest and activity can help.

- Keep or adapt family traditions that are important to you. Include the person with AD as much as possible.
- Recognize that things will be different, and have realistic expectations about what you can do.
- Encourage friends and family to visit. Limit the number of visitors at one time, and try to schedule visits during the time of day when the person is at his or her best.
- Avoid crowds, changes in routine, and strange surroundings that may cause confusion or agitation.
- Do your best to enjoy yourself. Try to find time for the holiday things you like to do, even if it means asking a friend or family member to spend time with the person while you are out.
- At larger gatherings such as weddings or family reunions, try to have a space available where the person can rest, be by themselves, or spend some time with a smaller number of people, if needed.

Source: National Health Institutes, National Institute on Aging. Available at: www.nia.nih.gov/Alzheimers/Caregiving/HomeAndFamily/. Accessed May 17, 2006.