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Ginkgo Biloba for Memory Enhancement: An Update

By Georges Ramalanjaona MD, DSc, MBA, FACEP

GINKGO BILOBA (GB) IS ONE OF THE MOST STUDIED AND COMMONLY used herbal remedies, with U.S. sales reaching $240 million annually.

Since our last publication on this topic in 1998, recent reports in peer-reviewed journals have shown conflicting results on GB's ability to enhance memory.[1-3]

We present an update on the findings of these recent trials and recommend the cautious use of GB in selected patients based on these studies.

Pharmacokinetics

Because *Ginkgo biloba* extracts (GBE) are composed of many active ingredients, it is difficult to define the pharmacokinetics of each component. Many studies have utilized the extract called EGb 761, containing 24% flavone glycosides and 6% terpenoids.

More than 60% of the extract is absorbed in the stomach and small intestines; the rest is absorbed in neuronal and glandular tissues and the eyes. Elimination occurs mainly in the feces (29%) and urine (22%) and the remaining through exhaled air.[4]

Mechanism of Action

The acute chemical compounds found in ginkgo leaf are too diluted to have any pharmacological effect. Thus, standardized extracts concentrate them by processing 50 pounds of leaves into one pound of extract (50:1 ratio).

GB's pharmacological effects are due to two main groups of active constituents that are present in various concentrates in the leaf of GB.[5] These two groups include flavonoids and terpenes: Forty different flavonoid and three main terpene groups have been isolated, including ginkgolides A, B, and C.

GBE has known bioactive properties. Flavone glycosides display antioxidant properties, inhibit platelet aggregation, and act as scavengers for free radicals that are mediators of the lipid peroxidation

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and cell destruction found in Alzheimer's disease.[6] Terpene lactones inhibit the binding of platelet-activating factor (PAF) to its membrane receptor in animal studies. Biological activities of PAF include induction of platelet aggregation and oxygen free radical production leading to increased microvascular permeability.

Clinical Studies

Few well controlled studies exist of the effect of GB on memory. The most recent and significant trials that provide level of evidence I on a scale of I to III are summarized in Table 1.

Rigney et al investigated the effects of GBE in a randomized, double-blind, placebo-controlled, five-way crossover design.[7] The study's goal was to determine the optimum dose required for significant effects on memory and psychomotor performance. The investigators administered tests every hour for 12 hours. Thirty-one healthy volunteers ages 30-59 years received either GBE 150 mg (50 mg PO tid), GBE 300 mg (100 mg PO tid), GBE 120 mg PO once daily, GBE 240 mg PO once daily, or placebo for two days.

A battery of nine memory tests was used including: Stroop task (test of selective attention), digit symbol substitution task (measures both a simple information process and psychomotor performance), wrist actigraphy (assesses both psychometric and subjective state of sedation and arousal), the line analogue rating scale (measures state of mental alertness on a 10 cm line scale), the Leeds sleep evaluation questionnaire (assesses effects of psychoactive compounds on sleep), the short-term memory test (STM, uses a reaction time method), the immediate and delayed recall of supraspan word lists (measures central executive component and explicit memory), the choice reaction time task (indicator of sensorimotor performance based on ability to respond to a critical stimulus), and critical flicker fusion test (CFFT, assesses the integrity of the CNS).

Results showed that the most effective acute dose for cognitive enhancement (as assessed by CFFT) was 120 mg in the morning compared to the other doses and placebo, and that enhancing effects on working memory (as assessed by STM) were more pronounced than they were on selective attention or arousal. The best results were observed in subjects ages 50-59 years.

Van Dongen et al conducted a 24-week, placebo-controlled, double-blind multicenter study to evaluate the efficacy, dose dependence, and durability of the effect of GBE in older people with dementia or age-associated memory impairment (AAMI).[8] Two hundred fourteen participants (34 men, 180 women, mean age 82.6 years) diagnosed with AAMI or mild-to-moderate dementia randomly received either 240 mg/d of GBE (high-dose group), 160 mg/d of GBE (usual dose group), or placebo for 24 weeks. Outcome measures were assessed after 12 and 24 weeks and included neuropsychological testing (trial making speech), digit memory span, verbal learning, severity and presence of geriatric symptoms, depressive mood, self-perceived health and memory status, and self-reported behavioral assessment.

An intent-to-treat analysis showed no significant effects on each of the outcome measures for all treatment groups compared with placebo for the entire 24-week period. No beneficial effects of a higher dose or a prolonged duration of GBE were found. The authors concluded that GBE is not as effective as placebo treatment for older people with mild-to-moderate dementia or AAMI.

The longest (52 weeks) randomized, placebo-controlled, double-blind trial was conducted by Le Bars et al.[9] This study evaluated the efficacy of GBE on 309 patients diagnosed with uncomplicated Alzheimer's disease or dementia according to ICD-10 and DSM-IIIR criteria. Patients were randomized to receive either 120 mg (40 mg PO tid) daily of GBE or placebo for 52 weeks. The primary outcome tests included the Alzheimer's Disease Assessment Scale-Cognitive

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Table

Recent clinical trials of ginkgo for memory

Study	Patients	Design	Treatment	Results
Rigney et al[7] (1999)	31 healthy volunteers (ages 30-59 years)	Randomized, double-blind placebo-controlled cross-over study	Four treatment groups vs. placebo for two days	Pronounced improvement in working memory in treatment groups vs. placebo
Kennedy et al[12] (2000)	20 healthy adults (ages 19-24 years)	Randomized double-blind placebo-controlled cross-over study	Three treatment groups vs. placebo for one day	Statistically significant improvement in cognitive drug research assessment of treatment groups vs. placebo
Mix and Crews[2] (2000)	48 healthy older adults (ages 55-86 years)	Randomized double-blind placebo-controlled parallel-group study	Treatment group vs. placebo for six weeks	Statistically significant improvement in neuro-cognitive functions of treatment group vs. placebo
Van Dongen et al[8] (2000)	214 elderly adults with dementia-associated memory impairment	Randomized double-blind placebo-controlled parallel-group study	Two treatment groups vs. placebo for 24 weeks	No significant difference in neuropsychological functions of treatment groups vs. placebo
Moulton et al[5] (2001)	30 healthy young males (mean age 20.5 years)	Randomized double-blind placebo-controlled study	Treatment group vs. placebo for five days	No significant difference in memory tests between treatment group vs. placebo
Stough et al[3] (2001)	61 healthy adults (ages 18-41 years)	Randomized double-blind placebo-controlled study	Treatment group vs. placebo for 30 days	Statistically significant improvement in validated neuropsychological tests of treatment group vs. placebo
Le Bars et al[9] (2002)	244 patients with dementia	Randomized double-blind placebo-controlled parallel-group study	Treatment group vs. placebo for 52 weeks	Statistically significant improvement in cognitive performance of treatment group vs. placebo
Solomon et al[1] (2002)	230 healthy older volunteers (mean age 68.7 years)	Randomized double-blind placebo-controlled parallel-group study	Treatment group vs. placebo for 30 days	No statistically significant difference in 14 standard neuropsychological tests between treatment group vs. placebo

subscale (ADAS-Cog), Geriatric Evaluation by Relative's Rating Instrument (GERRI), and Cognitive Global Impression of Change (CGIC). Compared to the placebo group, the treatment group scored 1.4 points significantly higher on the ADAS-Cog (P = 0.04) and 0.12 point higher on the GERRI (P = 0.007). There was, however, no clinically significant change in the CGIC in either group. Cognitive performances and social behavior did slightly improve in the treatment group for six months to a year. Whether this suggests a delay in progression of the disease within that period, as the author believes, is uncertain.

The most significant of all the negative studies was published by Solomon et al in the *Journal of the American Medical Association*.[1] This six-week, double-blind, placebo-controlled study randomized 230 healthy older adults (age range 60-82 years) to receive either GBE 40 mg PO tid (as specified by manipulation) (n = 115) or matching placebo (n = 115). Participants were required to have baseline Mini-Mental State Examination scores greater than 26 of 30, to be independent in daily living activities, and to be free of neuropsychiatric disorders.

Outcome measures included the digit symbol subscale of the Wechsler adult intelligence scale revised (WAIS-R, test attention and memory); the Stroop test; mental control and digit span; subscales of Wechsler memory scale revised (WMS-R); measurement of verbal and non-verbal learning and memory composed of logical memory (I and II); visual reproduction (I and II); subscales of WMS-R and the California verbal learning test; expressive language test including controlled category fluency test; and the Boston naming test.

Results showed that at six weeks, mean scores on 14 standardized neuropsychological tests of verbal and visual learning and memory, attention and concentration, and expressive language did not significantly differ between GB and placebo groups. Also, mean scores on self-reported memory function or global rating by

spouses, relatives, or friends did not differ between the two groups. The author concluded that when taking GB according to the manufacturer's instructions, GB provided no measurable benefit in memory (or function) to elderly adults with healthy cognitive function.

Lastly, to validate the efficacy of GB in healthy older adults, Mix et al used a six-week randomized, placebo-controlled, double-blind study.[2] Forty-eight cognitively intact adults ages 55-86 years were assigned to either a fixed dose of GBE (180 mg/d) or placebo control group. A series of neuropsychological tests were administered to evaluate subjects' cognitive and behavioral function prior to therapy (baseline) and after six weeks.

Results showed that the treatment group displayed a significant improvement ($P < 0.03$) on tasks assessing simple speed of processing abilities (Stroop color and word test color naming task) compared to the placebo group. Also, participants rated their overall memories as assessed by follow-up and self-report questionnaire by the end of treatment as significantly improved ($P < 0.03$) compared to placebo group. Furthermore, trends favoring improved performance in the GB group were seen in the timed cognitive processing speed, visual-motor scanning (trial making test, part A), complex cognitive processing speed (trial making test, part B), and cognitive flexibility. In contrast, no significant differences were found on any of the four objective memory tests.

Notwithstanding the high methodological quality of these clinical trials (evidence-based value grade I) with the ensuing validity of the results, their current limitations, including small sample size, short duration of trials, and lack of uniform memory tests, preclude meaningful comparison.

Ongoing Studies

The National Institute of Health (NIH) recently sponsored a five-year $15 million randomized double-blind placebo-controlled multicenter study to examine whether GB can prevent Alzheimer's disease. Participants include 3,000 men and women age 75 years and older with normal mental function. People with Parkinson's disease, Alzheimer's disease, or other disorders leading to dementia or on medications that interfere with performance on memory tests are excluded. Primary outcomes include rate and incidence of development of AD and cognitive and memory function changes.

A randomized, double-blind, placebo-controlled trial sponsored by the National Center for Complementary and Alternative Medicine (NCCAM) also is under way and will assess the effect of GBE on preventing or delaying cognitive decline in people age 85 years and older. Participants include 200 elderly cognitively healthy subjects, who will be followed for conversion to mild cognitive impairment. The magnitude of GB effect will be assessed with volumetric quantitative MRI (measured by a decrease in brain volume loss with treatment) and peripheral markers of oxidation status.

Adverse Effects

There were no significant side effects reported during recent clinical trials with standardized GBE.[1,2,9] The most common adverse reactions are mild gastrointestinal complaints (nausea), and allergic skin reactions from contact or ingestion of the fruit pulp of ginkgo.

Doses greater than 600 mg daily may cause diarrhea, nausea, and vomiting.

Contraindications and Precautions

GBE should not be combined with nonsteroidal anti-inflammatory drugs, heparin, or coumadin due to increased risk of spontaneous bleeding.[10] A recent literature review recommended GBE discontinuation at least 36 hours prior to surgery.[11]

GBE theoretically may potentiate the effects of monoamine oxidase inhibitors. Although the actual risk is unknown, patients should be informed about these drug interactions.

The safety of GBE in women who are pregnant or lactating and in children is unknown.

Also, GB products are contraindicated in subjects with hypersensitivity to the plant or its extracts (i.e., alkylphenols found in the seeds).

Formulation and Dosage

In Europe, GBE is sold as a prescription drug; in the United States and Canada, it is marketed and sold as a dietary supplement. GBE commonly is sold as capsules or tablets containing 40 mg, 60 mg, or 120 mg of concentrated leaf extract.

Four preparations are used in the reported clinical trials: Tebonin®, Tanakan®, Rokan®, and Kaveri®. The first three are composed of the extract EGb 761, containing 24% of flavone glycosides and 6% of terpenoids. Kaveri, known as EGb 1370, has a slightly different formula at 25% flavone glycosides and 6% terpenoids. During storage, GB should be protected from light and moisture to increase shelf life.

The majority of clinical trials used the standardized GB extract EGB 761 in a dosage of 40 mg PO tid or 80 mg PO bid for six weeks to three months.

Conclusion

Based on these short-term data, GBE appears to be relatively safe. However, trial results on its effectiveness

are mixed and inconsistent, ranging from probably effective to ineffective. These studies differ in duration of intervention, dosage used, subject age, and status of cognitive function of the population tested.

GBE appears to be probably effective in enhancing memory acutely and in a dose-dependent manner (120 mg daily) in healthy, middle-aged adults without memory impairment (ages 50-59 years). Chronic administration of GBE at a dose of 120 mg daily in healthy adults (ages 18-41 years) and in elderly subjects (ages 45-90 years) with dementia may be effective in improving neurocognitive functions for up to 52 weeks.

In contrast, a daily dose of 120 mg GBE is likely to be ineffective in healthy elderly adults age 65 years and older, and in subjects with dementia, at a dose of more than 160 mg daily, for enhancing neurocognitive function for up to 24 weeks.

Recommendation

Although the low cost, easy accessibility, and apparent overall safety of GBE make its use attractive in enhancing memory, broad recommendation should await the results of large, long-term, controlled clinical trials that are currently well-funded and under way. GBE's role in preventing or delaying neurocognitive impairment associated with age or Alzheimer's disease should be identified upon completion of ongoing NIH and NCCAM trials in five years.

In the meantime, upon a patient's request, physicians can recommend a trial of GBE at a dose of 120 mg daily for up to four weeks in young healthy adults ages 18-41 years to improve memory, or in patients ages 45-90 years with dementia for up to 52 weeks to improve neurocognitive functions. Caution should be exercised in the latter group due to polypharmacy. ❖

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Chitosan for Weight Loss and Cholesterol Lowering

By Robert J. Nardino, MD, FACP

"NEVER HAVE TO DIET AGAIN!" THESE FIVE WORDS have captivated many people who have waged the battle of the bulging waistline. Even though the Dietary Supplement Health and Education Act prohibits specific health claims for substances classified as supplements, word about many products' purported effectiveness gets around, especially when the issue is weight loss. Such claims have been attributed to chitosan, a product from the unlikely source of crustacean shells.

Mechanism of Action

Chitosan is derived from chitin, a polysaccharide found in the exoskeleton, or protective shell, of shellfish. Deacetylation of chitin results in a cationic biopolymer

that is thought to bind negatively charged molecules like fatty acids and bile acids and has the property of being indigestible. Therefore, the presumptive mechanism of chitosan in combating obesity is to decrease the absorption of fat from the gastrointestinal tract, though there is conflicting evidence about the mechanism in humans.

In animal studies chitosan's mechanism appeared to be inhibition of intestinal absorption.[1,2] But in a study comparing the effects of chitosan and orlistat in 12 human volunteers, fecal fat excretion was significantly elevated in those taking orlistat but not in subjects receiving chitosan.[3] This study employed a chitosan dose of 890 mg three times daily, and a standardized dietary fat content. A recent study in seven human volunteers fed a high-fat diet (> 120 g/d) also showed no increase in fecal fat excretion when the subjects were treated with 5.25 g/d of chitosan.[4]

Clinical Studies

There are few randomized controlled trials investigating the effectiveness of chitosan for weight reduction or cholesterol lowering.

Weight Reduction

A meta-analysis of five small Italian trials was performed in 1998; the mean difference in weight reduction between chitosan and placebo was 3.28 kg (7.2 lb), but methodological problems were identified.[5]

Pittler and colleagues at the University of Exeter recruited 34 volunteers (28 men, six women) to receive 1 g of chitosan (four capsules of 250 mg each) or placebo twice daily over a 28-day period.[6] For inclusion, subjects needed to be between ages 18 and 60, and meet the criteria for body mass index (BMI), which were 23.9-28.5 for women and 25.0-29.9 for men. People with diabetes mellitus, intestinal disorders, concomitant medication use, or pregnancy were excluded. There was no dietary intervention; subjects were required to record their food intake in a diary.

Four patients withdrew from the study (two from each group) leaving 15 patients in each treatment arm. In both the chitosan and placebo groups, BMI was unchanged during the four-week period. Adherence to the study drug was high, with more than 90% in both groups. There were no changes in any serum measurement except for vitamin K levels, which increased significantly in the chitosan group. No serious adverse effects were reported.

In a Finnish study looking at the cholesterol-lowering effects of chitosan in 51 obese women, no weight loss advantage in the chitosan-treated women was observed.[7] More recently, investigators in Poland recruited 50 women with BMI > 30 and randomized them to receive 1,500 mg of chitosan three times daily before meals. Each subject also was enrolled in a six-month program that included a 1,000 kcal diet and a group meeting every two weeks, plus recommendations about exercise and behavioral modification from a physician, psychologist, and dietitian. At the end of six months, weight loss was achieved in both the chitosan and placebo groups, but was significantly greater in the chitosan-treated patients (mean loss of 16 kg and 11 kg, respectively).[8]

Cholesterol Lowering

The data in humans are scant and conflicting. The aforementioned Finnish study showed a small reduction in LDL cholesterol compared with placebo.[7] In this trial, 51 women with BMI 28-35 received 1,200 mg of microcrystalline chitosan twice daily. Mean LDL decreased by 0.5 mmol (19 mg/dL), but was not statistically significant. A subset of women with BMI > 30 had a slightly more pronounced effect.

In a study of obese hypercholesterolemic subjects in Singapore, 1 g of chitosan (brand name Absorbitol) three times daily over four months showed no reduction of LDL; there was a small increase in HDL in the group receiving Absorbitol.[9] In the Polish weight-loss study cited above, there was no difference in either total or LDL cholesterol between the chitosan and placebo groups.[8]

Animal studies suggesting the combination of chitosan with glucomannan might be more potent than chitosan alone led to a pilot study in 21 overweight subjects.[10] They received 2.4 g/d of a supplement with equal content of chitosan and glucomannan. Total LDL and HDL cholesterol were lower at four weeks compared to baseline measurements. LDL cholesterol fell from a mean of 2.61 mmol/L at baseline to 2.36 mmol/L at 28 days (a decrease from 101 mg/dL to 91 mg/dL). As noted in other human studies of chitosan, fecal fat excretion did not increase.

Other Effects

A Japanese group showed that low molecular weight chitosan lowered serum glucose levels in a dose-dependent manner in diabetic mice.[11] There also is interest in chitosan and its derivatives for use in novel drug delivery systems, wound healing, and anticoagulation.[12]

Adverse Effects

In a review of multiple studies, it was found that mild, transient nausea and constipation were reported in 2.6-5.4% of subjects.[13] Swollen heels and wrists were observed in one study, but overall were not considered

Table

Chitosan product pricing

Product	Manufacturer	Dosage	Price
Absorbitol Fat Binder	Natrol	900 mg	$12.95 (60 count)
Chitosan	Natrol	500 mg	$21.95 (180 count)
Chitosol	Twinlab	1,000 mg (with 200 mg vitamin C)	$19.95 (60 count)
Chitosan Plus	Nature's Best	500 mg	$9.95 (100 count)

serious.[7] Manufacturers recommend that fat-soluble vitamins (D, E, A, and K) should be consumed four hours before or after chitosan, on the assumption that fat excretion induced by chitosan could lead to malabsorption of these vitamins. However, the one study that measured serum levels of fat-soluble vitamins did not demonstrate any reduction of levels.[6]

Regulation

Two manufacturers of chitosan products have been sanctioned for false claims of efficacy. The TRY-Lean Corp was warned by the Food and Drug Administration in 1999,[14] and the makers of "Fat Trapper," Enforma Natural Products Inc was penalized by the Federal Trade Commision and required to pay fines and refunds in 2000.[15] Despite this, products still have provocative names like "Fat Absorber," although the marketing emphasis is now on cholesterol lowering rather than weight loss.

Formulation

Chitosan is marketed as a dietary supplement in the United States. It is marketed by numerous companies, usually in dosages of 500-1,000 mg per tablet. It is sometimes combined with vitamin C, as one of the animal studies showed a synergistic effect of vitamin C and chitosan with respect to inhibiting fat digestion.[2] Table 1 shows a sampling of popular chitosan products.

Conclusion

Whether chitosan can reduce weight by itself is uncertain. The weight of the evidence seems to indicate it cannot, although the recent Polish study indicates that as part of a rigorous program of diet, exercise, and behavioral modification, chitosan may have adjunctive benefit. The data for cholesterol lowering also are mixed, although chitosan in combination with glucomannan shows some promise for this use.

Recommendation

Chitosan alone cannot be recommended as a weight loss agent. More study is needed to determine its role in the management of lipid disorders. As it appears safe, a trial for cholesterol lowering can be considered, perhaps for low-risk patients who are near their LDL goal. Because of its source, chitosan cannot be recommended for people who have an allergy to shellfish. ❖

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Anabolic-Androgenic Steroids for Athletes: Adverse Effects

By Dónal P. O'Mathúna, PhD

How many athletes use or have used testosterone and other anabolic-androgenic steroids (AAS) is difficult to determine, but estimates range from between 1 and 3 million Americans.[1] Up to 11% of high school males have used AAS, one-third of whom were not active in school sports.[2] Use of AAS among professional bodybuilders and baseball players is widespread, and use by recreational weightlifters is growing. In Britain, 9% of weightlifters use AAS, but some gyms have no users, while in other gyms, almost half the athletes use.[3]

Strict regulations have made AAS (like those in the Table) available only by prescription—or on the black market. In response, many products claim to be natural "testosterone boosters" available as dietary supplements. The most popular, androstenedione and DHEA (dehydroepiandrosterone), have been reviewed previously in *Alternative Medicine Alert*. Studies have found that these are neither effective performance enhancing agents nor do they increase serum testosterone levels. Therefore, they would not be expected to have the same adverse effects as AAS discussed here, although they do raise estrogen levels and lower HDL levels.

As testosterone replacement therapy becomes more popular, questions surrounding the adverse effects reported by athletes will become more common. All health care professionals should have some knowledge of AAS effects.

Mechanism of Action

AAS include natural and synthetic steroids that are similar to testosterone *(see Figure)*, with anabolic and androgenic effects. Anabolic effects are manifested primarily by the growth of non-reproductive tissues. Athletes seek anabolic effects like increased muscle mass and decreased fat mass. Androgenic effects are those that promote development of male sexual characteristics and reproduction. More than 1,000 steroids have been manufactured in attempts to increase anabolic effects while minimizing androgenic effects. Common oral and injection AAS are listed in the Table.

Common Usage

For many years, the medical community combated AAS use by denying its effectiveness for promoting lean body mass.[2] Early studies were flawed and did not reflect the way AAS are used. Athletes actually "cycle" on and off compounds, switching from one to another to avoid developing tolerance. They "stack" AAS, taking several different steroids at the same time to lower the dose of each and activate different steroid receptors. The scientific basis for stacking is highly questionable and has not been proven.[2]

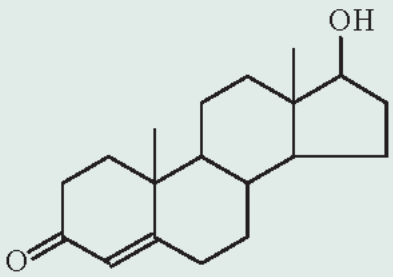
Table

Common oral and injection anabolic-androgenic steroids[1,2]

Chemical Name	Trade Name
Oral	
Danazol	Cyclomen, Danol, Danocrine
Ethylestrenol	Maxibolin, Orabolin
Fluoxymesterone	Halotestin, Stennox, Android-F
Methandienone	Danabol, Lanabolin, Dianabol
Methyltestosterone	Metandren, Oreton Methyl, Testred
Oxandrolone	Anavar, Lonavar, Oxandrin
Oxymesterone	Anamidol, Oranabol
Oxymethelone	Androl-50, Anapolon, Androyd
Stanozolol	Winstrol, Stromba
Injection	
Methenelone enanthate	Primobolan, Primobolan Depot, Primobolan-S
Nandrolone decanoate	Durabolin, Deca-Durabolin, Norandren
Nandrolone laurate	Laurabolin
Nandrolone phenylpropionate	Durabolin
Stanozolol	Winstrol-V, Strombaject
Testosterone cypionate	Depo-Testosterone, Testa-C, Andronate, Duratest
Testosterone enanthate	Delatestryl, Primoteston, Testone-LA, Testrin-PA
Testosterone nicotinate	Bolfortan
Testosterone propionate	Oreton, Testex, Virormone
Testosterone undecanoate	Andriol, Restandol

Figure

Testosterone



Clinical Trials

AAS are generally accepted as having the desired anabolic effects, provided athletes also consume adequate protein and exercise intensely. In a randomized controlled trial, those taking 600 mg testosterone intramuscular (IM) injections weekly for 10 weeks had significantly increased muscle mass, muscle strength, and fat-free mass compared to placebo ($P < 0.05$).[4] However, not all studies have found such strength gains.[5]

Athletes use many different steroids in different doses and varying regimens. Many take AAS at doses of 40-100 times the therapeutic recommendations.[2] So, even if AAS work, what harm might accompany the benefits?

Adverse Effects

Most professional and collegiate sports organization ban AAS. Even Major League Baseball agreed to start testing in 2003 because of claims that steroid use is running rampant among players.[6] The concerns are over the example given to younger players and the side effects. For example, Major League Baseball physicians report that serious muscle and tendon injuries occur 4-5 times more frequently since the use of steroids increased dramatically.[6]

Any examination of adverse effects is difficult because much AAS use is illegal. AAS use often is clandestine, with athletes often not telling their wives—even while attending infertility clinics.[7] Major League Baseball injury reports also are anecdotal, leading others to claim the adverse effects "have been historically overstated"[2] and "exaggerated."[1] A review of all adverse effects reported between 1966 and 1996 concluded that most reports were anecdotal and the side effects were minor, and many were reversible as soon as AAS use ceased.[1] Many of the adverse effects are never reported outside the locker room.

Cardiac Effects

The direct effects of AAS on cardiac tissue in humans has not been examined, although several deaths of athletes using AAS have been associated with cardiac damage.[8] In the first study of its kind, mice given testosterone for three weeks had their exercise-induced development of cardiac capillaries inhibited. Control mice showed normal exercise-induced capillarization.[9]

The first controlled study examining the cardiovascular effects of AAS on bodybuilders was published in 2001.[10] Adult male volunteers were divided into three groups of 10: bodybuilders using AAS for 6.6 years on average; bodybuilders who had never used AAS; and men who never were bodybuilders or AAS users. HDL levels were significantly lower in the steroid using group compared to the other bodybuilders (0.6 vs. 1.4 mmol/L; $P < 0.001$). The left ventricular mass was significantly higher ($P = 0.04$), though not the left ventricular volume. Blood pressure and endothelial function showed no differences between the groups.

Endothelial function is an early indicator of future risk of atherosclerosis and is measured by flow-mediated vasodilatation (FMD). Healthy arteries give higher FMD values as measured by ultrasound. Twenty male bodybuilding AAS users were matched to six non-users.[11] Athletes trained for eight weeks without AAS, for 8-12 weeks using AAS, and then for eight more weeks without AAS. Athletes selected and self-administered a wide variety of AAS, with testosterone esters commonly used. When AAS use commenced, HDL levels dropped dramatically ($P < 0.01$), but were no longer statistically different at the study's end. FMD levels were significantly lower in the bodybuilders at all stages of the study ($P < 0.01$).

A study with females using testosterone found negative cardiac effects.[12] Twelve female-to-male transsexuals were matched with 12 normal females. The transsexual subjects all took testosterone, two as IM injections and 10 as testosterone depots (200-800 mg). Significantly lower HDL levels were found in those using testosterone (1.2 vs. 1.6 mmol/L; $P < 0.001$), as was decreased arterial vasodilator response ($P = 0.01$).

Hepatic Effects

AAS are almost exclusively metabolized by the liver. Although liver damage can be detected by raised liver enzyme levels, intense weightlifting alone can raise these levels.[1] Such changes have been detected in athletes using AAS, but return to normal soon after AAS use is stopped. Five AAS-using weightlifters avoided steroids for eight weeks and then used increasing amounts of testosterone and other AAS for 26 weeks.[13]

Liver enzyme levels were significantly higher in the AAS group than the controls (six weightlifters) when AAS consumption began and ended ($P < 0.05$), but not 12-16 weeks later. Enzyme levels remained within the normal range, leading the researchers to conclude that liver impairment was slight and reversible after 12, but not eight, weeks.

A controlled study randomly divided 26 experienced bodybuilders into three groups.[14] One group self-administered AAS; the second group participated in an eight-week double-blind study of nandrolone injections or placebo; the third group participated in a 12-week double-blind cross-over study of nandrolone. At the end of the study no significant differences existed in liver-function enzyme levels.

A more serious adverse effect of AAS on the liver is peliosis hepatitis. Cystic blood-filled spaces in hepatic lobules can rupture leading to liver damage and liver failure. Only one case of peliosis hepatitis has been reported in an athlete using AAS;[1] otherwise, it may be HIV-associated.

Psychological Effects

Some claim AAS improve performance by increasing athletes' aggressiveness, called "roid rage."[1] Uncontrollable aggression from AAS use has been used in criminal cases as a legal defense called the "dumbbell defense."[15] In a controlled study, two behavioral assessment tools were given to male weightlifters: 30 current AAS users, 23 previous users, and 40 nonusers.[15] For aggression/hostility and tension/anxiety indicators, no statistically significant differences were found between the three groups, or in comparison with population norms. The only significant difference was that current AAS users had higher "guilt" scores compared to the two other groups.

Fertility Effects

Endogenous AAS lead to reduced serum testosterone levels that can influence spermatogenesis. In-depth interviews with 110 AAS users revealed that 56% of the males reported testicular atrophy; 62% of the females had menstrual irregularities.[3] A World Health Organization randomized controlled trial reported that testosterone (200 mg weekly IM injection) was an effective, reversible male contraceptive with few short-term side-effects.[16] A 20-year-old male bodybuilder and father began using AAS and was azoospermic 10 months later.[17] Five months after ceasing AAS he was oligospermic, and after 10 months his sperm count was normal.

However, cases have been reported where infertility persisted up to three years after AAS cessation.[7] In one assessment of the duration of AAS' effect, teenage boys predicted to grow excessively tall were administered 500 mg testosterone IM for one year.[18] Ten years later, the men were compared to a control group and had significantly more maldescended testes and varioceles, and lower sperm motility, along with non-significantly reduced sperm count, concentration, and normal morphology. Overall fertility was not negatively impacted.

Effects in Female Users

Use of AAS by female athletes has grown recently. Nine female weightlifters using various AAS, including testosterone, were compared to nine non-AAS using female weightlifters.[19] Those using AAS had markedly elevated serum testosterone (average, 48 mmol/L vs. 1 mmol/L). Seven AAS-using women exceeded normal male testosterone levels. All these women exhibited hirsuitism, male patterns of muscle development, acne, clitoromegaly, and menstrual disturbances. Serum HDL levels were 39% lower than in controls (average, 0.9 mmol/L; $P < 0.05$). LDL levels were increased, but not significantly ($P < 0.06$).

Conclusion

Female AAS users experience serious adverse effects from AAS that warrant immediate discontinuation. Among males, the durability of the adverse effects may not be as detrimental as once suspected, although controlled studies have demonstrated lowered HDL levels, some liver impairment, and infertility. These effects appear to be generally reversible, although in some cases the damage may have contributed to some newsworthy fatalities. The alleged negative psychological effects of AAS administration have not been borne out in controlled studies.

The use of AAS is banned in the Olympics and by the NFL, NBA, NCAA, and high schools. Obtaining and using these drugs is illegal except by prescription for "medically necessary" purposes. Many within the athletic community continue to view their use as inherently unethical and a form of cheating.

Recommendation

Athletes put their health at risk when taking AAS and should be actively discouraged from doing so. The willingness of athletes to risk their health and a criminal record stems from underlying societal values. The American College of Sports Medicine claims this willingness arises from "our societal fixations on winning and physical appearance."[20] The pressures are enormous. Ken Caminiti, former baseball MVP, stated that if he didn't use steroids, "the guy next to you is . . . going

to take your job and make the money."[6] Given that mentality, physicians should remain alert for the most common adverse effects of AAS when caring for athletes. ❖

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CME Questions

1. *Ginkgo biloba* (GB) is widely used to enhance memory.
a. True
b. False

2. In recent clinical trials for memory improvement, GB has been found to be effective but not safe.
a. True
b. False

3. Due to the potential risk of bleeding, it is recommended to discontinue GB at least how many hours prior to surgery?
a. 12 hours
b. 24 hours
c. 36 hours
d. 48 hours

4. Chitosan is derived from the shells of:
a. turtles.
b. shellfish.
c. sunflower seeds.
d. eggs.

5. The combination of chitosan and which of the following led to a reduction in mean LDL cholesterol from 101 to 91 mg/dL?
a. Glucosamine
b. Glucagon
c. Glucomannan
d. Glue

6. Which of the following are the most common side effects of chitosan?
a. Pain and hemorrhage
b. Hypocalcemia and hypoglycemia
c. Skin rash and hair loss
d. Nausea and vomiting
e. Renal and hepatic failure

7. Testosterone is metabolized almost exclusively by the:

a. heart.
b. liver.
c. kidney.
d. spleen.

8. Anabolic-androgenic steroids consistently lead to:

a. reduced HDL levels.
b. increased HDL levels.
c. unchanged HDL levels.
d. inaccurate HDL levels.

Clinical Briefs

With Comments from John La Puma, MD, FACP

Coenzyme Q_{10} and Parkinson's Disease

Source: Shults CW, et al. Effects of coenzyme Q_{10} in early Parkinson disease: Evidence of slowing of the functional decline. *Arch Neurol* 2002;59: 1541-1550.

PARKINSON'S DISEASE (PD) IS A DEGENerative neurological disorder for which no treatment has been shown to slow the progression. To determine whether a range of dosages of coenzyme Q_{10} (CoQ_{10}) is safe and well tolerated and could slow the functional decline in PD, the authors conducted a multicenter, randomized, parallel-group, placebo-controlled, double-blind, dosage-ranging trial.

Working in academic movement disorders clinics, the authors recruited 80 subjects with early PD in 10 sites who did not require treatment for their disability, and randomly assigned them to placebo or CoQ_{10} at dosages of 300, 600, or 1,200 mg/d. The subjects had all three cardinal features of PD (resting tremor, bradykinesia, and rigidity), which had to be asymmetrical. The diagnosis of PD was made within the previous five years in men or in women 30 years or older.

Subjects underwent evaluation with the Unified Parkinson Disease Rating Scale (UPDRS) at the screening, baseline, and one-, four-, eight-, 12-, and 16-month visits. They were followed for 16 months or until disability requiring treatment with levodopa had developed. The primary response variable was the change in the total score on the UPDRS from baseline to the last visit.

The primary statistical analyses were performed according to the intention-to-treat principle. The adjusted mean total UPDRS changes were +11.99 for the placebo group, +8.81 for the 300 mg/d group, +10.82 for the 600 mg/d group, and +6.69 for the 1,200 mg/d group. The P value for the primary analysis, a test for a linear trend between the dosage and the mean change in the total UPDRS score, was 0.09, which met the prespecified criteria for a positive trend for the trial. A prespecified, secondary analysis was the comparison of each treatment group with the placebo group, and the difference between the 1,200 mg/d and placebo groups was significant ($P = 0.04$).

The authors concluded that CoQ_{10} was safe and well tolerated at dosages of up to 1,200 mg/d. Less disability developed in subjects assigned to CoQ_{10} than in those assigned to placebo; the benefit was greatest in subjects receiving the highest dosage. CoQ_{10} appears to slow the progressive deterioration of function in PD, but these results need to be confirmed in a larger study.

Comment

Approximately 1% of American adults older than age 65 has PD. Although medication can slow the symptoms, no medication or procedure of which I'm aware actually slows its progression. Except, perhaps, CoQ_{10}.

This small study, funded by the National Institute of Neurological Disorders and Stroke, and centered at the University of California-San Diego, suggests that CoQ_{10} may actually slow progression. The work was designed as a dosage-ranging study, and attempted to identify a trend toward efficacy, instead of to demonstrate effectiveness or efficacy.

CoQ_{10} is a potent antioxidant, and is normally present in mitochondria; PD patients have reduced levels of CoQ_{10} in their platelet mitochondria, and have lower serum levels of CoQ_{10} than age-comparable patients with stroke.

Here, CoQ_{10} was administered in the form of a maple nut wafer, four times daily. The drop-out rate was low, although the exclusion criteria for the study were substantial—off PD meds, no history of stroke, no PD from medication, and many more.

Remarkably, the subjects who took 1,200 mg/d—the highest dose—had 44% less decline in activities of daily living (plus mental function and movement) than did the subjects who took placebo.

Side effects were mild, and when mild events were excluded, three events were experienced by at least four subjects: viral infection, pharyngitis, and sinusitis. No adverse effects were significantly related to any dosage administration. High carbon dioxide levels ($P = 0.01$), which were significantly related to CoQ_{10} administration, were not judged to be clinically significant.

How might this work? The authors note, "The assay of NADH to cytochrome-c reductase activity, which relies on endogenous coenzyme Q_{10}, demonstrated a significant increase in activity in subjects taking 1,200 mg/d of coenzyme Q_{10}." The authors hypothesize that the same benefit occurred in the brain and that mitochondrial dysfunction, if corrected, does in fact improve PD symptoms.

Because the greatest effect was seen in activities of daily living, this work should make a real difference. It will be tested in broader scale, and rightly so.

Recommendation

In the short term, it seems prudent to recommend 1,200 mg daily of CoQ_{10} to patients at risk for PD, and who would not have been excluded from this study. ❖

Supplement to *Alternative Medicine Alert*
January 2003

ALTERNATIVE MEDICINE ALERT™
A Clinician's Evidence-Based Guide to Alternative Therapies

Making Change in the New Year: Strategies for Success

WHETHER THEY WANT TO LOSE A FEW POUNDS THAT WERE ADDED OVER THE HOLIDAYS OR develop a more comprehensive weight-loss goal, many of your patients will resolve to lose weight in the new year. During the next few weeks, your patients may be more receptive to weight-loss counseling than at any other time of the year. Will you be ready to help them formulate a plan and offer the support they need to succeed?

This handout will focus on helping you work with your patients to develop a weight-loss plan, but the general principles could be applied to a variety of lifestyle changes.

The Process of Change

A smoker woke up one morning and decided to quit smoking. Some years later, he remains a nonsmoker. We've all heard this story, and we all know it's the exception to the rule. Back in the day when smoking-cessation patches were prescription-only, the pharmaceutical companies knew it too—and in response, they formulated multifaceted smoking-cessation programs to support their customers, replete with toll-free customer support services and encouragement via mail campaigns.

The vast majority of dieters go it alone, much like our cold-turkey nonsmoker, but with drastically different results. They are plagued by their inability to lose weight and keep it off. For those who can be counseled that weight loss is a process that requires careful planning, patience, and commitment, the chance of success improves dramatically.

Your role in this process is multifaceted and may vary from patient to patient. You many need to help the patient:

- identify motivating reasons for losing weight;
- develop a plan and goals that span the weight-loss process;
- provide strategies and tools; and
- refer to allied health professionals (i.e, dietitian and exercise physiologist) when necessary.

The Change Cycle

According to Prochaska et al the first step in lifestyle change counseling is to determine where the patient is in the change cyle. Get the patient talking and listen. Has she not yet begun to think about (precontemplation) or is she just beginning to consider (contemplation) change? Maybe she has established a target date for starting (preparation) or has just started a new diet (action). Has she lost a significant amount of weight and is struggling to keep it off (maintenance), or has she had a setback and put on a few pounds (recycling)?

Your approach should be tailored to where the patient is in the change cycle. The patient in the preparation cycle may need help establishing tangible and realistic goals, whereas the patient in the action, maintenance, or recycling cycle may need specific strategies or tools to help her stick to the plan.

Treatment

The National Heart, Lung, and Blood Institute (NHLBI) recommends the following steps to treat overweight and obesity:

- measure height and weight and estimate BMI *(see Table)*;
- measure waist circumference;
- assess patient motivation;
- recommend a diet; generally, a diet containing 1,000-1,200 kcal/d should be selected for women; a diet containing 1,200-1,600 kcal/d should be chosen for men and may be appropriate for women who weigh 165 lbs or more or who exercise regularly;
- discuss physical activity and establish a physical activity goal; a wide variety of activities may satisfy this goal, including walking, dancing, and gardening;
- encourage the use of a weekly food and activity diary;
- provide dietary information; and
- note goals in the patient record and track progress on subsequent office visits.

Identifying Motivators and Potential Barriers

Throughout the process, but especially as part of the prepration cycle, it is imperative to identify both motivators and potential barriers to success.

Staying motivated and keeping a positive attitude are major challenges in any weight-loss program. By identifying potential barriers, the patient can anticipate, and possibly avoid, difficult situations that may hinder progress and erode a positive attitude. For example, an overweight mother may need to arrange for childcare or join a gym that offers childcare in order to pursue an exercise program.

Establishing Goals

Most weight-loss patients already have an idea of how much weight they would like to lose. In addition to ensuring that this goal is reasonable, you should help establish several goals that are not related to weight:

- a change in size—clothes fit differently;
- an improved medical condition—lipid levels have changed sufficiently to require reduced medication;
- increased exercise capacity—walking longer or farther than at program inception;
- increased fruit and vegetable consumption; and
- improved body mass index (BMI).

Having multiple goals will not only create a balanced focus, but also will build confidence throughout the program as these goals are met.

Table

Classifications for body mass index (BMI)

Classification	BMI
Underweight	< 18.5 kg/m^2
Normal weight	18.5-24.9 kg/m^2
Overweight	25-29.9 kg/m^2
Obesity Class I	30-34.9 kg/m^2
Obesity Class II	35-39.9 kg/m^2
Extreme Obesity Class III	≥ 40 kg/m^2

Source: NHLBI Obesity Education Initiative

Just as importantly, patients should be encouraged to establish rewards for meeting significant milestones along the way.

When establishing these goals and rewards, keep in mind the patient's reasons for wanting to lose weight and plan accordingly. For example, if one of the patient's motivators is to be able to be more active with his children, a reward may involve a special outing with the family.

Tools and Strategies

The NHLBI's Practical Guide *(see Resources)* provides a useful counseling tool for primary care physicians that includes patient resources on shopping, dining out, and food preparation.

As with any behavioral change, it is important to:

- emphasize the positive over the negative—a simple recommendation to eat five fruits and vegetables daily may lead to better overall dietary habits;
- celebrate successes and progression from one change cycle to another;
- emphasize patience and the process in the face of a setback; and
- listen to the patient.

Resources

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