

ABSTRACTS

Page 1 of 4

Brain function-GPC

Oral choline alfoscerate counteracts age-dependent loss of mossy fibers in the rat hippocampus.

Mossy fibers represent a major intrahippocampal associative pathway. They consist of axons of granule cells of the dentate gyrus and show an age-dependent loss as do the granule cells of the dentate gyrus. The present study was designed to assess whether long-term treatment of rats with choline alfoscerate in their drinking water would be effective in countering the loss of mossy fibers and of granule cells occurring with aging. Choline alfoscerate is a precursor in the biosynthesis of brain phospholipids and increases the bioavailability of choline in nervous tissue. Male Sprague-Dawley rats of 18 months of age were divided into two groups. One group received a daily dose of 100 mg/kg choline alfoscerate for six months; the other group was used as an untreated control. Twelve-month-old untreated animals were used as a reference group. The area occupied by mossy fibers, as well as their density, was significantly reduced in 24-month-old control rats in comparison with 12-month-old rats. The same is true for the density granule cells of the dentate gyrus, which was decreased by about 20% in the oldest animals. In choline alfoscerate-treated rats both the area occupied by mossy fibers and their density were significantly higher than in age-matched controls. Moreover, the number of granule neurons of the hippocampus was higher by about 7% in choline alfoscerate-treated than in control 24-month-old rats. The above data suggest that choline alfoscerate treatment counteracts some anatomical changes of the rat hippocampus occurring in old age.

Mech Ageing Dev 1992;66(1):81-91

Long term choline alfoscerate treatment counters age-dependent microanatomical changes in rat brain.

1. The density of nerve cells and of silver-gold impregnated fibres were evaluated in the hippocampus and in the cerebellar cortex in adult (12-month-old) and old (24-month-old) Sprague-Dawley rats. 2. The effects of long-term choline alfoscerate (GFC) treatment (100 mg/kg/day for six months) on the above parameters were investigated in old rats. 3. The number of nerve cell profiles and the area occupied by silver-gold impregnated fibers were decreased both in the hippocampus and in the cerebellar cortex in old in comparison with adult rats. 4. GFC treatment countered the age-dependent reduction of nerve cells and silver-gold impregnated fibers. The hippocampus was more sensitive than the cerebellar cortex to the activity of GFC. 5. These results suggest that GFC treatment is effective in slowing down the expression of structural changes occurring in aging brain.

Prog Neuropsychopharmacol Biol Psychiatry 1994 Sep;18(5):915-24

Effect of L-alpha glycerylphosphorylcholine on muscarinic receptors and membrane microviscosity of aged rat brain.

1. Old rats showed a significant decrease in the number of muscarinic M(1) receptors and a significant increase in membrane microviscosity in the striatum and hippocampus as compared to young animals. In contrast, no significant changes in the density of muscarinic M(2) receptors were observed with aging. 2. Chronic treatment of aged rats with L-alpha-glycerylphosphorylcholine (L-alpha-GPC) restored the number of M(1) receptors to levels found in the striatum and hippocampus from young animals. The same treatment to aged rats partially restored membrane microviscosity in both regions studied and hence increased membrane fluidity. 3. None of the major metabolites of L-alpha-GPC (choline, glycerophosphate or phosphorylcholine) was able to restore the number of striatal and hippocampal M(1) sites and membrane microviscosity of aged rats, neither did any of these treatments (including treatment with L-alpha-GPC) modify the level of M(1) receptors and microviscosity values in young rats.

Prog Neuropsychopharmacol Biol Psychiatry 1996 Feb;20(2):323-39

Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain.

Recent evidence indicates that the nucleus basalis of Meynert, a distinct population of basal forebrain neurons, is a major source of cholinergic innervation of the cerebral cortex. Postmortem studies have previously demonstrated profound reduction in the

presynaptic markers for cholinergic neurons in the cortex of patients with Alzheimer's disease and senile dementia of the Alzheimer's type. The results of this study show that neurons of the nucleus basalis of Meynert undergo a profound (greater than 75%) and selective degeneration in these patients and provide a pathological substrate of the cholinergic deficiency in their brains. Demonstration of selective degeneration of such neurons represents the first documentation of a loss of a transmitter-specific neuronal population in a major disorder of higher cortical function and, as such, points to a critical subcortical lesion in Alzheimer's patients.

Science 1982 Mar 5;215(4537):1237-9

Treatment of cognitive dysfunction associated with Alzheimer's disease with cholinergic precursors. Ineffective treatments or inappropriate approaches?

The observations of the loss of cholinergic function in neocortex and hippocampus in Alzheimer's disease (AD) developed the hypothesis that replacement of cholinergic function may be of therapeutic benefit to AD patients. The different approaches proposed or tested included intervention with acetylcholine (ACh) precursors, stimulation of ACh release, use of muscarinic or nicotinic receptor agonists and acetylcholinesterase (AChE) or cholinesterase (ChE) inhibition. Inhibition of endogenous ACh degradation through ChE inhibitors and precursor loading were treatments more largely investigated in clinical trials. Of the numerous compounds in development for the treatment of AD, AChE and ChE inhibitors are the most clinically advanced, although clinical trials conducted to date did not always confirm a significant benefit of these drugs on all symptom domains of AD. The first attempts in the treatment of AD with cholinergic precursors did not confirm a clinical utility of this class of compounds in well-controlled clinical trials. However, cholinergic precursors most largely used, such as choline and phosphatidylcholine (lecithin), were probably not suitable for enhancing brain levels of ACh. Other phospholipids involved in choline biosynthetic pathways, such as CDP-choline, choline alfoscerate and phosphatidylserine clearly enhanced ACh availability or release and provided a modest improvement of cognitive dysfunction in AD, these effects being more pronounced with choline alfoscerate. Although some positive results cannot be generalized due to the small numbers of patients studied, they probably would justify reconsideration of the most promising molecules in larger carefully controlled trials.

Mech Ageing Dev 2001 Nov;122(16):2025-40

Multicentre study of l-alpha-glyceryl-phosphorylcholine vs ST200 among patients with probable senile dementia of Alzheimer's type.

A multicentre, randomized, controlled study compared the efficacy of l-alpha-glyceryl-phosphorylcholine (alpha GPC) and ST200 (acetyl-l-carnitine) among 126 patients with probable senile dementia of Alzheimer's type (SDAT) of mild to moderate degree. Efficacy was evaluated by means of behavioural scales and psychometric tests. The results showed significant improvements in most neuropsychological parameters in the alpha GPC recipients. Improvements also occurred in the ST200 recipients but to a lesser extent. Tolerability was good in both groups. These positive findings require replication in larger, double-blind, longitudinal studies coupling clinical and biological determinations.

Drugs Aging 1993 Mar-Apr;3(2):159-64

Alpha-glycerophosphocholine in the mental recovery of cerebral ischemic attacks. An Italian multicenter clinical trial.

The clinical efficacy and the tolerability of alpha-glycerophosphocholine (alpha-GPC), a drug able to provide high levels of choline for the nervous cells of the brain and to protect their cell walls, have been tested in a clinical open multicenter trial on 2,044 patients suffering from recent stroke or transient ischemic attacks. alpha-GPC was administered after the attack at the daily dose of 1000 mg im for 28 days and orally at the dose of 400 mg tid during the following five months after the first phase. The evaluation of the efficacy on the psychic recovery was done by the Mathew Scale (MS) during the period of im drug administration, and using the Mini Mental State Test (MMST), the Crichton Rating Scale (CRS) and the Global Deterioration Scale (GDS) during the following period of oral administration. The MS mean increased 15.9 points in 28 days in a statistically significant way ($p < 0.001$) from 58.7 to 74.6. At the end of the five month oral administration, the CRS mean significantly decreased 4.3 points, from 20.2 to 15.9 ($p < 0.001$); the MMST mean significantly increased ($p < 0.001$) from 21 to 24.3 at the end of the trial, reaching the "normality" score at the 3rd month assessment. The GDS score at the end of the trial corresponded to "no cognitive decline" or "forgetfulness" in 71% of the patients. Adverse events were complained of by 44 patients (2.14%); in 14 (0.7%) the investigator preferred to discontinue therapy. The most frequent complaints were heartburn (0.7%), nausea-vomit (0.5%), insomnia-excitation (0.4%), and headache (0.2%). The trial confirms the therapeutic role of alpha-GPC on the cognitive recovery of patients with acute stroke or TIA, and the low percentage of adverse events confirms its excellent tolerability.

Ann N Y Acad Sci 1994 Jun 30;717:253-69

Choline alfoscerate in cognitive decline and in acute cerebrovascular disease: an analysis of published clinical data.

This paper has reviewed the documentation on the clinical efficacy of choline alfoscerate, a cholinergic precursor, considered as a

centrally acting parasympathomimetic drug in dementia disorders and in acute cerebrovascular disease. Thirteen published clinical trials, examining in total 4,054 patients, have evaluated the use of choline alfoscerate in various forms of dementia disorders of degenerative, vascular or combined origin, such as senile dementia of the Alzheimer's type (SDAT) or vascular dementia (VaD) and in acute cerebrovascular diseases, such as transitory ischemic attack (TIA) and stroke. Analysis has assessed the design of each study, in particular with respect to experimental design, number of cases, duration of treatment and tests used to evaluate drug clinical efficacy. Most of the 10 studies performed in dementia disorders were controlled trials versus a reference drug or placebo. Overall, 1,570 patients were assessed in these studies, 854 of which in controlled trials. As detected by validated and appropriate tests, such as Mini Mental State Evaluation (MMSE) in SDAT and Sandoz Clinical Assessment Geriatric (SCAG) in VaD, administration of choline alfoscerate significantly improved patient clinical condition. Clinical results obtained with choline alfoscerate were superior or equivalent to those observed in control groups under active treatment and superior to the results observed in placebo groups. Analysis stresses the clear internal consistency of clinical data gathered by different experimental situations on the drug effect, especially with regard to the cognitive symptoms (memory, attention) characterizing the clinical picture of adult-onset dementia disorders. The therapeutic usefulness of choline alfoscerate in relieving cognitive symptoms of chronic cerebral deterioration differentiates this drug from cholinergic precursors used in the past, such as choline and lecithin. Three uncontrolled trials were performed with choline alfoscerate in acute cerebrovascular stroke and TIA, totaling 2,484 patients. The results of these trials suggest that this drug might favor functional recovery of patients with cerebral stroke and should be confirmed in future investigations aimed at establishing the efficacy of the drug in achieving functional recovery of patients with acute cerebrovascular disease.

Mech Ageing Dev 2001 Nov;122(16):2041-55

Behavioral effects of L-alpha-glycerylphosphorylcholine: influence on cognitive mechanisms in the rat.

The phosphorylcholine precursor, L-alpha-glycerylphosphorylcholine (alpha-GPC), was injected at the dose of 100 mg/kg/day for 20 days to aged male rats of the Sprague-Dawley strain, 24 months old, showing a deficit of learning and memory capacity. The drug was also administered to rats with amnesia induced pharmacologically with bilateral injections of kainic acid into the nucleus basalis magnocellularis (NBM). Learning and memory capacity of the animals, studied with tests of active and passive avoidance behavior, was improved after treatment with alpha-GPC in all experimental groups. These results indicate that this drug affects cognitive mechanisms in the rat through an involvement of central neurotransmission.

Pharmacol Biochem Behav 1992 Feb;41(2):445-8

Continued on Page 2 of 4

[Back to the Magazine Forum](#)

ABSTRACTS

Page 2 of 4

Brain function—Phosphatidylserine

A review of nutrients and botanicals in the integrative management of cognitive dysfunction.

Dementias and other severe cognitive dysfunction states pose a daunting challenge to existing medical management strategies. An integrative, early intervention approach seems warranted. Whereas, allopathic treatment options are highly limited, nutritional and botanical therapies are available which have proven degrees of efficacy and generally favorable benefit-to-risk profiles. This review covers five such therapies: phosphatidylserine (PS), acetyl-L-carnitine (ALC), vinpocetine, ginkgo biloba extract (GbE) and bacopa monniera (Bacopa). PS is a phospholipid enriched in the brain, validated through double-blind trials for improving memory, learning, concentration, word recall and mood in middle-aged and elderly subjects with dementia or age-related cognitive decline. PS has an excellent benefit-to-risk profile. ALC is an energizer and metabolic cofactor which also benefits various cognitive functions in the middle-aged and elderly, but with a slightly less favorable benefit-to-risk profile. Vinpocetine, found in the lesser periwinkle *Vinca minor*, is an excellent vasodilator and cerebral metabolic enhancer with proven benefits for vascular-based cognitive dysfunction. Two meta-analyses of GbE demonstrate the best preparations and offer limited benefits for vascular insufficiencies and even more limited benefits for Alzheimer's, while "commodity" GbE products offer little benefit, if any at all. GbE (and probably also vinpocetine) is incompatible with blood-thinning drugs. Bacopa is an Ayurvedic botanical with apparent anti-anxiety, anti-fatigue and memory-strengthening effects. These five substances offer interesting contributions to a personalized approach for restoring cognitive function, perhaps eventually in conjunction with the judicious application of growth factors.

Altern Med Rev 1999 Jun;4(3):144-61

Double-blind randomized controlled study of phosphatidylserine in senile demented patients.

A double-blind randomized controlled study was conducted in 42 hospitalized demented patients to evaluate the therapeutical effect of phosphatidylserine (BC-PS). Half of the patients received 3 X 100 mg of this product, and the other half a placebo of the same appearance. After a wash-out period, prescription lasted for six weeks. To evaluate the patients, two distinct rating scales were used: the Crichton Scale and an original one (Peri Scale) designed in our geriatric unit (see Appendix). A circle crossing test was added. Out of the 35 patients who completed the trial, 18 had received placebo and 17 BC-PS. The results indicated a trend toward improvement in the BC-PS treated patients and an analysis of covariance showed a significant (p less than 0.05) treatment effect on the Peri Scale. The results at the end of the treatment period were compared with those obtained three weeks later. Here again there was a statistically significant difference in the Peri Scale results, indicating that modifications are drug-related. The behavioral improvement shown in this study is in agreement with experimental studies on aged animals.

Acta Neurol Scand 1986 Feb;73(2):136-40

Effects of phosphatidylserine in age-associated memory impairment.

We treated 149 patients meeting criteria for age-associated memory impairment (AAMI) for 12 weeks with a formulation of phosphatidylserine (100 mg BC-PS tid) or placebo. Patients treated with the drug improved relative to those treated with placebo on performance tests related to learning and memory tasks of daily life. Analysis of clinical subgroups suggested that persons within the sample who performed at a relatively low level prior to treatment were most likely to respond to BC-PS. Within this subgroup, there was improvement on both computerized and standard neuropsychological performance tests, and also on clinical global ratings of improvement. The results suggest that the compound may be a promising candidate for treating memory loss in later life.

Neurology 1991 May;41(5):644-9

Cognitive decline in the elderly: a double-blind, placebo-controlled multicenter study on efficacy of phosphatidylserine administration.

This double-blind study assesses the therapeutic efficacy and the safety of oral treatment with phosphatidylserine (BC-PS) vs placebo (300 mg/day for six months) in a group of geriatric patients with cognitive impairment. A total of 494 elderly patients (age between 65 and 93 years), with moderate to severe cognitive decline, according to the Mini Mental State Examination and Global Deterioration Scale, were recruited in 23 Geriatric or General Medicine Units in Northeastern Italy. Sixty-nine patients dropped out within the six-month trial period. Patients were examined just before starting therapy, and three and six months thereafter. The

efficacy of treatment compared to placebo was measured on the basis of changes occurring in behavior and cognitive performance using the Plutchik Geriatric Rating Scale and the Buschke Selective Reminding Test. Statistically significant improvements in the phosphatidylserine-treated group compared to placebo were observed both in terms of behavioral and cognitive parameters. In addition, clinical evaluation and laboratory tests demonstrated that BC-PS was well tolerated. These results are clinically important since the patients were representative of the geriatric population commonly met in clinical practice.

Aging (Milano) 1993 Apr;5(2):123-33

Double-blind study with phosphatidylserine (PS) in parkinsonian patients with senile dementia of Alzheimer's type (SDAT).

Experimental and clinical studies showed that phosphatidylserine—special preparation from cow's brain by FIDIA, Abano Terme, Italy—is able to influence cerebral changes contributed to the symptoms of senile dementia of Alzheimer's type. The application of the computerized EEG (CEEG) method Dynamic Brain Mapping (HZI Research Center, Tarrytown, New York) is able to prove the therapeutic effect of phosphatidylserine: the acceleration of a slowed EEG in Parkinsonian patients with SDAT. These reactions were seen previous to the favorable clinical influence documented by the Sandoz Clinical Assessment Geriatric Scale (SCAG), which showed a significant amelioration in anxiety, motivation and affectivity by the verum drug. Acute and long-term CEEG results—till 18 months—showed that the so-called theta anteriorization can be reduced or even abolished; this is replaced by alpha waves. Even in preclinical cerebral changes this method open the possibility to show incipient alterations of the brain metabolism. Preliminary therapeutic results leads to this and not proven hypothesis that prevention or retardation of cerebral aging might be possible.

Prog Clin Biol Res 1989;317:1235-46

Phosphatidylserine in the treatment of clinically diagnosed Alzheimer's disease. The SMID Group.

Modifications in cellular membranes can be observed in aging and Alzheimer's disease (AD). These mainly concern the degree of the membrane's viscosity, with consequent reduction of the activity of some protein structures, such as enzymes, receptors and membrane carriers. Moreover, dendritic spine loss, found in aging and AD brain, is one of the most characteristic findings. BC-PS, a phospholipid, purified from bovine brain, is found to be able to influence positively the above cited modifications. Moreover, BC-PS administration to old rats improves the performances in some memory tests. In humans, the effects of BC-PS have been studied by some controlled trials in AD and related cognitive disorders. The most recent of these trials, conducted on an Italian population of AD patients is presented here, emphasizing in particular its methodological aspects.

J Neural Transm Suppl 1987;24:287-92

Effects of phosphatidylserine in Alzheimer's disease.

We studied 51 patients meeting clinical criteria for probable Alzheimer's disease (AD). Patients were treated for 12 weeks with a formulation of bovine cortex phosphatidylserine (BC-PS; 100 mg tid) or placebo, and those treated with the drug improved on several cognitive measures relative to those administered placebo. Differences between treatment groups were most apparent among patients with less severe cognitive impairment. Results suggest that phosphatidylserine may be a promising candidate for study in the early stages of AD.

Psychopharmacol Bull 1992;28(1):61-6

Double-blind cross-over study of phosphatidylserine vs. placebo in patients with early dementia of the Alzheimer type.

Thirty-three patients with mild primary degenerative dementia according to DSM-III (MMS between 15 and 27) took part in a double-blind cross-over study of phosphatidylserine (Fidia 300 mg/d) versus placebo. Both treatment phases lasted for eight weeks with an eight week washout phase in between and a four week washout phase before treatment phase one. Clinical global improvement ratings showed significantly more patients improving under phosphatidylserine (BC-PS) than under placebo during treatment phase one. The improvement carried over to the following wash-out and treatment phases. There were no significant improvements in GBS dementia rating scale, psychometric tests or P300-latency. 16-channel EEG mapping findings indicated that the patients initially showed higher power values in all frequency bands (except alpha), when compared to a younger, healthy control group. BC-PS reduced the higher power values compared to placebo, shifting EEG power more towards the normal level.

Eur Neuropsychopharmacol 1992 Jun;2(2):149-55

Effects of phosphatidylserine therapy in geriatric patients with depressive disorders.

The effects of phosphatidylserine (BC-PS) on cognitive, affective and behavioural symptoms were studied in a group of 10 elderly

women with depressive disorders. Patients were treated with placebo for 15 days, followed by BC-PS (300 mg/day) for 30 days. The Hamilton Rating Scale for Depression, Gottfries-Brane-Steen Rating Scale, Nurse's Observation Scale for Inpatient Evaluation and Buschke Selective Reminding Test were administered before and after placebo and after BC-PS therapy to monitor changes in depression, memory and general behavior. At the same time, basal plasma levels of noradrenaline, MHPG, DOPAC, HVA and 5-HIAA, and GH/beta-endorphin/beta-lipotropin responses to clonidine stimulation were measured. BC-PS induced consistent improvement of depressive symptoms, memory and behavior. No changes in amine metabolite levels or in hormonal responses to alpha 2-adrenoceptor stimulation were observed.

Acta Psychiatr Scand 1990 Mar;81(3):265-70

Blunting by chronic phosphatidylserine administration of the stress-induced activation of the hypothalamo-pituitary-adrenal axis in healthy men.

The effect of chronic administration of phosphatidylserine derived from brain cortex on the neuroendocrine responses to physical stress has been examined in a placebo-controlled study in nine healthy men. Phosphatidylserine 800 mg/d for 10 days significantly blunted the ACTH and cortisol responses to physical exercise ($P = 0.003$ and $P = 0.03$, respectively), without affecting the rise in plasma GH and PRL. Physical exercise significantly increased the plasma lactate concentration both after placebo and phosphatidylserine. The results suggest that chronic oral administration of phosphatidylserine may counteract stress-induced activation of the hypothalamo-pituitary-adrenal axis in man.

Eur J Clin Pharmacol 1992;42(4):385-8

Effects of phosphatidylserine on the neuroendocrine response to physical stress in humans.

The activity of brain cortex-derived phosphatidylserine (BC-PS) on the neuroendocrine and neurovegetative responses to physical stress was tested in eight healthy men who underwent three experiments with a bicycle ergometer. According to a double-blind design, before starting the exercise, each subject received intravenously, within 10 min, 50 mg or 75 mg of BC-PS or a volume-matched placebo diluted in 100 ml of saline. Blood samples were collected before and after the exercise for plasma epinephrine (E), norepinephrine (NE), dopamine (DA), adrenocorticotropin (ACTH), cortisol, growth hormone (GH), prolactin (PRL) and glucose determinations. Blood pressure and heart rate were also recorded. Physical stress induced a clear-cut increase in plasma E, NE, ACTH, cortisol, GH and PRL, whereas no significant change was observed in plasma DA and glucose. Pretreatment with both 50 mg and 75 mg BC-PS significantly blunted the ACTH and cortisol responses to physical stress.

Neuroendocrinology 1990 Sep;52(3):243-8

The influence of phosphatidylserine supplementation on mood and heart rate when faced with an acute stressor.

There have been previous reports that supplements of phosphatidylserine (PS) blunted the release of cortisol in response to exercise stress and that it improved mood. The present study extended these observations by considering whether PS supplementation influenced subjective feelings of stress and the change in heart rate when a stressful mental arithmetic task was performed. In young adults with neuroticism scores above rather than below the median, the taking of 300 mg PS each day for a month was associated with feeling less stressed and having a better mood. The study for the first time reports an improvement in mood following PS supplementation in a sub-group of young healthy adults.

Nutr Neurosci 2001;4(3):169-78

Continued on Page 3 of 4

[Back to the Magazine Forum](#)

ABSTRACTS

Page 3 of 4

Osteoporosis—Bisphosphonates

Bisphosphonates: safety and efficacy in the treatment and prevention of osteoporosis.

Osteoporosis affects more than 28 million Americans. With the advent of accessible and affordable diagnostic studies, awareness and recognition of this disease by patients and clinicians are growing. Osteoporotic fractures of the spine and hip are costly and associated with significant morbidity and mortality. Over the past decade, a surge of new antiosteoporotic drugs have been labeled or are awaiting labeling by the U.S. Food and Drug Administration. One class of agents used to treat osteoporosis is the bisphosphonates, which inhibit bone resorption, cause an increase in bone mineral density and reduce the risk of future fractures caused by aging, estrogen deficiency and corticosteroid use. Overall, bisphosphonates have been shown to have a strong safety and tolerability profile.

Am Fam Physician 2000 May 1;61(9):2731-6

Bisphosphonates: preclinical aspects and use in osteoporosis.

Bisphosphonates are synthetic compounds characterized by a P-C-P bond. They have a strong affinity to calcium phosphates and hence to bone mineral. In vitro they inhibit both formation and dissolution of the latter. Many of the bisphosphonates inhibit bone resorption, the newest compounds being 10,000 times more active than etidronate, the first bisphosphonate described. The antiresorbing effect is cell mediated, partly by a direct action on the osteoclasts, partly through the osteoblasts, which produce an inhibitor of osteoclastic recruitment. When given in large amounts, some bisphosphonates can also inhibit normal and ectopic mineralization through a physical-chemical inhibition of crystal growth. In the growing rat the inhibition of resorption is accompanied by an increase in intestinal absorption and an increased balance of calcium. Bisphosphonates also prevent various types of experimental osteoporosis, such as after immobilization, ovariectomy, orchidectomy, administration of corticosteroids or low calcium diet. The P-C-P bond of the bisphosphonates is completely resistant to enzymatic hydrolysis. The bisphosphonates studied up to now, such as etidronate, clodronate, pamidronate, and alendronate, are absorbed, stored and excreted unaltered. The intestinal absorption of the bisphosphonates is low, between 1% or less and 10% of the amount ingested. The newer bisphosphonates are at the lower end of the scale. The absorption diminishes when the compounds are given with food, especially in the presence of calcium. Bisphosphonates are rapidly cleared from plasma, 20% to 80% being deposited in bone and the remainder excreted in the urine. In bone, they deposit at sites of mineralization as well as under the osteoclasts. In contrast to plasma, the half-life in bone is very long, partially as long as the half-life of the bone in which they are deposited. In humans, bisphosphonates are used successfully in diseases with increased bone turnover, such as Paget's disease, tumoural bone disease, as well as in osteoporosis. Various bisphosphonates, such as alendronate, clodronate, etidronate, ibandronate, pamidronate and tiludronate, have been investigated in osteoporosis. All inhibit bone loss in postmenopausal women and increase bone mass. Furthermore, bisphosphonates are also effective in preventing bone loss both in corticosteroid-treated and in immobilized patients. The effect on the rate of fractures has recently been proven for alendronate. In humans, the adverse effects depend upon the compound and the amount given. For etidronate, practically the only adverse effect is an inhibition of mineralization. The aminoderivatives induce for a period of two to three days a syndrome with pyrexia, which shows a similitude with an acute phase reaction. The more potent compounds can induce gastrointestinal disturbances, sometimes oesophagitis, when given orally. Bisphosphonates are an important addition to the therapeutic possibilities in the prevention and treatment of osteoporosis.

Ann Med 1997 Feb;29(1):55-62

Osteoporosis - evidence based therapy.

Osteoporosis therapy has been controversially discussed in the past. In the meantime, several therapeutic options to prevent fractures are available for this disease. With respect to proven fracture benefit, however, the quality of evidence from randomized and controlled clinical trials varies substantially among therapies. From systematic research the best external evidence is available for a supplementation with calcium and vitamin D and a therapy with the bisphosphonates alendronate or risedronate, as well as the SERM raloxifene. For other therapeutic agents like fluorides, vitamin D metabolites, calcitonin and etidronate the quality of evidence is much lower. So far, there is no evidence for other pharmaceutical therapies. Hip protectors are effective in the prevention of hip fractures.

Z Gastroenterol 2002 Apr;40 Suppl 1:57-61

Bisphosphonate therapy in osteoporosis. Inhibition of trabecular perforation by aminobisphosphonate.

After many years of experience with bisphosphonates in the treatment of "tumor osteopathy" and Paget's disease, these substances have now also been approved for use in the treatment of osteoporosis. Owing to their high affinity for calcium hydroxyapatite, the bisphosphonates are deposited in the bony surface, and the aminobisphosphonates exert their effect at the site of active resorption via direct inhibition of active osteoclasts. As a result of this inhibition of the osteoclastic bone resorption, trabecular perforation is reduced and during the course of bone remodelling by the activity of the osteoblasts, boneformation occurs. In addition to an increase in bone density, both etidronate and alendronate have been shown to inhibit vertebral fractures in patients with osteoporosis. In addition, in patients with preexisting fractures, alendronate is able, at the same time, to lower the incidence of fractures of the femoral neck. With proper administration, the associated occasional gastrointestinal side effects can be avoided. The introduction of bisphosphonates into the treatment of osteoporosis is definitely an enrichment of the therapeutic spectrum in conjunction with the basic treatment comprising calcium, vitamin D, diet and physical measures.

Fortschr Med 1997 Oct 20;115(29):37-42

Bisphosphonates: from the laboratory to the clinic and back again.

Bisphosphonates (BPs) used as inhibitors of bone resorption all contain two phosphonate groups attached to a single carbon atom, forming a "P-C-P" structure. The bisphosphonates are therefore stable analogues of naturally occurring pyrophosphate-containing compounds, which now helps to explain their intracellular as well as their extracellular modes of action. Bisphosphonates adsorb to bone mineral and inhibit bone resorption. The mode of action of bisphosphonates was originally ascribed to physico-chemical effects on hydroxyapatite crystals, but it has gradually become clear that cellular effects must also be involved. The marked structure-activity relationships observed among more complex compounds indicate that the pharmacophore required for maximal activity not only depends upon the bisphosphonate moiety but also on key features, e.g., nitrogen substitution in alkyl or heterocyclic side chains. Several bisphosphonates (e.g., etidronate, clodronate, pamidronate, alendronate, tiludronate, risedronate, and ibandronate) are established as effective treatments in clinical disorders such as Paget's disease of bone, myeloma and bone metastases. Bisphosphonates are also now well established as successful antiresorptive agents for the prevention and treatment of osteoporosis. In particular, etidronate and alendronate are approved as therapies in many countries, and both can increase bone mass and produce a reduction in fracture rates to approximately half of control rates at the spine, hip, and other sites in postmenopausal women. In addition to inhibition of osteoclasts, the ability of bisphosphonates to reduce the activation frequency and birth rates of new bone remodeling units, and possibly to enhance osteon mineralization, may also contribute to the reduction in fractures. The clinical pharmacology of bisphosphonates is characterized by low intestinal absorption, but highly selective localization and retention in bone. Significant side effects are minimal. Current issues with bisphosphonates include the introduction of new compounds, the choice of therapeutic regimen (e.g., the use of intermittent dosing rather than continuous), intravenous vs. oral therapy, the optimal duration of therapy, the combination with other drugs, and extension of their use to other conditions, including steroid-associated osteoporosis, male osteoporosis, arthritis, and osteopenic disorders in childhood. Bisphosphonates inhibit bone resorption by being selectively taken up and adsorbed to mineral surfaces in bone, where they interfere with the action of osteoclasts. It is likely that bisphosphonates are internalized by osteoclasts and interfere with specific biochemical processes and induce apoptosis. The molecular mechanisms by which these effects are brought about are becoming clearer. Recent studies show that bisphosphonates can be classified into at least two groups with different modes of action. Bisphosphonates that closely resemble pyrophosphate (such as clodronate and etidronate) can be metabolically incorporated into nonhydrolysable analogues of ATP that may inhibit ATP-dependent intracellular enzymes. The more potent, nitrogen-containing bisphosphonates (such as pamidronate, alendronate, risedronate, and ibandronate) are not metabolized in this way but can inhibit enzymes of the mevalonate pathway, thereby preventing the biosynthesis of isoprenoid compounds that are essential for the post-translational modification of small GTPases. The inhibition of protein prenylation and the disruption of the function of these key regulatory proteins explains the loss of osteoclast activity and induction of apoptosis. These different modes of action might account for subtle differences between compounds in terms of their clinical effects. In conclusion, bisphosphonates are now established as an important class of drugs for the treatment of bone diseases, and their mode of action is being unraveled. As a result, their full therapeutic potential is gradual.

Bone 1999 Jul;25(1):97-106

Continuous therapy with pamidronate, a potent bisphosphonate, in postmenopausal osteoporosis.

There is a need for effective and acceptable therapies for postmenopausal osteoporosis. The bisphosphonates show promise in this role, but the effects of the potent bisphosphonates in established osteoporosis have not yet been reported. We performed a 2-yr, randomized, double blind, placebo-controlled trial of pamidronate (150 mg/day) in 48 postmenopausal osteoporotic women. Bone mineral density of the total body, lumbar spine and proximal femur was measured every six months by dual energy x-ray absorptiometry. Bone mineral density increased progressively in the total body (1.9 +/- 0.7%; P < 0.01), lumbar spine (7.0 +/- 1.0%; P < 0.0001), and femoral trochanter (5.4 +/- 1.3%; P < 0.001) in subjects receiving pamidronate, but did not change significantly in those receiving placebo. There were significant decreases in bone density at both the femoral neck (P < 0.02) and Ward's triangle (P < 0.01) in subjects taking placebo, which did not occur in the pamidronate group. The differences between the treatment groups were significant at all sites (0.0001 < P < 0.05) except Ward's triangle. Vertebral fracture rates were 13/100 patient yr in the

pamidronate group and 24/100 patient yr in those receiving placebo ($P = 0.07$), and there was a nonsignificant trend toward height loss being less in those receiving pamidronate ($P = 0.16$). It is concluded that pamidronate is an effective therapy in postmenopausal osteoporosis.

J Clin Endocrinol Metab 1994 Dec;79(6):1595-9

Continued on Page 4 of 4

[Back to the Magazine Forum](#)

ABSTRACTS

Page 4 of 4

Sports endurance

Health implications of creatine: can oral creatine supplementation protect against neurological and atherosclerotic disease?

Major achievements made over the last several years have highlighted the important roles of creatine and the creatine kinase reaction in health and disease. Inborn errors of metabolism have been identified in the three main steps involved in creatine metabolism: arginine: glycine amidinotransferase (AGAT), S-adenosyl-L-methionine: N-guanidinoacetate methyltransferase (GAMT) and the creatine transporter. All these diseases are characterized by a lack of creatine and phosphorylcreatine in the brain, and by (severe) mental retardation. Similarly, knockout mice lacking the brain cytosolic and mitochondrial isoenzymes of creatine kinase displayed a slightly increased creatine concentration, but no phosphorylcreatine in the brain. These mice revealed decreased weight gain and reduced life expectancy, disturbed fat metabolism, behavioral abnormalities and impaired learning capacity. Oral creatine supplementation improved the clinical symptoms in both AGAT and GAMT deficiency, but not in creatine transporter deficiency. In addition, creatine supplementation displayed neuroprotective effects in several animal models of neurological disease, such as Huntington's disease, Parkinson's disease or amyotrophic lateral sclerosis. All these findings pinpoint to a close correlation between the functional capacity of the creatine kinase/phosphorylcreatine/creatine system and proper brain function. They also offer a starting-point for novel means of delaying neurodegenerative disease, and/or for strengthening memory function and intellectual capabilities. Finally, creatine biosynthesis has been postulated as a major effector of homocysteine concentration in the plasma, which has been identified as an independent graded risk factor for atherosclerotic disease. By decreasing homocysteine production, oral creatine supplementation may, thus, also lower the risk for developing, e.g., coronary heart disease or cerebrovascular disease. Although compelling, these results require further confirmation in clinical studies in humans, together with a thorough evaluation of the safety of oral creatine supplementation.

Neuroscience 2002;112(2):243-60

Effects of creatine supplementation on exercise performance and muscular strength in amyotrophic lateral sclerosis: preliminary results.

Creatine supplementation in humans has been reported to enhance power and strength both in normal subjects and in patients with various neuromuscular diseases. The purpose of this study was to examine the effects of supplementation on exercise performance and maximal voluntary isometric muscular contraction (MVIC) in amyotrophic lateral sclerosis (ALS) patients. We report the results obtained in 28 patients with probable/definite ALS. In each patient we acquired the dynamometric measurement of MVIC in 10 muscle groups of upper and lower limbs and a measure of fatigue by means of a high-intensity intermittent protocol in elbow flexors and knee extensors muscles. All patients completed the protocols at the baseline and after supplementation of 20 g per day for seven days and after supplementation of 3 g per day for three and six months. MVIC increased after seven days of supplementation in 20 patients (70%) in knee extensors and in 15 (53%) of them also in elbow flexors. A statistically significant difference between pre and post-treatment mean values of MVIC was found both in elbow flexors ($P < 0.05$) and knee extensors ($p < 0.04$). The analysis of the slopes of fatigue test showed a statistically significant improvement after seven days of supplementation in 11 patients (39%) in elbow flexors and in nine patients (32%) also in knee extensors muscles. During the six month follow-up period all the examined parameters showed a linear progressive decline. In conclusion, our preliminary results have demonstrated that supplementation temporarily increases maximal isometric power in ALS patients so it may be of potential benefit in situations such as high intensity activity and it can be proposed as a symptomatic treatment.

J Neurol Sci 2001 Oct 15;191(1-2):139-44

DHEA treatment reduces fat accumulation and protects against insulin resistance in male rats.

The purpose of this study was to determine whether administration of dehydroepiandrosterone (DHEA) protects male rats against the accumulation of body fat and the development of insulin resistance with advancing age. We found that supplementation of the diet with 0.3% DHEA between the ages of five months and approximately 25 months resulted in a significantly lower final body weight (DHEA, 593 +/- 18 g vs control, 668 +/- 12 g, $p < 0.02$), despite no decrease in food intake. Lean body mass was unaffected by the DHEA, and the lower body weight was due to a approximately 25% reduction in body fat. The rate of glucose disposal during a euglycemic, hyperinsulinemic clamp was 30% higher in the DHEA group than in the sedentary controls due to a greater insulin responsiveness. The DHEA administration was as effective in reducing body fat content and maintaining insulin responsiveness as exercise in the form of voluntary wheel running. The DHEA had no significant effect on muscle GLUT4 content. A preliminary

experiment provided evidence suggesting that insulin signaling, as reflected in binding of phosphatidylinositol 3-kinase to the insulin receptor substrate-1, was enhanced in the DHEA-treated and wheel running groups as compared to controls. These results provide evidence that DHEA, like exercise, protects against excess fat accumulation and development of insulin resistance in rats.

J Gerontol A Biol Sci Med Sci 1998 Jan;53(1):B19-24

Herbal ephedra/caffeine for weight loss: a six month randomized safety and efficacy trial.

OBJECTIVE: To examine long-term safety and efficacy for weight loss of an herbal Ma Huang and Kola nut supplement (90/192 mg/day ephedrine alkaloids/caffeine). **DESIGN:** Six month randomized, double-blind placebo controlled trial. **SUBJECTS:** A total of 167 subjects (body mass index (BMI) 31.8 \pm 4.1 kg/m²) randomized to placebo (n=84) or herbal treatment (n=83) at two outpatient weight control research units. **MEASUREMENTS:** Primary outcome measurements were changes in blood pressure, heart function and body weight. Secondary variables included body composition and metabolic changes. **RESULTS:** By last observation carried forward analysis, herbal vs placebo treatment decreased body weight (-5.3 \pm 5.0 vs -2.6 \pm 3.2 kg, P<0.001), body fat (-4.3 \pm 3.3 vs -2.7 \pm 2.8 kg, P=0.020) and LDL-cholesterol (-8 \pm 20 vs 0 \pm 17 mg/dl, P=0.013), and increased HDL-cholesterol (+2.7 \pm 5.7 vs -0.3 \pm 6.7 mg/dl, P=0.004). Herbal treatment produced small changes in blood pressure variables (+3 to -5 mmHg, P \leq 0.05), and increased heart rate (4 \pm 9 vs -3 \pm 9 bpm, P<0.001), but cardiac arrhythmias were not increased (P>0.05). By self-report, dry mouth (P<0.01), heartburn (P<0.05), and insomnia (P<0.01) were increased and diarrhea decreased (P<0.05). Irritability, nausea, chest pain and palpitations did not differ, nor did numbers of subjects who withdrew. **CONCLUSIONS:** In this six month placebo-controlled trial, herbal ephedra/caffeine (90/192 mg/day) promoted body weight and body fat reduction and improved blood lipids without significant adverse events.

Int J Obes Relat Metab Disord 2002 May;26(5):593-604

Nutrition and dietary supplements.

Quality and number of subjects in blinded controlled clinical trials about the nutrition and dietary supplements discussed here is variable. Glucosamine sulfate and chondroitin sulfate have sufficient controlled trials to warrant their use in osteoarthritis, having less side effects than currently used nonsteroidal anti-inflammatory drugs, and are the only treatment shown to prevent progression of the disease. Dietary supplements of ephedrine plus caffeine for weight loss (weight loss being the current first line recommendation of physicians for osteoporosis) show some promise, but are not sufficient in number of study subjects. Phenylpropanolamine is proven successful in weight loss. Both ephedrine and phenylpropanolamine have resulted in deaths and hence are worrisome as an over-the-counter dietary supplement. Other commonly used weight loss supplements like Cola acuminata, dwarf elder, yohimbine and garcinia cambogia are either lacking controlled clinical trials, or in the case of the last two supplements, have clinical trials showing lack of effectiveness (although garcinia has been successful in trials as part of a mixture with other substances, it is unclear if it was a necessary part of the mixture). Safety of these weight loss supplements is unknown. Chromium as a body building supplement for athletes appears to have no efficacy. Creatine may help more in weight lifting than sprinting, but insufficient study subjects and safety information make more studies necessary. Carbohydrate loading is used commonly before endurance competitions, but may be underused as it may be beneficial for other sport performances. Supplements for muscle injury or cramps have had too few studies to determine efficacy. Although proper rehydration with fluids and electrolytes is necessary, a paucity of actual studies to maximize prophylactic treatment for exercise induced cramping still exists. Nutritional supplements for cardiovascular disorders are generally geared to prevention. The United States Department of Agriculture has good recommendations to prevent atherosclerosis; a stricter version by Ornish was shown to reverse coronary heart disease, and the low meat, high fruit, and vegetable DASH diet has been found to decrease hypertension. The epidemiologic studies of hyperhomocysteinemia are impressive enough to give folic acid (or vitamin B6 or B12) supplements to those with elevated homocysteine levels and test patients who have a history of atherosclerotic disease, but no controlled clinical trials have been completed. Soluble fiber has several positive studies in reduction of cholesterol levels and generally is accepted. The data on vitamin E are the most confusing. This vitamin was not helpful in cerebrovascular prevention in China and not helpful at relatively small doses (50 mg) in the United States or Finland against major coronary events. Levels of 400 mg appeared to decrease cardiovascular disease in the United States in studies based on reports by patients and in one large clinical trial. Vitamin E also was successful in prevention of restenosis after PTCA in one clinical trial. Both of these clinical trials need to be repeated in other developed country populations. Some nutritional and dietary supplements are justifiably useful at this point in time. Several meet the criteria of a late Phase 3 FDA clinical trial (where it would be released for public use), but many dietary supplements have insufficient numbers of studies. Some deaths also have occurred with some supplements. If these supplements were required to undergo clinical trials necessary for a new drug by the FDA, they would not be released yet to the public. Several nontoxic supplements appear promising, though need further study. Because they have essentially no toxicity (such as folic acid with B12, soluble fiber and vitamin E) and may have efficacy, some of these supplementations may be useful now, without randomized clinical trials.

Phys Med Rehabil Clin N Am 1999 Aug;10(3):673-703

Ephedrine, caffeine and aspirin: safety and efficacy for treatment of human obesity.

The safety and efficacy of a mixture of ephedrine (75 to 150mg), caffeine (150mg) and aspirin (330mg), in divided premeal doses, were investigated in 24 obese humans (mean BMI 37.0) in a randomized double blind placebo-controlled trial. Energy intake was not restricted. Overall weight loss over eight weeks was 2.2kg for ECA vs. 0.7 kg for placebo ($p < 0.05$). Eight of 13 placebo subjects returned five months later and received ECA in an unblinded crossover. After eight weeks, mean weight loss with ECA (ephedrine, caffeine and aspirin) was 3.2 kg vs 1.3 kg for placebo ($p = 0.036$). Six subjects continued on ECA for seven to 26 months. After five months on ECA, average weight loss in five of these was 5.2 kg compared to 0.03 kg gained during five months between studies with no intervention ($p = 0.03$). The sixth subject lost 66 kg over 13 months by self-imposed caloric restriction. In all studies, no significant changes in heart rate, blood pressure, blood glucose, insulin, and cholesterol levels, and no differences in the frequency of side effects were found. ECA in these doses is thus well tolerated in otherwise healthy obese subjects, and supports modest, sustained weight loss even without prescribed caloric restriction, and may be more effective in conjunction with restriction of energy intake.

Int J Obes Relat Metab Disord 1993 Feb;17 Suppl 1:S73-8

Detection and determination of anabolic steroids in nutritional supplements.

A method is described for the determination of anabolic steroids including testosterone, 19-nor-4-androstene-3,17-dione, 4-androstene-3,17-dione and nandrolone in food supplements. Initial clean-up is done by HPLC followed by determination with GC/MS. A 'contaminated' food supplement was analyzed and appeared to contain 19-nor-4-androstene-3,17-dione and 4-androstene-3,17-dione. One capsule of this nutritional supplement was ingested by five male volunteers. Urine samples were collected and analyzed by GC/MS and GC/MS-MS. Neither the ratio testosterone/epitestosterone, nor the ratio androstenedione/epitestosterone increased significantly. Concentrations above 2 ng/ml for norandrosterone, the major metabolite of nandrolone, were detected until 48-144 h after ingestion of the food supplement.

J Pharm Biomed Anal 2001 Jul;25(5-6):843-52

Effect of oral androstenedione on serum testosterone and adaptations to resistance training in young men: a randomized controlled trial.

CONTEXT: Androstenedione, a precursor to testosterone, is marketed to increase blood testosterone concentrations as a natural alternative to anabolic steroid use. However, whether androstenedione actually increases blood testosterone levels or produces anabolic androgenic effects is not known. OBJECTIVES: To determine if short- and long-term oral androstenedione supplementation in men increases serum testosterone levels and skeletal muscle fiber size and strength and to examine its effect on blood lipids and markers of liver function. DESIGN AND SETTING: Eight-week randomized controlled trial conducted between February and June 1998. PARTICIPANTS: Thirty healthy, normotestosterogenic men (aged 19 to 29 years) not taking any nutritional supplements or androgenic-anabolic steroids or engaged in resistance training. INTERVENTIONS: Twenty subjects performed eight weeks of whole-body resistance training. During weeks 1, 2, 4, 5, 7 and 8, the men were randomized to either androstenedione, 300 mg/d ($n = 10$), or placebo ($n = 10$). The effect of a single 100-mg androstenedione dose on serum testosterone and estrogen concentrations was determined in 10 men. MAIN OUTCOME MEASURES: Changes in serum testosterone and estrogen concentrations, muscle strength, muscle fiber cross-sectional area, body composition, blood lipids, and liver transaminase activities based on assessments before and after short- and long-term androstenedione administration. RESULTS: Serum free and total testosterone concentrations were not affected by short- or long-term androstenedione administration. Serum estradiol concentration (mean [SEM]) was higher ($P < .05$) in the androstenedione group after two (310 [20] pmol/L), five (300 [30] pmol/L) and eight (280 [20] pmol/L) weeks compared with presupplementation values (220 [20] pmol/L). The serum estrone concentration was significantly higher ($P < .05$) after two (153 [12] pmol/L) and five (142 [15] pmol/L) weeks of androstenedione supplementation compared with baseline (106 [11] pmol/L). Knee extension strength increased significantly ($P < .05$) and similarly in the placebo (770 [55] N vs 1095 [52] N) and androstenedione (717 [46] N vs 1024 [57] N) groups. The increase of the mean cross-sectional area of type 2 muscle fibers was also similar in androstenedione (4703 [471] vs 5307 [604] mm²; $P < .05$) and placebo (5271 [485] vs 5728 [451] mm²; $P < .05$) groups. The significant ($P < .05$) increases in lean body mass and decreases in fat mass were also not different in the androstenedione and placebo groups. In the androstenedione group, the serum high-density lipoprotein cholesterol concentration was reduced after two weeks (1.09 [0.08] mmol/L [42 (3) mg/dL] vs 0.96 [0.08] mmol/L [37 (3) mg/dL]; $P < .05$) and remained low after five and eight weeks of training and supplementation. CONCLUSIONS: Androstenedione supplementation does not increase serum testosterone concentrations or enhance skeletal muscle adaptations to resistance training in normotestosterogenic young men and may result in adverse health consequences.

JAMA 1999 Jun 2;281(21):2020-8

Androgen use by athletes: a reevaluation of the health risks.

It has been estimated that one to three million male and female athletes in the United States have used androgens. Androgen use has been associated with liver dysfunction, altered blood lipids, infertility, musculotendinous injury and psychological abnormalities. Although androgens have been available to athletes for more than 50 years, there is little evidence to show that their use will cause

any long-term detriment. Furthermore, the use of moderate doses of androgens results in side effects that are largely benign and reversible. It is our contention that the incidence of serious health problems associated with the use of androgens by athletes has been overstated.

Can J Appl Physiol 1996 Dec;21(6):421-40

[Back to the Magazine Forum](#)

All Contents Copyright © 1995-2009 Life Extension Foundation All rights reserved.

LifeExtension®

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.