

Citicoline: The *New* Phospholipid Prescription

The cell membrane plays a crucial role in the health and functioning of cells. In the case of the brain, membrane structure is even more crucial. Brain function depends on communication between nerve cells (neurons). Although it happens at lightning speed, the process by which these brain cells talk to one another is amazingly complex – and every step along the way is dependent on proper cell membrane structure and function. Part of the reason why the brain seems to go downhill with “normal” aging is changes to the amounts, balance, and chemistry of fatty molecules called **phospholipids** in the brain.

When we’re young, well-nourished, and healthy, our brains naturally produce their own phospholipids, creating exactly the fatty molecules it needs, in the ratios required. The failure to maintain the level and balance of new phospholipids is at the root of much **Age-Associated Memory Impairment (AAMI)**. So it seems logical that boosting brain levels of declining phospholipids would help to slow, and even to reverse, aspects of AAMI.

And for *some* phospholipids, this is a proven fact. And one example to which many people concerned about brain health would point is **phosphatidylserine** (conveniently abbreviated “P.S.” – a catchy marketing name for a brain nutrient!). PS has a reputation as a core nutrient for those looking – a reputation with *seemingly* firm foundations in several clinical trials.

Despite this fact, and the fact that many reputable supplement companies continued to sell PS supplements in the interim, the team at *Advances* (formerly *The Holistic Lifestyle*) has been recommending for years now that people upgrade from PS to a superior brain phospholipids supplement called **Citicoline** (see “P.S.: Remember Your Citicoline!” in *The Holistic Lifestyle* 1(4)).

At the time, the main reasons related to the greater *versatility* of **Citicoline**. Unlike PS supplements, which nonselectively dump more phosphatidylserine into all the membranes of the body, **Citicoline enhances the brain’s ability to synthesize its own phospholipids**. As a result, studies in experimental animals show that **Citicoline increases levels of all phospholipids** in neural membranes – yet the normal, youthful *proportions* of the various phospholipids are not altered. And in controlled trials, **Citicoline has been proven to provide support in a wider range of cognitive disorders** than has PS.

But now there’s an even stronger reason to make the switch – or, at the very least, to stop pinning your hopes on PS. The results from the first double-blind, placebo-controlled trial to use soy-derived PS have finally been revealed – and



they show that **currently-available “PS” supplements you can buy in health food stores today actually don’t work any better than dummy pills** at supporting memory or other aspects of brain function!

“What do you mean, ‘the first trial’?!” the cries of outrage echo. “There have been reams of controlled trials using PS!” Indeed there have. But **currently-available “PS” supplements do not provide the form of phosphatidylserine that was used in these trials**. And it’s the *currently-available, soy-derived* PS which has finally been put to the test for the very first time – and which has been demonstrated to be totally ineffective as a brain-booster.

How did this happen? Let’s start with a little history.

Of Memory and Mad Cows

When scientists first thought about using PS supplements to restore the aging neuronal membrane's structure, they logically enough used a form of PS closest to what's actually found in the brain itself. They weren't about to test their ideas through a ghoulish raid on local mortuaries to get PS directly from human brains, of course, so they sought out an alternative source of PS that could ultimately be manufactured on a large scale. As a result, **the original clinical trials on PS used raw material extracted from cow brains.**

And – as numerous clinical trials documented – it worked. The original trials, performed in the early 1990s, found this bovine brain PS to be effective in both patients with Alzheimer's Disease,² **mild cognitive impairment (MCI** – a state of memory impairment that frequently precedes full-blown Alzheimer's)³⁻⁸ and AAMI.⁹ It looked as if PS were set to revolutionize the world of neuropsychiatry.

Then, the BSE epidemic struck Britain.

Frantic not to contribute to a plague of mad cow disease, manufacturers went looking for another source of PS. And they quickly came across one: soya lecithin. While there wasn't a lot of PS in lecithin, there was *some* – and with sophisticated extraction and purification processes, a supplement with a high enough concentration of PS to provide the dosages used in clinical trials was developed.

There was just one snag: **the "PS" derived from soya lecithin is not the same as the phosphatidylserine in mammalian brain.** Phospholipids are made up of three basic parts: a "backbone" of glycerol, a polar "head" group, and two fatty acid "tails" (see **Figure 1**). By definition, *any* phospholipid that has the amino acid **serine** for the "head" group is "phosphatidylserine." But this means that any number of

different molecules can be called "PS," because there are many different possible fatty acid "tails." And crucially, **where mammalian brain PS has the omega-3 fatty acid docosahexaenoic acid (DHA), soybean "PS" contains other, shorter-chain fatty acids, such as linoleic acid (LA) or alpha-linolenic acid (ALA).**

The difference in structure between the two forms of PS might be expected to make a considerable difference in the level of fluidity of the brain cell membranes into which it was incorporated and the molecule's ability to fulfill its biological function of modulating the activity of ion channels, receptors, enzymes, and signaling molecules. But based on the way that radiolabelled bovine brain PS was taken up into brain cell membranes,¹⁰ it was believed that the body would simply remove the inappropriate fatty acid and replace it with the right one.

To be fair, this idea wasn't *pure* hand-waving speculation. There were a couple of small, nonrandomized, uncontrolled experiments performed in people,^{11,12} which seemed to support the notion that the body would respond to the plant PS the same way that it did to the original, brain-derived material.

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But these kinds of studies can't be considered proper proof. It's well-known that people who are subjected to repeated testing on assays of memory and intelligence get better each time they take the test, because they become more familiar with the testing process itself. And the

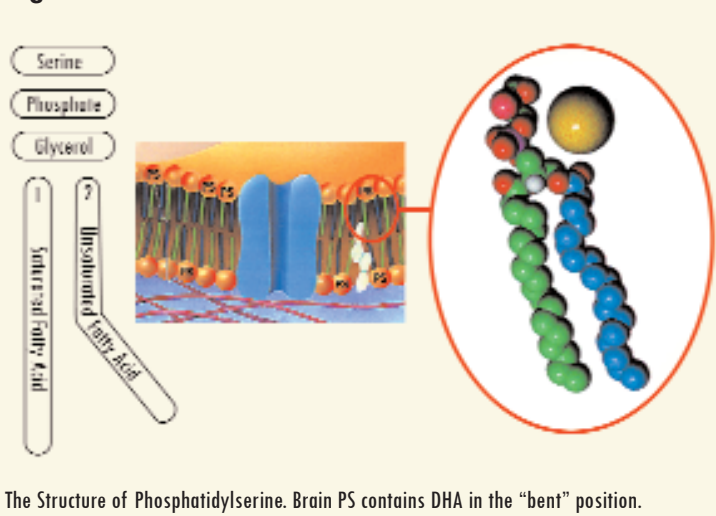
placebo effect – the amazing power of the mind – is most active in areas where the mind *itself* is the target, whether you look at intelligence, mood, or even pain. The studies were of such low quality that it took *seven years* from the completion of one study until it was accepted for publication in a peer-reviewed scientific journal format¹¹ – while the other study¹² never passed peer review in any forum whatsoever.

Indeed, the authors of the small pilot studies were well aware of these limitations. "These results are encouraging. However, **they await double-blind controlled verification in a large sample before suggesting that this may be a viable approach to the treatment of age-related cognitive decline**" they wrote.¹¹

The Disproof in the Pudding

Finally, a decade after this original study, a group of scientists took up this challenge. In 2002, a proper, double-blind, placebo-controlled trial was performed to compare the effects of Leci-PS[®] (the most widely-used soy-derived PS) with a dummy pill.¹³

Figure 1



Funded by Leci-PS's® manufacturer, Lucas Meyer (now Degussa Bioactives), the trial¹ involved 120 men and women over the age of 57 with age-associated memory impairment, but not dementia. These people first took a



battery of tests for learning and memory, choice reaction time, planning, and attention, with a focus on delayed recall and recognition of a word list that had been learned previously. They were then randomly assigned to take either the soy-based PS supplement (300 or 600 milligrams daily), and were re-tested six weeks later, and then again at twelve weeks.

The results were plain. After exhaustively double-checking the data – looking at it frontways, sideways, upside-down – **the researchers were forced to conclude that “No significant differences were found in any of the outcome variables between the treatment groups.** There were also no significant interactions between treatment and ‘severity of memory complaints.’ In conclusion, **a daily supplement of S[oy-derived] PS does not affect memory or other cognitive functions in older individuals with memory complaints.”¹**

What Was That Other Stuff Again?

The dark horse of the brain phospholipids world is **Citicoline** – the nickname for *cytidine 5'-diphosphate choline* (CDP-choline). A remarkable brain nutrient with a proven track record, C is more than just another source of choline: while it does *contain* this important brain-function nutrient, **Citicoline's** real “business end” is its *other half* – **cytidine diphosphate (CDP)**. CDP is the lynchpin in the **Kennedy**

then other phospholipids through a series of branches in the biosynthetic “tree.” In mammals, PS is formed further downstream, using phosphatides formed from the Kennedy pathway via the enzyme **CDP-diacylglycerol-serine O-phosphatidyltransferase** (or more simply, **phosphatidylserine synthetase**).¹⁴

Studies in lab animals show that cytidine itself, or cytidine delivered as **Citicoline**, **boosts PS by 37.2%, PC by 22-30%, PI by 16%, and PE by 11-13% in brains and neurons.**¹⁵⁻¹⁷ By supporting the brain's ability to make its own phospholipids, the total brain phospholipid content is increased, yet the brain's natural, youthful phospholipid proportions are retained.

And, at the same time, new research suggests that **Citicoline allows the body to make better use of phospholipids derived directly from the diet or from other supplements.** As the fatty acid “tails” of phospholipids have to be changed to match the tissue-specific needs of cell membranes as they are taken from the blood, then brought into the cell's outer membrane, and ultimately nestled into their final “home” in the cell. Studies in isolated neuron precursor cells show that **Citicoline** selectively enhances the ability of phospholipids to incorporate a variety of fatty acids into their “tails,”¹⁷ facilitating this “customization” process. As well, **Citicoline** increases the manufacture or release of key brain messenger molecules, such as acetylcholine,¹⁸ norepinephrine, dopamine, and serotonin.¹⁹

Thus, **Citicoline is a fundamentally different approach to brain phospholipid restoration.** While taking PS alone can “top up” the level of this *one* phospholipid in neuron membranes, it does nothing to restore the *overall* youthful phospholipid balance of neuronal phospholipids. Because of this, taking PS can only be a partial – and even unbalanced – way to restore the health of the brain. Taking PS alone – or PC, or lecithin supplements – corrects *part* of the problem, while leaving other parts unaddressed, and may even upset the harmony of the whole. In other words, when your martini runs low, topping it up with straight gin is likely to lead to increasingly unsatisfactory results with every refill. Needless to say, the same goes for simple PC or lecithin supplements: they provide some of the pieces, but not the balance of the synergistic whole. **Citicoline represents a path toward total brain phospholipid renewal.**

And it Works!

Extensive test-tube and animal studies have been performed to establish **Citicoline's** mechanisms of actions. But biochemistry is one thing, and results in real people's lives are another. **Double-blind, controlled studies prove that Citicoline delivers effective nutritional support in a**

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pathway, the biological assembly line through which the brain naturally produces its own phospholipids – first phosphatidylcholine and phosphatidylethanolamine, and

broad variety of cognitive disorders, including cognitive impairment associated with Parkinson's disease,^{20,21} acute stroke,²²⁻²⁵ head trauma,^{26,27} and Alzheimer's Disease,²⁸ and that it improves the odds of a good outcome after high-risk brain surgery.²⁹ These trials are evidence in addition to the many successful human studies which have been run with less formal structure.³⁰⁻⁴³ The fact that **Citicoline** – unlike even the authentic, bovine brain PS – has been proven to be effective in providing support against such a sweeping range of mental impairments is a testament to its powers as an universal “phospholipid booster.”

But most people taking brain boosting nutrients are not Alzheimer's patients, nor are they on a waiting list for risky neurosurgery. Instead, most “smart nutrient” users are either proactively working to prevent the onset of cognitive decline *in the first place*, or are already beginning to feel the effects of what is often referred to in defeatist terms as the “normal” loss of brain function with age. We'd expect that a supplement with such global effects on brain function, and which is effective in such a wide array of severe conditions, would also help support the brain that is not suffering with any *specific* age-related neurodegenerative disease, but which is still beginning to feel the losses associated with the aging process.

And we'd be right. Double-blind, placebo-controlled trials have also shown that **Citicoline significantly improves memory function in persons with “normal” age-associated memory impairment.**

In one such trial,⁴⁴ older subjects who were experiencing problems with their memories, but who were not suffering dementia, were tested on a battery of memory tests, and found to perform more poorly than young controls. Then the subjects were given each of four treatments, for four weeks each, at different times. All volunteers underwent three periods with different **Citicoline** regimens (a high (1000 mg) or moderate (500 mg) dose of **Citicoline**, or a low (300 mg) dose combined with **nimodipine** (a blood pressure drug also used to treat some neurological deficits)). Subjects also underwent a placebo phase, in which they took inactive lookalike pills. The results showed that **Citicoline significantly improves performance on several memory tasks**, including the free recall of word lists and the ability to remember a set of objects (either immediately after seeing them or later on). **All Citicoline groups showed some improvement over the course of the trial compared to when they were on the placebo** (see **Figure 2**). The only side effects were a decrease in blood pressure, and immunomodulatory effects shown as minor changes in the populations of white blood cells.

Citicoline was also tested in AAMI in a randomized, double-blind, placebo- controlled trial run by MIT in conjunction with US Army Research Institute of

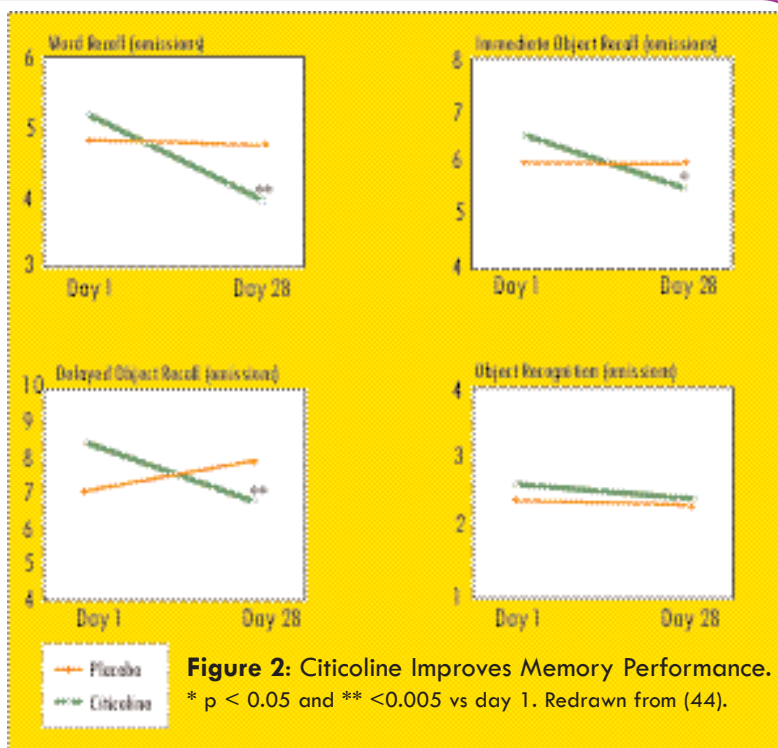


Figure 2: Citicoline Improves Memory Performance. * p < 0.05 and ** < 0.005 vs day 1. Redrawn from (44).

Environmental Medicine.⁴⁵ In the first phase, ninety-five older volunteers with no active psychiatric or neurological disorders, and who were within the normal range on tests of mental status, were randomly assigned to take either a dummy pill or **Citicoline** for three months. Those subjects with poorer memories at baseline showed **improvements in recall** (remembering details of a story heard one half hour previously). Subjects who began the study with poorer memories were then used in an additional study, in which they received one of two high doses of **Citicoline** for two months each. The higher dosage of **Citicoline** was “**clearly associated with improved immediate and delayed logical memory.**”⁴⁵ And while some side effects were reported, no one side effect was more commonly reported in patients receiving **Citicoline** than those receiving the dummy pill. In fact, **the total incidence of side effects was actually higher in the placebo group than in people actually taking Citicoline!**

Of course, there's more to optimizing mental performance than phospholipids. **Vinpocetine**, the periwinkle phytochemical, helps bring needed oxygen and fuel to the far reaches of the brain. **Pyroglutamic acid** opens up the gates of communication between the hemispheres, letting your conscious mind fully plumb the depths of its creative resources. And the ‘cocktail’ of mitochondrial superchargers, **acetyl-L-carnitine (ALCAR)** and **R(+)-lipoic acid**, keep the mental fires burning clean and bright. But if the weak link in your chain of mental functioning is the loss of brain phospholipids – to age, to injury, or to a toxic environment – then **Citicoline** is the blacksmith that you need on the job, restoring the deficit and returning your neuronal membranes to youthful structure and functionality.

Bring the Balance Back

Our minds are what make us who we are. Memories are our connection to our history, and the foundation of who we are today. The workings of the mind reflect the structure of the brain, and phospholipids play a vital part in that structure. **Citicoline** restores more youthful levels and balance of brain phospholipids, carrying us from our past into a clear future.

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