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## Regular Aerobic Exercise for the Mitigation of Alzheimer Dementia

By Susan Marcolina MD, FACP

Dr. Marcolina is a board-certified internist and geriatrician in Issaquah, WA; she reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

PART 2 OF A SERIES ON ALZHEIMER'S DISEASE

ALZHEIMER'S DISEASE (AD) IS THE MOST COMMON CAUSE OF ADULT-onset dementia and one of the most dreaded sequelae of the aging process.<sup>1</sup> Its clinical features include insidious but progressive memory loss and severe cognitive decline, which result in the loss of independent functioning and increased caregiver burden. Patients experiencing such cognitive decline often eventually need long-term nursing home care with its attendant increased costs. Approximately 75% of dementias are diagnosed as the Alzheimer type.<sup>2</sup>

Several risk factors for cognitive impairment (*see Table*),<sup>3</sup> specifically cardiovascular disease, are amenable to lifestyle modifications.<sup>4</sup> The relationship between physical fitness levels, cognition, and overall general health in older adults is well established; therefore, regular physical exercise can be a common pathway through which to prolong neurocognitive health in the context of improved overall health.<sup>5</sup>

### Changes in Cognition and the Brain with Aging

There is considerable heterogeneity in the patterns of cognitive senescence among individuals due both to genetic as well as environmental factors (*see Table*).<sup>6</sup> The aging process also does not affect the central nervous system uniformly. Between the ages of 30 and 90, approximately 15% of the cerebral cortex and 25% of the cerebral white matter of the average human brain has diminished disproportionately in the areas of the prefrontal, frontal, and temporal brain regions. Because these areas control executive thought processes, language, memory, and learning, this pattern of loss is closely matched by declines in cognitive performance.<sup>7,8</sup>

Colcombe et al demonstrated this localized pattern of cortical loss in an MRI morphometric imaging study of 55 community-dwelling

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older adults aged 55-79. Notably, persons with the best aerobic fitness as measured by  $VO_2$  scores experienced significant gray and white matter tissue sparing in these crucial areas even after correction for alcohol and caffeine consumption, hormone replacement therapy, years of education, and hypertension.<sup>9</sup>

### Definition of Types of Brain-Enhancing Exercise

Aerobic exercises (e.g., walking, hiking, bicycling, calisthenics, cross country skiing, and swimming) are defined as those that require continuous and rhythmic use of large muscle groups and increase resting heart rate by at least 60% of heart rate reserve. Optimal cardiovascular benefit is obtained when these exercises are done for at least 30 minutes on most but preferably all days of the week.<sup>10</sup>

### Physiologic Effects of Exercise on Brain Function

Regular exercise has been postulated to enhance brain function through various physiological mechanisms including decreased brain deposition of beta amyloid plaques, increased cerebral blood flow, and reduced accumulation of reactive oxygen species. All of these processes have been implicated in the pathogenesis of AD.<sup>11,12</sup> Regular physical exercise upgrades neural growth proteins, especially brain-derived neurotrophic factor (BDNF) and fibroblast growth factor-2 (FGF-2) in the hippocampus, an area particularly vulnerable to the effects of AD and other dementias. These growth factors have roles in promoting proliferation and reactivity of

astrocytes, as well as survival and growth of neurons and capillary formation.<sup>13,14</sup>

Regular exercise also reduces the incidence of cardiovascular disease and stroke. Spirduso noted that higher levels of fitness enhance the activity of monoamine neurotransmitters in the brain, particularly dopamine. Such enhancement moderates the effects of aging, which decreases the levels of these neurotransmitters.<sup>15</sup>

Additionally, the physical training of regular exercise can have a direct beneficial effect on psychological variables such as improved self-image and sense of control and elevated mood. Some of these psychological variables may mediate patterns of chronic cardiovascular reactivity in response to stress.<sup>16</sup>

Several lines of evidence deal with a pathogenetic role of stress hormones on the occurrence and progression of cognitive disorders in elderly subjects. The hippocampus is particularly sensitive to stress hormones due to its high concentration of corticosteroid receptors. Magri et al studied cortisol secretion in clinically healthy old subjects, age-matched demented patients, and young controls. Both healthy elderly and the demented patients, especially those with AD, had significantly higher cortisol levels at nighttime compared to the healthy young controls. Qualitative and quantitative changes of the adrenal secretory pattern were significantly and directly correlated with a decrement in hippocampal volumes as measured by MRI.<sup>17</sup>

### Gender Susceptibility and AD

Epidemiologic studies have shown higher prevalence rates of AD in women, but the underlying physiologic reason for the gender predilection is not known. A meta-analysis by Colcombe and Kramer revealed that fitness training programs had a larger impact on cognition if the study samples had at least 50% female enrollment. They speculated that this effect may be due to the influence of estrogen (as estrogen replacement therapy) on BDNF: Estrogen causes the up-regulation of BDNF.<sup>13,18</sup> Both estrogen and BDNF are important for synaptogenesis and neurogenesis, particularly in the region of the hippocampus.<sup>19,20</sup>

This speculation, however, was not borne out clinically by the recent Women's Health Initiative Memory Study, which showed no improvement in memory or other cognitive abilities for women older than age 65 on hormone replacement therapy.<sup>21</sup>

### Clinical Studies

A Fratiglioni et al review of nine observational studies concluded that physical exercise in the elderly is

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Table

**Risk factors for cognitive impairment**

<b>Risk Factor</b>	<b>Remarks</b>
Age	Increased risk with increased age
Sex	2:1 female:male ratio
Education	Increased number of years confers decreased risk
Head trauma	
Family history of dementia	
Cardiovascular disease	Amenable to lifestyle modification
Atherosclerosis	Amenable to lifestyle modification
Hypertension	Amenable to lifestyle modification
Diabetes mellitus (Type 2)	Amenable to lifestyle modification
Total serum cholesterol level	Amenable to lifestyle modification
Serum fibrinogen	Amenable to lifestyle modification
Apolipoprotein E e4 allele carrier	

*Adapted from:* Schuit AJ, et al. Physical activity and cognitive decline, the role of apolipoprotein e4 allele. *Med Sci Sports Exerc* 2001;33:772-777.

inversely correlated with risk for all-cause dementia and Alzheimer disease.<sup>22</sup> Over a follow-up period of 5-7 years, risk reductions varied from 20% to 50%. The limitation of the included studies was the fact that they enrolled healthy persons free of dementia and evaluated the association of baseline physical activity with subsequent onset of dementia. Although these studies measured baseline physical activity prior to the clinical onset of dementia, they could not exclude the possibility that lower baseline exercise levels were a consequence of early, subclinical cognitive impairment. Such reverse causation bias, which can occur in the context of chronic diseases such as dementia, makes it difficult to know for certain whether the diminished physical activity was an epiphenomenon of the preclinical dementia or a cause of subsequent dementia.<sup>22,23</sup>

Larson et al made a special effort to overcome this bias in their prospective longitudinal cohort study of 1,740 persons 65 years and older followed biennially over six years by setting a high threshold score for participants in the Cognitive Ability Screening Instrument (CASI).<sup>24</sup> Only participants with scores between 91 and 100 were enrolled in an effort to exclude persons with incipient dementia. (The CASI scores range from 1 to 100; a score of 86 corresponds to a Mini-Mental Status Examination score of 25-26).

Persons who exercised three or more times per week had a relative hazard of 0.68 for developing dementia compared to those who exercised fewer than three times per week when adjustments were made for the potential covariates of alcohol consumption, smok-

ing, supplement use, education, presence of the apolipoprotein E e4 alleles, diabetes, hypertension, cerebrovascular disease, self-rated health, coronary disease, physical performance, depression, and cognitive functioning. Within this homogeneous, primarily white and well-educated study group, physical exercise resulted in an overall 32% risk reduction for dementia. Interestingly, regular exercise was associated with the greatest risk reduction in participants with a baseline of poor physical functioning.

Teri et al demonstrated in a randomized prospective controlled trial of 153 community-dwelling AD patients and their caregivers that patients assigned to the combined exercise and caregiver training program had improved health outcomes and depression scores after three months when compared to the routine care group.<sup>25</sup>

### **Exercise Prescribing**

The Centers for Disease Control and Prevention (CDC) and the American College of Sports Medicine (ACSM) currently recommend 30 minutes or more of moderate-intensity physical activity on most or preferably all days of the week for all adults, including the elderly.<sup>26</sup> The Institute of Medicine recommends that all adults, including the elderly, perform 60 minutes of moderate-intensity physical activity daily to promote health and vigor and to decrease the risk for chronic illnesses and early death.<sup>27</sup>

Patients can be started on a walking regimen utilizing the PBS Personal Health and Fitness Program,<sup>28</sup> which

contains information about starting and ramping up an exercise program to a goal of 10,000 steps or more. This distance approximates the daily exercise recommendations of the CDC and the ACSM. Patients should be encouraged to record their daily exercise and monitor their progress. The ACSM offers patients color brochures on the use of exercise equipment such as a stability balls and resistance bands.<sup>29</sup> A free newsletter downloaded from the ACSM web site (available at: [www.acsm.org](http://www.acsm.org)) gives important information about fitness, diet, and exercise.

In addition to physical exercise, mental exercise activities such as reading, playing board games, assembling puzzles, or playing a musical instrument have been associated with a decreased risk for subsequent dementia among older adults.<sup>30</sup>

### Public Health Initiatives

Successfully changing individual behavior for the long term requires more than personal change strategies. Institutional and public policy changes are critical to achieving sustained behavioral change in individuals. For example, initiatives such as the U.S. Department of Health and Human Services' Steps to a Healthier U.S. encourage families and individuals to take small manageable steps to increase their physical activity within their current lifestyles rather than drastic changes to ensure long-term health. Since its inception in Fiscal Year 2003, the Steps program has awarded \$100 million to 40 communities nationwide to implement evidence-based activities that contribute to increased physical fitness. Additionally, Steps funds the YMCA of the USA as a partner to expand the reach of community based programs.<sup>31</sup> Specific information about Steps communities throughout the United States is available at [www.cdc.gov/steps/steps\\_communities/index.htm](http://www.cdc.gov/steps/steps_communities/index.htm).

The National Institutes of Health has published an informative and helpful booklet for patients entitled *Energize Yourself! Stay Physically Active* which can be downloaded from [www.nhlbi.nih.gov/health/public/heart/other/chdblack/energize.htm](http://www.nhlbi.nih.gov/health/public/heart/other/chdblack/energize.htm).

Both the AARP (formerly the American Association of Retired Persons) and the Alzheimer's Association have started initiatives to increase the awareness of strategies both to preserve and enhance cognitive functioning among older adults. The Alzheimer Association's *Maintain Your Brain* encourages older adults to make "brain healthy life choices" such as maintaining physical, social, and mental fitness and choosing a diet low in saturated fats and rich in antioxidant-containing fruits and vegetables.<sup>32</sup> Similarly, the AARP's *Staying Sharp* initiative encourages older adults to involve them-

selves in regular physical, social, and mental exercises and to practice the techniques of repetition, visualization, building associations, planning, and prioritization to sharpen memory. *Staying Sharp* offers a two-hour forum in certain cities to present these memory-enhancement concepts.<sup>33</sup>

### Conclusion

Regular aerobic physical exercise is a cost-effective addition to the primary preventive and secondary treatment of dementia. Its potential benefits extend beyond cardiovascular risk factor modulation to also positively impact brain health in delaying the onset of age-related cortical grey and white matter frontal, parietal, and temporal losses. This provides another compelling reason to promote its incorporation into a patient's lifestyle prescription.

### Recommendation

Physicians should prescribe regular daily aerobic exercise for themselves and for their patients. Exercise benefits all individuals at all levels of ability but is particularly important for persons who currently have functional limitations. Exercise as a therapeutic modality is cost-effective, has few adverse side effects, and provides positive health effects for the entire body. Performing regular mental exercise in the form of board games, crossword puzzles, and playing musical instruments is another useful way to practice cognitive flexibility, thus building cognitive reserve.

To implement specific exercise interventions, physicians should refer patients and their families to the information presented in the NIH, AARP, and Alzheimer Association initiatives mentioned above and follow their progress. Local community resources such as the YMCA and community centers may also have specific fitness programs and personal training professionals that can provide geriatric patients with appropriate and enjoyable physical activities, which, when incorporated into their daily lives, will improve their overall general medical and neurocognitive health. ❖

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# Supplements Commonly Used for Weight Loss: What's the Skinny?

By David Kiefer, MD

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THERE ARE MANY REASONS WHY PEOPLE CONSIDER trying to lose weight. It may be yet another attempt after the New Year as the energy to stick to a resolution is still fresh, or the upcoming beach vacation during the summer swimsuit season. Certainly, all of the press surrounding the rising obesity epidemic brings the issue to the forefront of discussions, from the medical clinic to people's homes.

The weight-loss plan may include fad diets, new exercise regimens, pharmaceutical interventions, surgery, or a myriad of dietary supplements, or a combination of all of the above, to achieve ideal body weight. With respect to weight-loss supplements, there are many claims of efficacy that may be difficult for consumers and health care practitioners to interpret. This evidence-based review will explore the research and proven efficacy for some of the most common products for sale on the shelves of pharmacies and health food and supplement stores.

## Introduction

The weight-loss supplement industry is huge. Sales for approximately 50 individual supplements and 125 combination products totaled over \$1.3 billion in 2001.<sup>1</sup> Some demographic groups may be more likely to purchase weight-loss products; for example, in 1999, almost one-third of young, obese women used over-the-counter supplements for weight loss.<sup>1</sup> Until ephedra was banned, approximately 12 million people in the United States were using it.<sup>2</sup>

Weight-loss supplements are found in grocery stores, pharmacies, supplement shops, and health food stores. A recent survey of seven such establishments in the Seattle metropolitan area found six to 103 different products for sale over the counter for weight loss, with a mean of 46 products per store; health food stores stocked more weight-loss products, as did the health food stores and pharmacies with a section dedicated specifically to weight-loss products (unpublished data, study conduct-

ed by author). Some of the products that you or your patients may see for sale are listed in the Table. The rest of this article will review six of the most common supplements for weight loss, examining their mechanism of action, adverse effects, and evidence for efficacy.

## Individual Supplement Mechanisms of Action and Clinical Evidence

**Ephedra.** Ephedra refers to a genus of plants that contains 40 different species.<sup>2</sup> The ones that were most commonly used medicinally in the United States are from three Asian species (*Ephedra sinica*, *E. intermedia*, *E. equisetina*) that are particularly high in physiologically active alkaloids. These alkaloids (40-90% of which is ephedrine) act as alpha- and beta-adrenergic agonists, leading to bronchodilation, decongestion, vasopressant activity, and a variety of cardiovascular effects such as increased blood pressure and increased heart rate.<sup>2</sup>

Clinical trials have demonstrated approximately 1 kg/month of weight loss when ephedra or ephedrine is used in adequate doses,<sup>3</sup> though such doses are associated with a two- to fourfold increase in the incidence of adverse effects, including such severe conditions as myocardial infarction and stroke.<sup>3-6</sup>

Despite some difficulty in establishing a direct cause-and-effect relationship between the documented adverse effects and ephedra use,<sup>3</sup> and the safe use of ephedra in traditional Chinese medicine in low doses,<sup>7</sup> the decision was made in 2004 by the FDA to ban the sale of ephedra products (*see Alternative Medicine Alert March 2004*).

**Bitter orange.** Bitter, or sour, orange weight-loss products refer to extracts from the fruit or rind of *Citrus aurantium*, one of the many orange species. The active compounds in bitter orange are a family of adrenergic amines, including synephrine (with a structure similar to ephedrine) and octopamine (with a structure similar to norepinephrine);<sup>8</sup> basic science supports a sympathomimetic effect of these compounds, with synephrine more specifically having an alpha-1-adrenergic effect.<sup>9</sup> A beta-adrenergic effect of these compounds may cause some lipolysis, in animals more than humans, and with octopamine more than synephrine.<sup>8</sup> Synephrine has very poor oral absorption that is improved significantly by coadministration with caffeine.<sup>9</sup>

One randomized, double-blind clinical trial in 23 individuals on an 1,800 calorie/d diet compared placebo to a combination product that contained 975 mg of bitter orange, 528 mg caffeine, and 900 mg of St. John's wort for six weeks.<sup>10</sup> The study participants were able to exercise three times a week, and, after six weeks, lost 1.4 kg of weight and 2.9% of their body fat. There was no documented change in mood or cardiovascular parameters,

Table

**Common dietary supplements for weight loss and a sampling of brand names****Common Dietary Supplements**

Bovine thyroid, caffeine, chitosan, chromium, citrus, coleus, conjugated linoleic acid, elderberry ginseng, green tea, guarana, gymnema, hoodia, iodine, mate, peppermint, St. John's wort, stevia, turmeric

**Brand Names**

Carb Intercept, Once Daily Weight Wise, Mega T, Mega G, Schiff Natural Green Tea Diet, Thermo Trim, Diet Prep, Meta-Burn EF, Meta-Burn XTP, Super Dieter's Tea, Burnmore, Craveless, Get Lean and Defined, Burn Fat Six Ways, Ripped Fuel, Ripped Fuel Extreme, Omega Burn, Xenadrine EFX, Xenadrine Cytodyne 40+, System Six Ripped Man, Green Tea Fat Metabolizer, SlimStyles with PGX (PolyGlycopleX), 4.3.2.1 Diet, Binge Buster

but there were three dropouts who were not included in the final analysis on an intention-to-treat basis.

Adverse effects from bitter orange could be surmised from its phytochemical constituents. Animal research has shown a hypertensive effect of the adrenergic compounds in bitter orange, and some human trials show increased blood pressure from isolated synephrine (which may not occur from the complete bitter orange extract).<sup>8</sup> Bitter orange, with 46.9 mg of synephrine, also led to an increased heart rate in 10 individuals.<sup>9</sup> Compared to ephedrine, synephrine appears to be less lipophilic and less able to cross the blood-brain barrier, though there have still been isolated case reports of stroke, myocardial infarction, and exercise-induced syncope with synephrine; the myocardial infarction appeared to be the result of synephrine tablet abuse.<sup>8,9</sup>

**Chitosan.** Chitosan is a positively charged compound derived from chitin, which makes up the shells of crustaceans. The theory is that in the lumen of the intestine chitosan binds fat particles because they are negatively charged. Animal research has found decreases in cholesterol absorption, serum cholesterol, liver cholesterol, and atherosclerosis, but one human trial investigating the proposed mechanism of action demonstrated only a clinically negligible increase in fecal fat excretion in 15 men taking 4.5 g of chitosan daily for four days.<sup>11</sup>

With respect to weight loss in humans, there have been two meta-analyses. One review of 14 trials found a 1.7 kg weight loss with chitosan when compared to placebo, and decreases in serum cholesterol and systolic and diastolic blood pressure.<sup>12</sup> The meta-analysis found a similar effect on fecal fat excretion and side effect profile for chitosan when compared to placebo. The authors commented on the poor quality of the research available for this meta-analysis, and a wide variance in research results. Another meta-analysis on the use of chitosan for 1-6 months also found a 1.7 kg weight loss when compared to placebo.<sup>13</sup> The effective dose remains to be

determined definitively, but one study using 1 g of chitosan twice daily failed to demonstrate any changes in body mass index or lipid parameters;<sup>14</sup> the thought was that this study was probably under-dosed.

The primary adverse effects of chitosan are flatulence and constipation.<sup>15</sup>

**Conjugated Linoleic Acid.** Conjugated linoleic acid (CLA) is a collection of isomers of linoleic acid, one of the omega-6 fatty acids. CLA is created by mixing cis/trans isomers at several double-bond positions; some experts classify it, therefore, as a trans-fatty acid.<sup>16</sup> There is approximately 200 mg of CLA (especially the cis9-trans11 form) naturally in our diet, primarily occurring in dairy and meat. In contrast, the dose for weight-loss purposes is generally 3-4 g daily.<sup>16</sup> In animals, especially murine trials, there is convincing evidence that CLA supplementation leads to a variety of physiological effects such as inhibition of adipogenesis, loss of fat mass, increase in lean tissue mass, attenuation of fat cell differentiation, and overall weight loss, possibly through feeding aversion versus increased energy expenditure.<sup>16,17</sup> Of note, approximately 130 g of CLA daily would have to be used in humans to match the amount used in some of these animal trials.

One review of 13 human clinical trials using 1-8 g daily of CLA for 4-13 weeks found no effect on lean body mass nor weight.<sup>16</sup> However, one recent double-blind, randomized, controlled trial compared 3.4 g of CLA daily to placebo in 157 overweight, otherwise healthy adults for 24 months.<sup>18</sup> For the 125 people who completed the trial, results showed a 1.5-2.4 kg decrease in body weight and a 6-8% decrease in body fat mass in the CLA group. No intention-to-treat analysis was done for the study dropouts.

Numerous adverse effects have been documented with the use of CLA, some of which could have been predicted from what is known regarding trans-fatty acids. Human trials have shown liver hypertrophy and

insulin resistance<sup>16</sup> and increased lipoprotein A.<sup>18</sup> Further adverse effects surfaced with another randomized, controlled trial that compared 3.4 g of CLA (trans10-cis12 form) to placebo for 12 weeks in 60 men with metabolic syndrome.<sup>17</sup> The results showed a 110% increase in CRP and a 578% increase in PGE2-alpha, measures of inflammation and lipid peroxidation, respectively.

**Hoodia.** Ethnobotanical research continues to add plants to our modern medical treatment repertoire. One plant early in the continuum from traditional medicine to basic science research to clinical trials is hoodia, a plant from southern Africa that is one of either two species (*Hoodia gordonii* or *H. lugardii*) in the milkweed family, Asclepiadiaceae. The sap from this cactus-like plant has the reputation in traditional medicine to curb appetite, leading researchers to consider its use in humans.<sup>19</sup>

A steroidal glycoside P57AS3 has been isolated from *H. gordonii* and tested in rats; for rats fed a low-calorie diet, P57AS3 seems to have a central nervous system effect, by inhibiting the decreases in hypothalamic ATP that normally occur with starvation.<sup>19</sup> Though P57AS3 has a similar structure to cardiac glycosides, it appears to have a different mechanism, perhaps, as per the above study, acting centrally on hypothalamic control of nutrient sensing. Other research by pharmaceutical and supplement companies is alluded to on various web sites, but remains unpublished and inaccessible.

**Green tea.** Green tea (*Camellia sinensis*) is a common addition to weight-loss supplements. It is used for this purpose not only for its caffeine content (a cup of green tea may have 40-50 mg caffeine), but because of procyanidin flavonoid compounds, also called polyphenols, such as epigallocatechin gallate (EGCG). Caffeine is well known as a central nervous system stimulant and causes increases in systolic blood pressure, probably through adenosine inhibition. Also, as mentioned above, caffeine can enhance other sympathomimetics such as bitter orange, leading to some changes in cardiovascular parameters including increased diastolic blood pressure and increased heart rate.

Animal research shows that caffeine and the polyphenols may synergize to cause thermogenesis and weight loss through a combination of decreased food intake and decreased fat tissue accumulation; one biochemical mechanism that may be involved is polyphenolic inhibition of catechol-o-methyltransferase, an enzyme that degrades norepinephrine.<sup>20</sup> Further research demonstrates the importance of the polyphenol component to possible weight-loss effects, as an injection of pure EGCG (the equivalent of 6-12 cups of tea daily for

humans) in rats for one week led to reduced food intake, decreased body weight, and decreased cholesterol and triglyceride.<sup>21</sup>

A human clinical trial tested a green tea extract (50 mg caffeine, 90 mg EGCG), caffeine (50 mg), or placebo three times daily on the 24-hour energy expenditure in 10 healthy men.<sup>22</sup> The green tea extract caused a 4% increase in energy expenditure, a decrease in respiratory quotient (used in calculations of basal metabolic rate), and a 40% decrease in urinary norepinephrine relative to placebo, with a fat oxidation contribution to energy expenditure of 41.5% (vs. 31.6% for placebo); the caffeine treatment did not have any significant effects. There was no change in urinary nitrogen excretion, which when combined with the above results, led the researchers to conclude that the green tea extract did not affect protein oxidation, but did increase fat oxidation and lower carbohydrate oxidation; they did not believe this to be the result of caffeine's effects alone.

**Caffeine.** Many weight-loss supplements contain either purified caffeine and/or plants that naturally contain caffeine and related compounds. Caffeine has been shown in human clinical trials on both healthy and overweight individuals to have a variety of effects that may contribute to weight loss, such as increasing thermogenesis and energy expenditure, and increasing oxygen consumption and serum free fatty acids, which could indicate enhanced lipolysis.<sup>23</sup> There are numerous botanicals that are added to weight-loss supplements as a caffeine source. For example, guarana (*Paullinia cupana* and *P. sorbilis*) contains 3-5% caffeine by dry weight, compared to 1-2% for dry coffee beans.<sup>24</sup> Other herbs that provide "hidden" caffeine include yerba mate (*Ilex paraguariensis*) and kola nut (*Cola nitida*). The side effects of excess caffeine intake, or even minimal caffeine intake in people not used to it, include tremor, insomnia, anxiety, and gastrointestinal upset.

## Conclusion

Numerous supplements are being marketed for their weight-loss effects. For some of them, there are both basic science and clinical trial data that permit adequate risk-benefit analyses to be conducted. For others, such as hoodia, there is a paucity of published literature to guide clinical decision-making.

Ephedra is effective in weight loss (about 1 kg per month), but it is associated with unacceptable, though rare, side effects such as myocardial infarction and stroke. These side effects ultimately led the FDA to take ephedra products off the market.

Two supplements, chitosan and green tea, have some positive efficacy data. Meta-analyses show a 1.7 kg

weight loss with chitosan but the dose used and time periods studied were variable; it appears that 1 g twice daily is not an adequate dose. Green tea has one small human trial exploring physiological effects of an extract that appears promising; there needs to be more clinical research focused on weight loss in humans.

Accumulating data suggest that bitter orange and CLA may be unsafe. Bitter orange contains synephrine, an adrenergic agonist, which may have some of the same adverse effects as ephedra, and CLA appears to increase inflammation and have adverse effects on the liver, as well as on insulin resistance.

Caffeine, primarily through an increase in energy expenditure, may contribute to weight loss, though this needs to be balanced against the well-known side effects associated with excessive caffeine intake.

There are still many unknowns about these and other weight-loss supplements, such as the clinical efficacy of hoodia, the exact mechanism of action of CLA or green tea and its polyphenols, and the best dosing for almost all of these products.

### Recommendation

There is no substitute for a healthy diet and lifestyle that contains adequate amounts of activity to facilitate weight loss. For people looking for an extra edge, the medical literature provides some clues about weight-loss supplements but no firm answers at this point.

Avoid bitter orange and CLA, due to potentially serious side effects combined with unconvincing efficacy data. A green tea extract could be useful for weight loss, but more data are needed before a detailed recommendation can be made about whether the EGCG component or the caffeine, or both, is the most important part. A person not overly sensitive to caffeine could incorporate a green tea extract into their weight-loss program that notes percentage and amount of EGCG.

Chitosan seems to be reasonably safe and may have some effect. Until more data accumulate, chitosan can be used on a trial basis in doses of at least 2 g twice daily as adjunctive therapy for weight loss. ❖

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## Correction

**A**N ATTENTIVE READER RECENTLY BROUGHT AN ERROR to our attention. The handout of the April issue of *Alternative Medicine Alert* stated that dietary supplement manufacturers must provide their address and telephone number on the supplement label. In fact, according to the FDA, if manufacturers are listed in the local telephone directory, only the name, city, state, and postal zip code are required on the product label.

Comments about content are always welcome. They may be forwarded to Paula Cousins, Managing Editor, at (816) 237-1833 or paula.cousins@thomson.com.

## Clinical Briefs

*With Comments from Russell H. Greenfield, MD*

*Dr. Greenfield is Medical Director, Carolinas Integrative Health, Carolinas HealthCare System, Charlotte, NC, and Clinical Assistant Professor, School of Medicine, University of North Carolina, Chapel Hill, NC.*

### Juiced About Pomegranates

**Source:** Pantuck AJ, et al. Phase II study of pomegranate juice for men with rising prostate-specific antigen following surgery or radiation for prostate cancer. *Clin Cancer Res* 2006;12:4018-4026.

**Goal:** To determine the effects of drinking pomegranate juice on progression of prostate-specific antigen (PSA) in men who continued to have a rising PSA despite conventional therapy for prostate cancer (PC).

**Design:** Single-center, open-label, phase II, Simon two-stage clinical trial.

**Subjects:** Forty-eight men with rising PSA following surgery or radiotherapy for PC (data evaluable on 46). PSA had to be > 0.2 and < 5.0 ng/mL and documented as rising following surgery or radiotherapy, and Gleason score ≤ 7.

**Methods:** Subjects received 8 oz of commercially available (POM Wonderful®, LLC) pomegranate juice daily and were followed at three-month intervals. Clinical endpoints included effect on serum PSA variables (including doubling time) and serum lipid peroxidation and nitric oxide levels, among others. In vitro assays were also performed to determine the effect of sub-

jects' sera on androgen-dependent LNCaP prostate tumor cell growth and apoptosis.

**Results:** Estimated mean PSA doubling time (PSADT) at 33 months increased from a baseline mean of 15 months to 54 months posttreatment, with 83% of participants experiencing a prolongation in PSADT. A decrease in PSA was seen in 16 men (35%). In vitro assays revealed a 23% increase in nitric oxide, significant reductions in serum lipid sensitivity to oxidation and measurements of oxidative stress, a 17% increase in apoptosis, and a 12% decrease in LNCaP cell proliferation. No differences between pre- and post-treatment hormone levels were found.

**Conclusion:** In men with recurrent prostate cancer following conventional curative approaches to treatment, regular ingestion of pomegranate juice produces statistically and potentially clinically significant effects on PSADT, as well as in vitro lessening of cell proliferation, and pro-apoptotic effects. Further study is required.

**Study strengths:** Dosing based on antioxidant effect in human dose-response studies; in vivo and in vitro effects documented; close follow-up.

**Study weaknesses:** Small sample size; as yet unvalidated assays were

employed to assess antiproliferative and proapoptotic effects.

**Of note:** Subjects had no evidence of metastatic disease and had not received hormone therapy prior to entering the trial; the 8 ounces of pomegranate juice was equivalent to 570 mg/d total polyphenol gallic acid equivalents (flavonoids comprise 40% of total polyphenols in pomegranate juice); a significant improvement in PSADT may correlate with delay in disease progression, and may prove to be a surrogate marker for prostate cancer mortality (men with a greater PSADT could expect longer survival); radical prostatectomy is the most commonly used therapy for curative intent of PC, however, approximately one-third of men with clinically confined disease will develop biochemical recurrence; epidemiologic and basic science data suggest that dietary interventions and plant-derived phytochemicals may play a role in prevention or treatment of PC; African American men have the highest prostate cancer rate in the world while Chinese and Japanese men native to their countries who eat the typical low-fat, high-fiber diets of the region have the lowest rates; the pattern of slowing of PSA progression rather than achieving significant PSA declines is consistent with a cytostatic

rather than cytotoxic mechanism; pomegranate phytochemicals have previously been shown to inhibit the in vitro proliferation of LNCaP, PC3, and DU145 prostate cancer cell lines.

**We knew that:** Adenocarcinoma of the prostate comprises 29% of all cancers, is the most common malignancy in men, and remains the second most common cause of cancer death in men despite significant improvements in survival rates over the past 20 years; limited options exist for men with progressively rising PSA levels following primary therapy for curative effect and without evidence of metastatic spread; hormonal ablation therapy is associated with significant side effects and adverse effects on quality of life; a wide variety of phytochemicals called polyphenols can be found in fruits and specific food products, and some of these polyphenols appear to have anti-cancer activity; commercial pomegranate juice possesses potent antioxidant and antiatherosclerotic properties due in large part to its polyphenol content; studies have shown that mild levels of oxidative stress stimulate cancer cell proliferation and increase DNA damage; commercial pomegranate juice is often quite high in sugar and potassium content; soy isoflavones, red wine resveratrol, and green tea catechins may also stimulate apoptosis and lessen cell proliferation.

**Clinical import:** This preliminary trial of pomegranate juice for men with recurrent prostate cancer offers reason for excitement. Imagine being able to share with a man recently found to have a rising PSA level after having gone through surgery or radiation therapy that simply developing a taste for pomegranate juice might extend his life. Excitement in this case must be tempered by the study limitations of sample size and the nature of some of the tests employed, but the data are certainly compelling if not downright amazing. Results of the new trial recently initiated by the authors evaluating dose response using two dosing regimens and a placebo control will doubtless shed additional light on the potential use of pomegranate juice as a chemopreventive agent. In

the meantime, it appears there may be reason to recommend that men enjoy pomegranate juice regularly (with at least some attention paid to managing sugar and potassium intake).

**What to do with this article:** Make copies to hand out to your peers (and buy stock in pomegranates). ❖

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## CAM, PPO, POS, and HMO (!)

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**Source:** Lafferty WE, et al. Insurance coverage and subsequent utilization of complementary and alternative medicine providers. *Am J Manag Care* 2006;12:397-404.

**Goal:** To evaluate how insured people use complementary and alternative medicine (CAM) providers and to what extent such use impacts health care utilization and expenditures.

**Design:** Cross-sectional analysis of western Washington health insurance enrollees for 2002.

**Subjects:** Data were available for review on more than 600,000 enrollees aged 18-64 years who were continuously engaged with a single private health insurance plan for 12 months.

**Methods:** Review of insurance data from three large health insurance companies (covering 75% of western Washington state's private insurance market) that included demographics, diagnoses, CAM and conventional provider utilization, provider type, line item charges, pharmacy files, claims files, benefit information, and health care expenditures. These data were compared to those obtained from the 2002 National Health Interview Survey supplemental survey on CAM use to provide a U.S. comparison.

**Results:** Just more than 80% of enrollees made claims, while nearly 14% of enrollees made CAM claims (11% for chiropractic, 2% for massage therapy, 2% for naturopathy, and 1% for acupuncture). Available expenditure data revealed that CAM services accounted for almost 18% of outpatient provider visits but only 2.9% of total medical expenditures. In contrast, prescription drug (23%) and inpatient hospital expenditures (22%) were high.

Musculoskeletal complaints were the most common diagnoses for both CAM and conventional medical visits. With the exception of visits to naturopathic physicians and massage therapists (both much lower), U.S. CAM use in 2002 was comparable to that seen in western Washington. In both the United States and the Washington state subset, enrollees in preferred provider organizations (PPO) and point-of-service (POS) programs (that typically offer greater consumer choice) utilized CAM more than those enrolled in health maintenance organizations (HMOs).

**Conclusions:** Specifically regarding enrollees in three large western Washington health insurance companies during 2002, the number of people using CAM insurance benefits was substantial, yet impact on insurance expenditures was modest. Insurance coverage of licensed CAM providers does not lead to runaway utilization and costs.

**Study strengths:** Large sample size; modeled predictors of CAM use employing logistic regression analysis; made use of adjusted clinical groupings to counter selection bias.

**Study weaknesses:** No assessment of therapeutic efficacy of CAM therapies; one of the three companies did not provide expenditure data and only provided information on their HMO product line, not including the one-third of clients using POS products; those covered by self-insured employer plans and Medicaid and Medicare recipients were not included in the analysis.

**Of note:** In 1996, Washington state implemented a law mandating that all commercial health insurance companies cover the services provided by every category of licensed provider (a mandatory chiropractic benefit has been in place since 1983); insurance company selection was based on willingness to participate, data retrieval capacity, and market penetration; CAM providers were defined as chiropractors, naturopathic physicians, acupuncturists, and massage therapists; osteopaths were included under the heading of conventional providers; in this study HMO coverage was most common, followed by PPO coverage; predictors of CAM

use included female sex and age 31-50 years; in Washington, CAM use was lowest in urban areas due to lower utilization of chiropractic services than in rural areas, where chiropractic has historically played a significant role; two of the three companies treated massage therapy as a rehabilitation benefit with associated visit limits; the number of CAM providers is expected to double over the next 10 years in response to consumer demand.

**We knew that:** All 50 states license chiropractors; a 2004 survey found that 87% of covered employees had chiropractic coverage, whereas 47% had acupuncture coverage; 67% of HMOs offer some type of alternative care; in 2000, Washington state also mandated the ability to self-refer to chiropractic care for up to 10 visits, but all other referrals to CAM providers need to come from a physician; the requirement for referral from a physician for mas-

sage therapy likely impacts utilization rates in Washington; approximately one-third of all licensed naturopaths in the United States practice in Washington state; patients likely self-select available insurance products based not only on affordability, but also on expected need for specific medical services; requiring a gatekeeper's recommendation limits insurance-financed CAM utilization.

**Clinical import:** In the face of increasing consumer demand for CAM therapies, relatively little data exist with which to assess the impact of insurance coverage of CAM therapies on health care costs. Carriers have largely avoided blanket coverage of specific CAM therapies both out of fear of over-utilization and associated cost escalation, and due to the perception that insufficient data exist to execute cost-benefit analyses with respect to therapeutic efficacy. The present study results serve to quell fears

over the issue of utilization to some degree, but not that of efficacy, leaving us with important but incomplete information. Though data on a significant number of people and associated expenditures were not fully captured, six years after CAM benefits were mandated in Washington state expenditures appear to be controlled. In addition, enrollees with high utilization rates were often identifiable in advance (responsible for 34% of CAM, 41% of outpatient conventional, and 50% of total expenditures). Such information should be of interest to insurers. Lack of assessment of clinical benefit of CAM therapies to enrollees severely limits the scope of conclusions that can be made, but from an economic standpoint this study offers a rare glimpse into the potential impact of insurance coverage for select CAM therapies.

**What to do with this article:** Keep a hard copy in your file cabinet. ❖

## 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:

- present evidence-based clinical analyses of commonly used alternative therapies;
- make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
- 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.

**27. Between the ages of 30 and 90, approximately 15% of the cerebral cortex and 25% of the cerebral white matter of the average human brain has diminished disproportionately in which of the following areas?**

- The prefrontal region
- The frontal region
- The temporal region
- All of the above

**28. Which of the following risk factors for Alzheimer's disease are amenable to lifestyle modification?**

- Atherosclerosis
- Cardiovascular disease
- Hypertension
- All of the above

**29. The Centers for Disease Control and Prevention and the American College of Sports Medicine currently recommend 30 minutes or more of moderate-intensity physical activity on most or preferably all days of the week for all adults.**

- True
- False

**30. Which of the following dietary supplements commonly used for weight loss may be unsafe based on adverse effects that are similar to those reported with ephedra?**

- Hoodia
- Chitosan
- Bitter orange
- Conjugated linoleic acid
- All of the above

Answers: 27. d, 28. d, 29. a, 30. c.

# ALTERNATIVE MEDICINE ALERT™

*A Clinician's Evidence-Based Guide to Alternative Therapies*

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## Alzheimer's Disease: A Caregiver's Guide, Part 2

CARING FOR A PERSON WITH ALZHEIMER'S DISEASE (AD) AT HOME IS A DIFFICULT TASK AND can become overwhelming at times. Each day brings new challenges as the caregiver copes with changing levels of ability and new patterns of behavior. Dressing, bathing, eating—basic activities of daily living—often become difficult to manage for both the person with AD and the caregiver.

### Bathing

Bathing can be a frightening, confusing experience. Advance planning can help make bath time better for both of you.

- Plan the bath or shower for the time of day when the person is most calm and agreeable. Be consistent. Try to develop a routine.
- Respect the fact that bathing is scary and uncomfortable for some people with AD. Be gentle and respectful. Be patient and calm.
- Tell the person what you are going to do, step by step, and allow him or her to do as much as possible.
- Prepare in advance. Make sure you have everything you need ready and in the bathroom before beginning. Draw the bath ahead of time.
- Be sensitive to the temperature. Warm up the room beforehand if necessary and keep extra towels and a robe nearby. Test the water temperature before beginning the bath or shower.
- Minimize safety risks by using a handheld showerhead, shower bench, grab bars, and non-skid bath mats. Never leave the person alone in the bath or shower.
- Try a sponge bath. Bathing may not be necessary every day. A sponge bath can be effective between showers or baths.

### Dressing

For someone who has AD, getting dressed presents a series of challenges: choosing what to wear, getting some clothes off and other clothes on, and struggling with buttons and zippers. Minimizing the challenges may make a difference.

- Try to have the person get dressed at the same time each day so he or she will come to expect it as part of the daily routine.
- Encourage the person to dress himself or herself to whatever degree possible. Plan to allow extra time so there is no pressure or rush.
- Allow the person to choose from a limited selection of outfits. If he or she has a favorite outfit, consider buying several identical sets.
- Arrange clothes in the order they are to be put on to help the person move through the process.
- Provide clear, step-by-step instructions if the person needs prompting.
- Choose comfortable clothing that is easy to get on and off, and easy to care for. Elastic waists and Velcro enclosures minimize struggles with buttons and zippers.

## Eating

Eating can be a challenge. Some people with AD want to eat all the time, while others have to be encouraged to maintain a good diet.

- Ensure a quiet, calm atmosphere for eating. Limiting noise and other distractions may help the person focus on the meal.
- Provide a limited number of food choices and serve small portions. You may want to offer several small meals throughout the day in place of three larger ones.
- Use straws or cups with lids to make drinking easier.
- Substitute finger foods if the person struggles with utensils. Using a bowl instead of a plate also may help.
- Have healthy snacks on hand. To encourage eating, keep the snacks where they can be seen.
- Visit the dentist regularly to maintain oral health.

## Exercise

Incorporating exercise into the daily routine has benefits for both the person with AD and the caregiver.

- Think about what kind of physical activities you both enjoy, perhaps walking, swimming, tennis, dancing, or gardening. Determine the time of day and place where this type of activity would work best.
- Be realistic in your expectations and build slowly.
- Be aware of any discomfort or signs of overexertion. Talk to the person's doctor if this happens.
- Allow as much independence as possible, even if it means a less-than-perfect garden or a scoreless tennis match.
- See what kinds of exercise programs are available in your area. Senior centers may have group programs for people who enjoy exercising with others.

## Activities

Finding activities that the person with AD can do and is interested in can be a challenge. Building on current skills generally works better than trying to teach something new.

- Don't expect too much. Simple activities often are best, especially when they use current abilities.
- Help the person get started on an activity. Break the activity down into small steps and praise the person for each step he or she completes.
- Watch for signs of agitation or frustration with an activity. Gently help or distract the person to something else.
- Incorporate activities the person seems to enjoy into your daily routine.

- Take advantage of adult day services, which provide various activities for the person with AD, as well as an opportunity for caregivers to gain temporary relief from tasks associated with caregiving.

## Sleep Problems

For many people with AD, nighttime may be a difficult time. Many people with AD become restless, agitated, and irritable around dinnertime, often referred to as "sundowning" syndrome. Getting the person to go to bed and stay there may require some advance planning.

- Encourage exercise during the day and limit daytime napping, but make sure that the person gets adequate rest during the day because fatigue can increase the likelihood of late afternoon restlessness.
- Try to schedule more physically demanding activities earlier in the day.
- Set a quiet, peaceful tone in the evening to encourage sleep. Keep the lights dim, eliminate loud noises, even play soothing music if the person seems to enjoy it.
- Try to keep bedtime at a similar time each evening. Developing a bedtime routine may help.
- Restrict access to caffeine late in the day.
- Use night lights in the bedroom, hall, and bathroom if the darkness is frightening or disorienting.

## Home Safety

Caregivers of people with AD often have to look at their homes through new eyes to identify and correct safety risks. Creating a safe environment can prevent many stressful and dangerous situations.

- Install secure locks on all outside windows and doors, especially if the person is prone to wandering. Remove the locks on bathroom doors to prevent the person from accidentally locking himself or herself in.
- Use childproof latches on kitchen cabinets and any place where cleaning supplies or other chemicals are kept.
- Label medications and keep them locked up. Also make sure knives, lighters and matches, and guns are secured and out of reach.
- Keep the house free from clutter. Remove scatter rugs and anything else that might contribute to a fall. Make sure lighting is good both inside and out.
- Consider installing an automatic shut-off switch on the stove to prevent burns or fire.

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

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