A Review of Nutrients and Botanicals in the Integrative Management of Cognitive Dysfunction

Parris M. Kidd, PhD

Abstract

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 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;4(3):144-161)

Introduction

Progressive memory loss, dementia, and related cognitive dysfunction states have become a catastrophic medical and social problem in Western societies. According to the U.S. National Institute on Aging, in the United States alone there are as many as four million cases of the most extreme form of cognitive breakdown, namely the dementia of Alzheimer's Disease.[1]

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Other types of dementia add to the burden imposed on society by this tragic human affliction. For every case of diagnosed dementia there are probably several additional cases of individuals with Mild Cognitive Impairment (MCI)[2] or ARCD (Age-Related Cognitive Decline).[3]

Cognitive dysfunction often is taken for granted, both by health-care practitioners and by the public at large. A pattern of progressive cognitive decline which usually becomes noticeable in middle age has traditionally been dismissed as part of "getting old." This assumed causal link between aging and cognitive dysfunction is not scientifically supportable, as many individuals age into their 90s with only modest loss of mental skills.[4] But for subjects who show measurable cognitive decline, failure to positively intervene can prove disastrous, as abnormally lowered cognitive performance during the sixth decade has been linked to increased risk of dementia in later life.[1] The dementias, as with other degenerative diseases, necessitate an integrative-wholistic approach which stresses early intervention.

Despite intensive clinical testing over the past two decades, the allopathic management of dementia and other cognitive dysfunction states is still not much better than palliative. On the other hand, numerous controlled clinical trials have demonstrated improved cerebral performance from dietary supplementation with specific nutrients and botanicals, generally with a minimum degree of risk. Any nutrient can benefit brain function when a systemic deficiency state exists, but a handful of nutrients and botanicals offer clinically-significant benefits to memory and the allied cognitive functions. Included in this unique group are phosphatidylserine, acetyl-L-carnitine, vinpocetine, *Ginkgo biloba* extract, and *Bacopa monniera*. This review examines the proven cognition-enhancing effects of each of these five nutritional supplements.

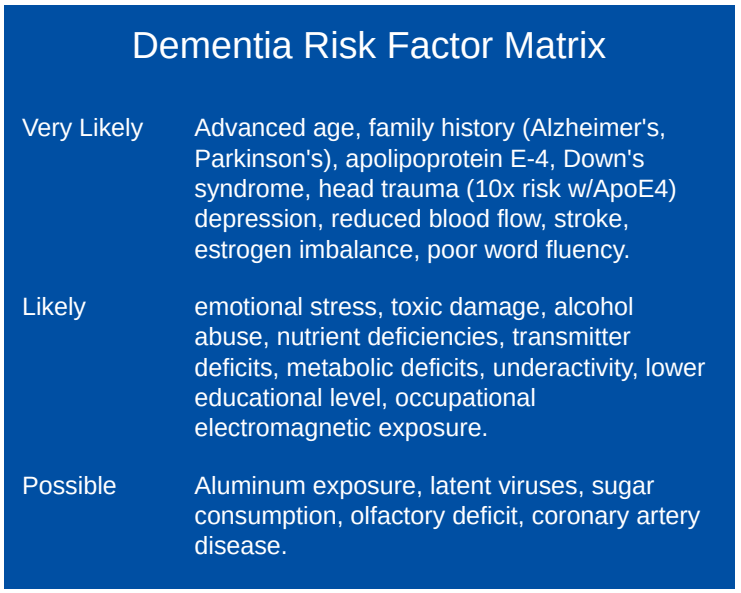
Nature and Scope of The Cognitive Dysfunction Problem

The term "dementia" connotes cognitive deterioration so severe that social and occupational functioning is markedly impaired, to the extent the afflicted individual can no longer be a fully independent and productive citizen.[5] As the disease progresses, personality changes emerge, and subsequently mood lability and social withdrawal take hold. Advanced dementia is characterized by progressive loss of the personality and increasing inability to perform even the simplest tasks. Mild Cognitive Impairment (MCI) features abnormal memory loss relative to one's age, but without the other changes which characterize dementia.[2] Age-Related Cognitive Decline (ARCD) is a diagnosis reserved for abnormal cognitive function less severe than dementia in persons older than 50.[3]

Currently, the majority of diagnosed dementias are thought to be Alzheimer's Disease, and "Alzheimer's" has now become a popular icon used to stigmatize memory problems of any degree. Sadly, this societal preoccupation with Alzheimer's is not without factual basis; within the general U.S. population one in 10 of those aged 75-85 could progress to Alzheimer's, and as many as one in three of those 85 and over.[1] Such widespread occurrence of severe cognitive dysfunction, featuring uncoupling from one's personal history, detachment from one's surroundings, and finally the loss of one's very personality, is without historical precedent.

A workable approach to curbing this virtual epidemic of dementia hinges on the development of a strategy for halting (or at least slowing) cognitive decline before it crosses the threshold to dementia. Research is progressing towards the definition of a "window of opportunity" for effective intervention to halt the progression to dementia. From the point of birth forward, the old adage, "Use it or lose it," applies to the brain. The brain's situation

Figure 1. The matrix of interactive risk factors for dementia.[10-18]



is somewhat analogous to skeletal mass, in that the more dense the brain circuitry is earlier in life, the more that can be lost later in life before function becomes seriously compromised.[6]

With the tragic exception of those individuals who suffer early-onset forms of cognitive breakdown, the window of opportunity for positive intervention against dementia can extend at least into the sixth decade of life. For many subjects this is the stage during which cognitive losses become measurable, sometimes with the diagnosis of Age Related Cognitive Decline. ARCD signifies a symptom cluster of accelerated mental decline documented after the age of 50. By definition ARCD is an age-linked condition, not a disease. Although ARCD is not as severe as dementia, the worst cases of ARCD are at higher risk for dementia,[3,7] as are subjects with MCI.[2]

Earlier prediction of dementia risk is urgently needed, and probably will come from advances in non-invasive brain imaging techniques.[8] Small et al have found measures of cerebral metabolism, objective memory performance, and educational level may predict subsequent cognitive decline in middle-age.[9] By quantitatively imaging the baseline metabolic activities of the brain and the capacities of the various zones to "turn on" in response to stimulation, it should become possible to define a "pre-clinical" stage of accelerated nerve network loss, which for many subjects is possible as early as the fourth decade of life.

The window of opportunity for salvaging brain function probably is closed when so many circuits have been lost that the remaining circuits cannot sufficiently adapt to maintain an acceptable level of learning, recollection, or concentration. Past this point, the individual will be hard-pressed to remain productive and live independently. Patients with moderate-to-severe dementia are likely to experience only symptomatic improvement from therapeutic intervention, since so little brain circuitry remains from which to attempt to rebuild. Whatever the diagnostic advances, early intervention in cognitive dysfunction states will remain crucial to their management.

The Matrix of Risk Factors for Dementia

As with other degenerative disease, dementia progression is associated with various risk factors. The reduction or elimination of known risk factors is one manageable step toward the prevention or slowing of dementia, and of course can be set into motion prior to the onset of noticeable signs and symptoms. A matrix of risk factors for dementia is presented in Figure 1, as assembled from various sources.[10-18] The listed factors all have some association with dementia initiation or progression, and are likely to interact in additive or even synergistic fashion. These dementia risk factors are likely to differ greatly in their mechanisms, timing of onset, and degrees of impact, but all would tend to accelerate the functional breakdown of cells, networks, and eventually entire circuits within the brain.

The body of evidence supporting a multifactorial etiology for dementia continues to expand. Simplistic cause-and-effect relationships are rare, as, for example, *dementia pugilistica* described for brain-damaged boxers.[5] Genetic contributions to Alzheimer's are being clarified by way of study of the ApoE4 system (apolipoprotein E4). ApoE4 does increase the risk of Alzheimer's, particularly early-onset (clinically evident prior to the age of 65), but ApoE4 penetrance is far from complete, as subjects homozygous for ApoE4 can have a normal lifespan without developing Alzheimer's. Notably, a history of head trauma may interact with ApoE4 homozygosity to generate a ten-fold risk of Alzheimer's.[15]

Many adverse exogenous factors have been linked to abnormal memory loss. One example is the environmental pollutants. Brain tissue, with its high metabolic rate and high content of polyunsaturated lipids, is particularly susceptible to peroxidative toxic attack. As has been documented,[19] almost without exception substances foreign to the body (the "xenobiotics") are potentially toxic by way of oxidative mechanisms. The massive degree to which xenobiotics now contaminate the environment invites analysis of their causal contribution to the catastrophic cerebral breakdown now widespread in industrialized societies.

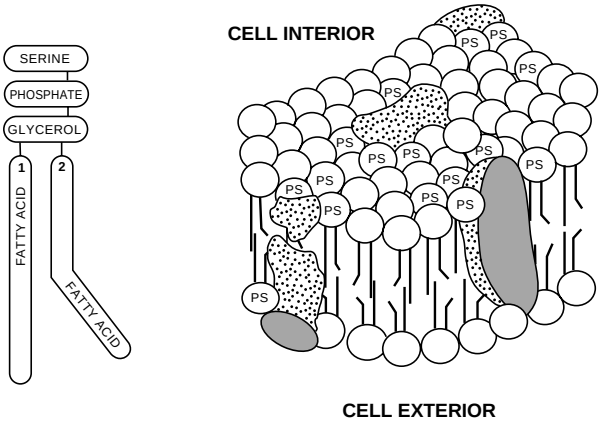
The implications for human health of ongoing and *de novo* xenobiotic contamination could not fail to challenge the rational observer. In 1995 more than 220 billion pounds of synthetic organic chemicals were synthesized around the planet, and undoubtedly much of this material found its way into the air, water, soils, and foodstuffs.[20] The entire planet is affected: breast milk from every country now shows contamination with organics, most often chlorinated hydrocarbons, at the parts per million level, and children are functionally affected.[21,20] Chlorinated hydrocarbons often persist in the environment: DDT residues continue to thin the eggshells of the United States' national bird, the golden eagle, more than 20 years after DDT's commercial use was banned by law.

Other known risk factors for dementia are legally sanctioned and even promoted for consumption by the general population. One category is pharmaceutical drugs—as much as 10 percent of all apparent dementia cases may be induced by sleep aids, sedatives, antidepressants, or drugs from other categories. Fortunately, these are reversible to some degree, if the responsible physician is sufficiently alert to make the connection.[22]

Another agent likely to be a major risk factor for dementia is chronic emotional stress and/or the inability to cope with it. A 1998 McGill University study confirmed with human subjects the results of research from many primate and other animal studies.[23] This study tracked good stress copers and bad stress copers for five years, and found poor stress coping is linked to hippocampal atrophy and accelerated cognitive deterioration. This rather dramatic human outcome is consistent with animal studies, in which sustained emotional stress reduced the circulation to the brain and caused the death of nerve cells in the hippocampus, the major brain region responsible for memory acquisition.

Interactions and overlaps between definite, likely, and possible risk factors of the dementia matrix (refer to Figure 1) will tend to cumulatively reduce the functional and structural capacities of the human brain. At its peak performance state, which generally is in place around the third to fourth decade of life, the human brain may have up to 10,000 connections per each of its approximately 100 billion nerve cells, yielding a "ball-park" figure of as many as 1,000 trillion cell-to-cell connections—literally a quadrillion separate pathways. Extreme losses of circuitry are the hallmark of dementia. Dementia is not simply accelerated aging; different rates of loss and patterns of loss occur. In the cortex, healthy

Figure 2. The molecular organization of phosphatidylserine (left) and its preferred positioning close to integral membrane proteins (right). [52]



Left: Molecular organization of phosphatidylserine (PS). Right: PS is preferentially distributed in the bilayer portion of the cell membrane which faces the cell's interior. PS associates with key membrane proteins.

individuals typically lose up to 20 percent of their connections by the ninth decade, but in Alzheimer's up to 90 percent is lost.[24] By the end of life, an Alzheimer's patient may have virtually nothing remaining of the CA1 region of the hippocampus, an area crucial for memory formation.[25]

The cholinergic hypothesis of geriatric brain dysfunction, first articulated by Bartus, until recently provided the dominant rationale for the development of drugs to treat dementia.[26] In brief, this hypothesis suggested that since (a) acetylcholine (ACh) and the cholinergic neurons which secrete ACh are important for memory and cognition, and (b) ACh and cholinergic pathways are among the first to become impaired in Alzheimer's, then (c) drugs which increase ACh levels or cholinergic activities in the brain should fruitfully treat Alzheimer's. After many cholinergic-acting candidates were tested over more than twenty years, two of them emerged with licenses for use in the United States against Alzheimer's disease. Both have poor benefit-to-risk profiles. Tacrine, the first to be approved, gave little benefit and had high liver toxicity.[27,28] Donepezil had less liver toxicity, but had other side-effects of its own, and also gave only minimal benefit.[29,30] With the cholinergic hypothesis now proven to be inadequate, better consideration should be afforded to therapies which work by other mechanisms.

Phosphatidylserine (PS)

Phosphatidylserine (PS) is active at cell membranes, and is a major building block for nerve cells, which are rich in membranes.[31] Phospholipids make up the continuous matrix of the outer membrane which separates every cell's living interior from the non-living exterior. All the cells of the human body contain PS and rely on its presence for such survival functions as ATP production, ionic homeostasis, and cell-level activation and deactivation. PS is particularly enriched in the membrane systems of nerve cells, including synaptic membrane zones which link each nerve cell to others. Extensive double-blind trials and other clinical testing have established that PS consistently benefits memory, learning, concentration, word choice, and other measurable cognition parameters, as well as mood and the capacity to cope with stress.[31-36]

Clinical research on PS began in Europe and extends back more than two decades. Double-blind trials conducted in Italy, Belgium, and Germany, as well as in the United States, demonstrate PS benefits older subjects with mild to moderate dementia, as well as middle-aged subjects with the accelerated cognitive decline which characterizes ARCD.[37-42] In the 1991 U.S. trial on ARCD conducted by Crook et al, PS seemed to partially restore certain learning and recall capacities.[7] On name-face matching, for example, PS improved performance from a functional age of 64 to a functional age of 52.

PS is extremely versatile in its clinical application. In addition to its recognized cognitive benefits, in patients with advanced dementia PS will often improve sociability, attention to personal welfare, and cooperation with caregivers.[33, 36, 37, 42] PS consistently improves mood, relieving symptoms of anxiety and depression in elderly women.[43] PS also improves hypothalamic-pituitary-adrenal integration, thereby improving adaptability to stress and restoring hormone rhythms which often decompensate with advancing age.[44] Thus, in elderly men PS partially restored thyroid-stimulating hormone and prolactin secretion rhythms.[45]

The benefits of PS are not restricted to the middle-aged and elderly. In young, healthy males PS also can improve the process of coping with stress. Three double-blind trials established that in young, healthy male athletes subjected to heavy exercise regimens PS reduced cortisol production while controlling muscle soreness and other aspects of "overtraining."[32, 34, 35]

PS also can benefit children. Two open-label, pilot studies found PS improved attention, behavior, and learning performance, and ameliorated negative mood in 15 out of 20 children aged 4-19 years.[46, 47] PS reinforced medical interventions which were already in place, such as Ritalin® therapy, and further raised the degree of functioning of these children.

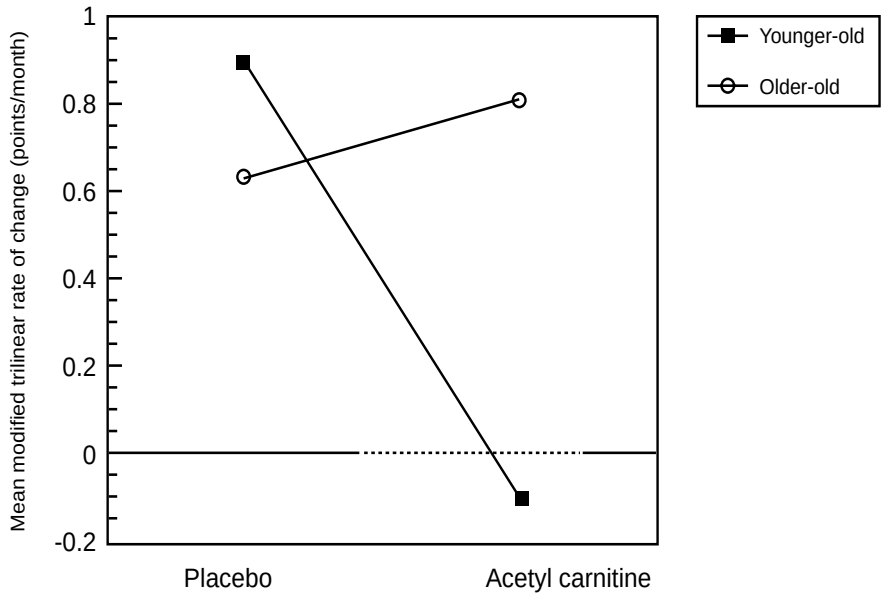
The original source of PS for nutritional supplementation was bovine brain, but as this source came into disrepute in Europe the production source was switched to soy. Although few clinical trials have been conducted utilizing soy-PS, it appears to work as well as PS from bovine brain.[48,49] The molecular organization of PS is illustrated in Figure 2, alongside a diagrammatic representation of its preferred intra-membrane associations with key proteins, such as the ATPases, ion gates, and signal transduction assemblies. The "tails" of soy PS may differ from those of bovine brain PS, but in any case these are "customized" for use on an organ-by-organ basis after the greater PS molecule is absorbed.[50] The indispensable "business end" of the PS molecule is the headgroup, for which native serine amino acid or other phospholipids cannot substitute.[51]

Findings from numerous experiments conducted with PS on aging animals, and on nerve cell preparations in culture, suggest PS may have trophic action in aging brain tissues, i.e., PS somehow encourages the regrowth of damaged nerve networks. In old rats, PS conserved nerve cell number, size, and functional capacities at the levels normal for young rats.[53] PS also may work synergistically with growth factor substances to bring about the addition or restoration of nerve networks in the brain. Imaging techniques performed on demented individuals demonstrate PS can revitalize metabolism across the brain.[54]

The protein known as NGF (Nerve Growth Factor) has been demonstrated to regulate nerve development and help maintain nerve networks already in place, also boosting cellular antioxidant defenses.[55] NGF operates by way of NGF receptors situated on the outer surfaces of nerve cells, particularly in the hippocampus and the cortex, which are the brain's main memory centers. As rats age, the receptors for NGF in the hippocampus tend to decline in number. For example, old rats with the lowest receptor densities performed most poorly on memory tests. In such aged rats, treatment with PS conserved the densities of receptors for NGF at higher levels characteristic of young rats. Simultaneously, PS improved the "intelligence" of these impaired rats toward levels resembling young, non-impaired rats.[53]

Effective intakes of PS range from 100 mg per day (for smaller children and for maintenance in healthy adults), through 300 mg/day for memory loss, and up to 600 mg/day for mood enhancement.[31] PS has an extremely favorable benefit-to-risk profile: its benefits are often remarkable, adverse effects from its

Figure 3. Acetyl-L-carnitine benefit for the "younger-old" over the "older-old" in Alzheimer's Disease, as elucidated by trilinear analysis. The line trending downward indicates deterioration, the line upward indicates improvement. From Brooks et al.[62]



use are virtually never seen, and its compatibility with most common drugs is established.

Acetyl-L-Carnitine

Acetyl-L-Carnitine (ALC) is an orthomolecule which offers major metabolic benefits to the brain. ALC is a metabolic cofactor for the conversion of fatty acids into energy within the mitochondria of the nerve cells, thereby helping to keep them supplied with energy.[56] ALC also provides acetyl-equivalents for the production of acetylcholine, one of the chemical transmitters. ALC is better absorbed than carnitine, its simpler analogue, and crosses the blood-brain barrier better than l-carnitine. A number of double-blind clinical trials suggest ALC may have clinical utility for the management of some forms of cognitive dysfunction.[57-61]

The latest and most sophisticated trial assessing ALC's benefit in Alzheimer's Disease (average subject age, 71 years)[61] failed to find statistically-significant differences for the ALC group versus the placebo group. However, a subsequent "trilinear analysis" by Brooks et al,[62] (see fig. 3) based on calculating the rates of change between successive time points over the one-year period of the trial, found ALC benefited the "younger-old" patients (ages 65 or less) over the "older-old" patients. The younger-old patients showed a slower rate of deterioration on the cognitive portion of the ADAS, the Alzheimer's Disease Assessment Scale.[63] They may actually have experienced slight improvement, while the older-old continued to lose ground to the disease during the course of the trial.

This finding helps explain some of the inconsistencies seen in previous controlled trials with ALC. There is no evidence to suggest ALC could delay the onset of dementia, but delaying dementia progression would still be a clinically meaningful benefit. Based on further calculations and projections, Brooks et al predicted the best age cut-off for ALC in dementia will prove to be 61 years.[62]

ALC has been employed in the management of other cognitive breakdown states. In one double-blind trial conducted with cognitively impaired ex-alcoholics aged 30-60 years, ALC improved memory, visuo-spatial capacity, and vocabulary recall when given at two grams per day over a test period of three months.[64] ALC's beneficial effects on the brain also extend beyond cognition enhancement. In controlled trials, ALC improved depression as well as cooperation, sociability, and attention to personal appearance, though it did not consistently improve anxiety.[65]

Metabolic studies, many of them conducted in animals and a few non-invasively in humans with NMR (nuclear magnetic resonance) indicate ALC helps the brain maintain the constant supply of energy needed for effective homeostasis. Pettegrew et al found, using ^{31}NMR, that in demented patients ALC boosted the levels of phospholipid precursors for membrane synthesis, while benefiting various measures of cognitive performance.[66] This study represents a rare pairing of metabolic investigation with the clinical documentation of a beneficial agent. Its findings specifically suggest ALC facilitates phospholipid metabolism and could potentially synergize with PS.

As a general brain energizer, ALC partially protects against ischemic brain damage, and can be helpful for stroke victims.[67] ALC also offers survival potential to damaged neurons. In one *in vitro* study, ALC increased the production of nerve growth factor (NGF) by cultured nerve cells, and helped them respond better to NGF.[68] Treatment of aged rats with ALC partially halted the loss of NGF receptors, while improving performance on maze tests. These findings also suggest ALC, like PS, has trophic effects with potential clinical utility.

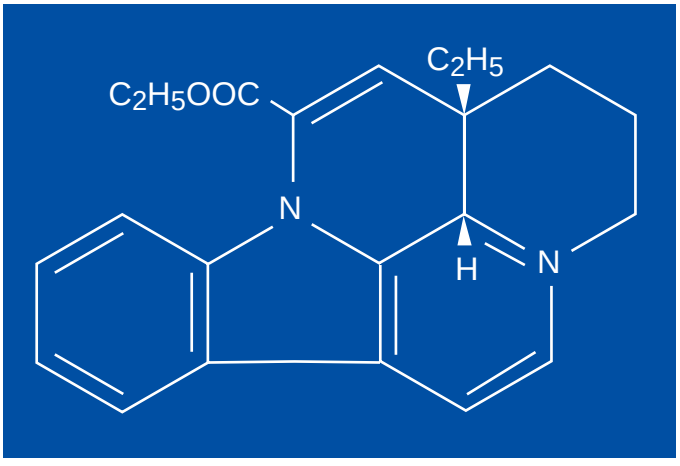
Relatively high intakes of ALC are required in order to best ensure chances for benefit. In the trials with cognitively impaired subjects, intakes ranged from 1,500 to 3,000 mg per day, with most trials using two grams or more. At these intake levels, ALC can intensify dream activity, and it may be contraindicated for subjects with epilepsy or bipolar conditions.[56]

Vinpocetine

Vinpocetine is an alkaloid found in the lesser periwinkle plant, *Vinca minor*. The structure of vinpocetine is illustrated in Figure 4. Vinpocetine has the most clinical promise for the management of vascular insufficiencies involving the brain. In double-blind trials conducted with patients suffering from mild-to-moderate vascular dementia, vinpocetine benefited memory, learning, and global clinical measures of cognitive performance.[69-71] Speech and language, but not mood or coordination, also was improved by vinpocetine. In the only double-blind trial conducted to date assessing vinpocetine's effect against Alzheimer's Disease, no significant benefits were reported.[72]

Vinpocetine may have clinical utility in the management of stroke sequelae, as suggested by an open-label trial conducted at 40 centers in Japan. The treatment design involved crossover every four weeks between vinpocetine, ifenprodil tartrate, and dihydroergotoxine mesylate.[73] Administered at 15 mg per day, vinpocetine produced slight-to-marked improvement in two-thirds of the patients, which was superior to the other two agents tested. This finding was in general accord with a review by these researchers of the results of 13 other similar trials. The rare vascular dementia of the Binswanger type features multiple small infarcts of the cerebral white

Figure 4. Structure of the alkaloid vinpocetine.



matter; the white matter which remains is highly vulnerable to further destruction because of widespread impairment of the microcirculation. In eight Binswanger patients vinpocetine improved the delivery of oxygen to these endangered zones, perhaps by adding to its primary vasodilating action an increase of red cell ATP levels.[74]

Vinpocetine is a highly potent vasodilator, acting by direct relaxation of the vascular smooth muscle. Vinpocetine enhances cerebral blood flow in patients with cerebrovascular disorders.[75] Patients from this population who also manifest increased blood viscosity are at greater risk for thrombotic complications. In one such group of patients, vinpocetine had a viscosity-lowering effect on the blood and plasma.[76] Vinpocetine is known to decrease platelet and red cell aggregation, and to increase red cell membrane flexibility in stroke patients, as well as in healthy subjects.[77-80] Any or all of these mechanisms could be involved in vinpocetine's capacity to lower the viscosity of the blood *in vivo*.

Vinpocetine has clinically substantiated anti-ischemic activity. Here vinpocetine does not have a "stealing" effect, i.e., to remove blood away from underperfused zones of ischemic damage, perhaps because it lowers blood viscosity sufficiently to allow blood flow to continue uninterrupted through these areas. In animal models of anoxia, vinpocetine reduced cerebral edema and prolonged survival.[71]

Many possible mechanisms underlie vinpocetine's clinical effects (see Nicholson[71] for a review). It partially blocks hypoxic damage to brain tissue, and is a good scavenger of hydroxyl radicals.[81] It has anticonvulsant action, possibly linked to its neuronal protective capacity and/or its modulation of several chemical transmitter systems. In these respects vinpocetine resembles adenosine, thought to be a major endogenous anticonvulsant and cerebral protectant; Vinpocetine happens to be an effective adenosine re-uptake inhibitor. It increases cerebral metabolism and raises ATP levels in nerve cells, perhaps also raising neuronal excitability more directly by modulating cellular enzymatic control systems.

The clinically validated dose range for vinpocetine is 15-45 mg per day. Side-effects may include skin eruptions, flushing, and sometimes gastrointestinal side-effects, but these are rarely serious enough to warrant discontinuation of therapy. A relatively unique aspect of vinpocetine's enhancement of blood flow is that it increases cerebral blood flow more than at the periphery, even though its vasodilator action is similar around the body. Its capacity to selectively enhance brain metabolism may account for this discrepancy, but in any case this property renders vinpocetine potentially safer than many pharmacologic vasodilators. Yet another clinically useful property of vinpocetine is its metal-chelating capacity, which was successfully put to use reversing tumoral calcinosis in hemodialysis patients with renal failure.[82]

With its highly effective vasodilatory action and capacity to improve small-vessel perfusion, vinpocetine could rival *Ginkgo biloba* extract as a therapy for vascular insufficiency. In any case, vinpocetine offers impressive benefits for retinal microcirculation and the circulation of the inner ear, joining Ginkgo as a rare treatment for tinnitus.[83]

Ginkgo biloba

Ginkgo biloba extract (herein abbreviated GbE) is the most clinically proven plant extract for the nutritional support of cerebral function. Many double-blind trials have been conducted with GbE, but generally these have been small and fraught with methodological errors; however, these errors have been sorted out in two meta-analyses. The meta-analysis is a statistically sophisticated re-assessment of an agent, generally based on grouping together all the double-blind trials in order to better assess benefits and risks. Out of the Ginkgo

meta-analyses have emerged somewhat more objective estimates of its benefit-to-risk profile.[84, 85]

Ginkgo's benefits for cognitive dysfunction and other symptoms of vascular insufficiency withstood the analytical rigor of a 1992 meta-analysis.[84] Out of the 40 double-blind trials compiled from the scientific literature, the six best were evaluated. These showed benefits—for as few as 17 percent of the elderly patients to as many as 71 percent of the younger patients—at dosages most typically 160 mg per day. Safety overall was rated quite good. Thus, for cognitive problems linked to vascular insufficiency, GbE stands with its limitations as an available therapeutic tool.

Ginkgo's benefits for the non-vascular dementia of Alzheimer's Disease are relatively minor. When carefully scrutinized, the highly-publicized double-blind trial of LeBars and his collaborators which appeared in a prestigious publication actually demonstrates a minimal degree of benefit.[86] LeBars et al reported that only 29 percent of their patients benefited from 120 mg per day of GbE, to an extent comparable to a six-month delay in disease progression. According to their analysis, the small proportion of patients who benefit from Ginkgo and the minor extent of benefit are both exceeded by high doses (160 mg per day) of tacrine, the first of the two pharmaceuticals approved for Alzheimer's Disease. But when prescribed at such high doses, tacrine is linked to a high frequency and severity of liver damage.[28]

In late 1998, Oken et al published a meta-analysis of Ginkgo for Alzheimer's.[85] Including the LeBars et al trial, they found only four trials which met their quality criteria. These totaled 212 subjects in each of the Ginkgo and placebo groups. The calculated "effect size" for benefit was 0.40, or a three-percent difference in the ADAS (Alzheimer Disease Assessment Scale)-cognitive subtest. This effect size was modest, even when compared against donepezil (Aricept®), the second approved drug for Alzheimer's, which they calculated had an effect size of 0.42-0.48.

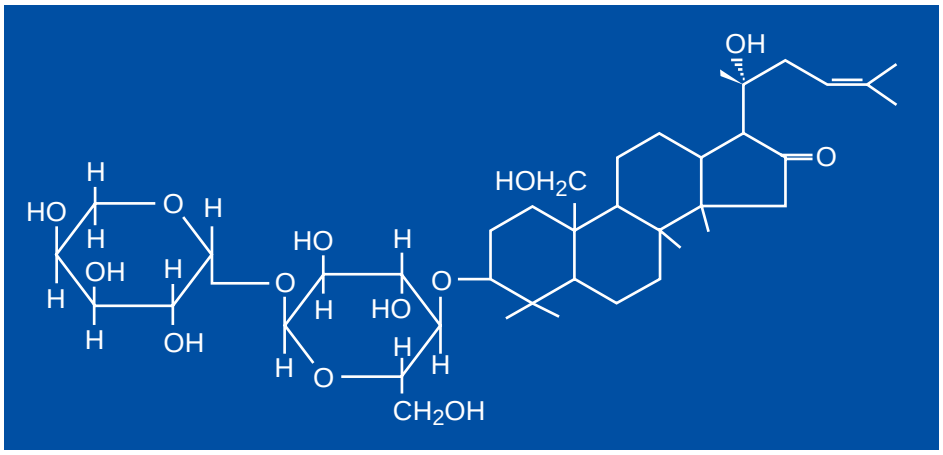
The clinical implications of this relatively small effect size for Alzheimer's patients' quality of life is unclear. The four GbE trials disagreed in the evaluations by clinicians, the patients' capacities for "activities of daily living," and the Relative's Rating Instrument, their functional rating scale. The four trials employed GbE doses of 120 or 240 mg per day; however, there was some suggestion from the data that the higher dose of 240 mg could be more effective.[85]

Ginkgo biloba extracts from different sources seem to have differing degrees of benefit.[84,87] Current moves by certain suppliers to increase the "potency" of their extracts by changing the makeup of Ginkgo's flavonoids and terpenes are rarely grounded in clinical testing, and could prove dangerous to consumers. There are reasons to expect that alteration of the basic profile of the standardized *Ginkgo biloba* extract could transform its anti-inflammatory, protective character into pro-inflammatory biochemistry.

In the face of the tremendous level of commercial promotion of Ginkgo extract, it is important for both consumers and health professionals interested in Ginkgo to understand "Ginkgo" has now become a kind of commodity in an opportunistic marketplace. Beyond the conclusions of the meta-analyses, which indicate the source of GbE can affect its clinical efficacy, electro-encephalographic (EEG) scanning techniques further indict the commodity preparations. The EEG studies confirm various GbE preparations have different EEG activation patterns, which might translate into varying degrees of clinical efficiency.[87,88]

The mechanisms of action of GbE are reasonably well established. The flavonoid constituents contribute mainly free radical scavenging and other antioxidant effects. The terpenes are antagonists of platelet-activating factor (PAF), which has myriad

Figure 5. Structure of a bacoside from *Bacopa monniera* (Bacoside A). From Badmaev.[93]



pro-inflammatory effects, including adverse effects on neuronal function. With respect to the brain, the compound extract has been found to (1) partially protect against experimental cerebral lipid peroxidation and edema; (2) protect brain neurons against heightened oxidative stress; (3) decrease neuronal injury following ischemia; and (4) protect receptors for chemical transmitters.[86] The clinical benefits observed with any Ginkgo extract are an outcome of the compounded actions of its many constituents, so not surprisingly the optimum activity of a GbE preparation depends on having a crucial internal balance between all these active constituents.

Ginkgo biloba extracts are not easy to manufacture, but are a necessary vehicle for the administration of Ginkgo. The use of whole Ginkgo leaf by itself or as an additive to the standardized extract, whether undertaken by naive herbalists or by parties with other motivations, is potentially harmful, since the whole leaf can carry toxic compounds.[89] Nor is the standardized extract guaranteed to be free of adverse effects. Documented side-effects of standardized GbE include very infrequent, but life-threatening, subdural bleeding.[90-92] *Hence the use of GbE in combination with blood-thinning drugs is emphatically contraindicated.* The doses of GbE used in controlled trials generally ranged from 112 mg to 360 mg per day of the 24:6 standardized extract (standardized to contain at least 24 percent ginkgo heterosides and six percent terpenes). Current indications are that doses from 160 mg and up will prove most consistently beneficial. GbE's cognition-enhancing effects are real, if modest, but quality extracts are called for and their application to some patients with serious conditions should be kept under professional supervision.

Bacopa monniera ("Brahmi")

Bacopa (*Bacopa monniera*) or water hyssop, is the source of a centuries-old plant extract with specific cognition-enhancing benefits. In India it is a revered Ayurvedic herbal, popularly accepted for its effectiveness against mental illness and epilepsy.[93] Its popular name "Brahmi" is derived from "Brahma," the mystical creator of the Hindu pantheon. Early references to Brahmi sometimes confusingly referred to *Centella asiatica*, the Indian penniwort more correctly known as "mandukaparni."[93]

Bacopa has been an important constituent of the Ayurvedic materia medica since at least the sixth century AD.[94] According to Hindu concepts, the brain is the center for creative activity, so the agent which best improves this faculty of the brain was christened Brahmi. The active principles of Bacopa, derived from its leaves, are steroidal saponins, which include the bacosides (see Figure 5). These latter compounds are attributed with the capability to enhance nerve impulse transmission and thereby strengthen memory and general cognition.

In 1990, Singh and Singh published the results from their open trial with Bacopa, conducted in India on 35 adult patients with anxiety neurosis.[95] The dose was 12 g per day of the dried plant in syrup form, for four weeks. Concentration and immediate memory span were both significantly increased ($p>0.05$ and $p>0.01$, respectively). On-the-job mental fatigue, measured as total work output and errors committed per unit time, also was improved ($p>0.001$). Other major symptoms were significantly improved, including nervousness, palpitation, insomnia, headache, tremors, and irritability. The mean total anxiety level was significantly decreased ($p>0.05$). Mean maladjustment level also significantly improved ($p>0.01$), as did the disability level ($p>0.05$). In some cases, disability status was overcome. Side-effects were minor and not clinically important.

Bacopa can also be beneficial to children. Traditionally it was used to anoint newborns with the hope of improving their intelligence, to "open the gate of Brahma." Nowadays it is given to schoolchildren for the same purpose. In 1987, Sharma and colleagues performed a single-blind trial in India, administering Bacopa to 40 schoolchildren aged 6-8. Maze learning improved, as did immediate memory and perception, and the children's reaction/performance times. The dose given was 1.05 grams per day for three months, of the dried plant extracted into a syrup form. No side-effects were seen.[96] Animal experimentation in Indian laboratories has provided further indications of the memory-enhancing effects of Bacopa, and its protective effects in epilepsy.[93, 94] Research continues into the biochemistry and pharmacology of the bacosides.

The Coming Golden Age for Brain Restoration

The time is already here when personalized brain restoration programs can be implemented for individuals who have measurable cognitive impairment, are at increased risk for dementia, or simply are seeking to improve their baseline level of cognitive performance. Along with mental and physical exercise, dietary and lifestyle revision, and avoidance of toxins, cognitive-enhancing substances will be rationally applied and their benefits monitored non-invasively until results are achieved.

The first decade of the 21st century is likely to see the widespread emergence of cognitive restoration clinics, organized to evaluate, diagnose, and counsel citizens with a view to correcting their brain flaws in order to help them improve their mental performance on the job and in social settings. A prototype of this kind of clinic has already been created by Dharma Singh Khalsa, M.D. The Khalsa program for early intervention against cognitive dysfunction is particularly strong and resourceful because it draws from both Eastern and Western medical traditions, while remaining deeply rooted in ongoing clinical and basic science research.[97] It uses the widest variety of available options to encourage the brain to heal itself, among them:

- Nutritional supplementation and dietary revision
- Lifestyle improvements, exercise (physical and mental)
- Stress management, meditation, yogic relaxation
- Pharmaceutical intervention, where indicated.

According to Khalsa, the number of cases of Alzheimer's could reach 10 million fifteen years from now. Dr. Khalsa's program is aimed at delaying or preventing Alzheimer's or other dementia in a majority of these susceptible individuals, in the process saving society tremendous pain and financial cost. An ancillary benefit could be to swell the ranks of the elderly with people who are healthy overall, with revitalized mental function.

The prospect of a total cure for Alzheimer's is hardly to be envisioned, yet

Figure 6. Five cognition enhancers and their established benefits.

	PS	Ginkgo	ALC	Vinpo	Bacopa
Age-related cogn. decline	+	NT	+	NT	NT
Alz. dementia (non-vasc)	+	+	+	–	NT
Dementia (vascular)	NT	+	+	+	NT
Childhood	+	NT	NT	NT	+

NT = No trials available

research findings suggest even when brain circuits are becoming severely restricted there still may be a chance to intervene and restore function. For the brain at this late stage of nerve tissue degeneration, the key challenge is to regrow nerve cells. Until recently, the dogma in this field was that nerve cells cannot be replaced once they die. But solid research has proven that damaged human brain tissue can and does renew itself.

One clue as to how much the damaged brain can bounce back is recovery following stroke. Motor abilities lost in the hands and feet as a result of a stroke sometimes will return to the areas affected, although complete recovery is rare. Using monkeys, Nudo and collaborators found the recovery of lost motor function is linked to a "re-assignment" of a part of the brain's motor cortex; an area of undamaged motor cortex lying near to the damaged area takes over the function of the damaged area.[98] This capacity of the brain to re-assign responsibility is called plasticity. No doubt plasticity involves the formation of new circuit connections between the undamaged motor area and its newly assigned limb.

Following stroke, nerve cells located close to the zone of damage remain alive, possibly for years. Neubauer and associates reported successful revitalization of this population of "idling neurons."[99] In the case of a woman fully 14 years past a stroke, they achieved partial functional reactivation of this zone using hyperbaric oxygen treatments. Stroke recovery certainly seems to be an area of promise, where combinations of nutrients and growth factors could be applied with the hope of achieving a more complete clinical recovery.

Just within the past few years, it has been confirmed beyond reasonable doubt that the adult brain does carry cells which endow the capacity to regenerate.[100] These are classic "stem cells," with the capacity to divide and make new cells which can go on to become any type of cell (nerve, glia, other) needed in the brain. As Dr. Evan Snyder from Harvard Medical School enthusiastically described this, "It's like a bone-marrow transplant to the brain."[101] Kempermann and Gage have used NGF and other growth factors to coax damaged nerve cells into putting forth new outgrowths, so as to facilitate the reconstruction of circuits in zones near severed areas.[102]

This landmark discovery that the human brain has the potential to replace dead neurons, taken together with older findings that brain tissue already in place is sufficiently "plastic" to partially replace damaged circuitry, have now changed the old dogma that the brain cannot recover from serious damage. Other factors also help stimulate brain restoration. In adult rodents, certain types of learning and physical exercise appear to enhance survival

of new brain cells.[102,103]

As the research on trophic brain factors (various "nerve growth factors") matures, selected factors could be investigated under appropriately controlled conditions, in rational combinations with trophic orthomolecules, such as PS and acetylcarnitine, circulatory protectants, including *Ginkgo biloba* extract and vinpocetine, even perhaps with the time-proven Bacopa extract. Eventual clinical breakthroughs in slowing, halting, or reversing traumatic, degenerative, or age-associated cognitive decline are likely to come only from exhaustive investigation of all the avenues for biological support of the brain's nerve networks.

The ramifications of severe cognitive breakdown are obviously horrific both for the individual and for society. Vascular dementia and other less common dementias will sometimes degrade quality of life comparably with Alzheimer's, and mild cognitive impairment or age-related cognitive decline can seriously undermine productivity and self-esteem. Thus it stands to reason that all measures which contribute to the successful management of dementia or pre-dementia states should be implemented. Prominent among such measures will be nutritional supplementation with cognitive enhancers. As the 21st century dawns, cognitive breakdown states pose an ultimate challenge to the emergent integrative practice of medicine.

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