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## Phosphatidylserine

### Evidence Summary

May promote cognitive function and protect from decline, especially for DHA-enriched phosphatidylserine. It has a good safety profile but has limited bioavailability.

**Neuroprotective Benefit:** Mixed evidence from clinical trials, and considerable bias in results reporting. Has poor bioavailability and it's unclear how well it gets into the brain.

**Aging and related health concerns:** No clear rationale or data. One study reported a minor increase in mobility in elderly, but effect can't be clearly tied to phosphatidylserine.

**Safety:** Well-tolerated with no serious adverse events reported in short trials. May slightly reduce blood pressure. Information on long-term safety is not available.

**What are they?** Phosphatidylserine (PS) is a class of phospholipids that help to make up the plasma membranes in the brain. Varying the levels and the symmetry of PS in cell membranes (i.e. on the inside or outside of a membrane) can affect signaling pathways that are central for cell survival (e.g. Akt, protein kinase C, and Raf-1) and neuronal synaptic communication [1]. It is comprised of two fatty acids attached to a serine.

PS and other phospholipids are thought to be hydrolyzed before they are absorbed by the gut, although there are claims to suggest otherwise (e.g. [2]). It is also unknown whether PS would be transported intact through the blood and/or able to penetrate the brain [1]. In other words, if PS supplementation increases PS concentration in cell membranes in the brain, the effect is likely to occur via its separate components of serine and the fatty acid (DHA or other).

**Neuroprotection:** Mixed evidence from clinical trials, and considerable bias in results reporting. Has poor bioavailability and it's unclear how well it gets into the brain.

- o meta-analyses or systematic reviews
- over 20 small clinical trials on various formulations in young, old, or impaired adults
- numerous preclinical studies for the rationale

Many clinical trials have reported the effects of PS supplementation, usually up to 6 months duration. In theory, PS supplementation could shift membrane compositions within days, but the effects have not been rigorously studied. Most studies were small and/or poorly designed.

The brain's composition of PS is largely constant throughout life although slight changes in varying directions have been reported in Alzheimer's [3], Parkinson's [4], schizophrenia [5], and aging [6]. However, most PS in the brain is synthesized locally [1] and it is not clear whether PS supplementation will raise levels in the brain. Although one mouse study suggests that PS supplementation could increase brain PS [7], this may have been an indirect effect of the DHA in the PS. The local synthesis of PS is typically done from DHA-phospholipids (phosphatidylcholine and phosphatidylethanolamine) in cell membranes, so by supplying the precursors, DHA supplementation may increase PS levels in neuronal membranes [1].

Multiple small clinical trials have reported that *PS-DHA derived from bovine cortex* could improve cognitive function and sometimes depression in elderly people with dementia, mild cognitive impairment, or age-associated memory impairment. In the largest of these trials, a double-blind trial from Italy, PS-DHA from bovine cortex (300 mg/d) reportedly improved memory, learning, motivation, and socialization over 3-6 months in 494 patients [8].

Due to concerns of mad-cow disease, the PS-DHA from bovine cortex is no longer available but alternatives have been generated from marine sources. Their composition is different from the bovine-cortex supplements but in one randomized double-blind trial and an open-label follow-up [9, 10], **DHA-enriched PS** from marine sources (e.g. **Vayacog®**) for 15 weeks improved some but not most aspects of cognitive function in elderly people with memory impairment. The number of patients who were rated as clinically improved was not significantly different despite a positive trend of 37% of treated patients versus 28% control [9]. Longer treatment (i.e. 30 weeks instead of 15) did not lead to further improvements in cognitive function.

**PS derived from soy (PS-soy)** has been tested in several clinical trials with varying and unconvincing effects in elderly people with memory complaints. The best designed study reported that PS-soy at 300 or 600 mg/day had no effects over 12 weeks [11]. A couple of uncontrolled studies have reported cognitive benefits [12, 13] but these are unconvincing given that, in another randomized trial, the placebo and treated groups all improved to the same degree [14].

In theory, the effects of DHA-enriched PS could be replicated by DHA/fish-oil given with PS-soy because the molecular components will be separated before reaching the brain. In 6 month RCTs, combined supplements failed to influence cognition or hemodynamics in healthy adults aged 50-70 years with subjective memory deficits [15] but improved scores on 2 of 4 cognitive assays in high-performing elderly women [16].

**ApoE4 interactions?** Although DHA itself has evidence for interaction with APOE4, little research is available on whether potential PS benefits (whether PS-DHA or other) will vary across E4 carriers vs non-carriers. A couple of rodent studies suggest that apolipoprotein E can affect PS composition of cell membranes [17] but that E4 is similar to E2 or E3 alleles [18].

**Aging and related health concerns:** No clear rationale or data. One study reported a minor increase in mobility in elderly, but effect can't be clearly tied to phosphatidylserine.

- o meta-analyses
- 1 clinical trial on mobility
- o preclinical studies on longevity, mortality, etc.

A combination supplement that includes 70 mg of PS (Efalex active 50+) was reported to modestly improve mobility in high-performing elderly women after 6 months of treatment in a randomized double-blind trial [16]. Whether the effect is due to PS is unclear.

The rationale for aging biology effects beyond the brain is weak. Changes with age have been investigated with phosphatidylserine asymmetry across peripheral cell membranes (e.g. [19]) without mention of a loss of PS in cell membranes outside of the brain.

**Safety:** Well-tolerated with no serious adverse events reported in short trials. May slightly reduce blood pressure. Information on long-term safety is not available.

Small clinical trials suggest that PS supplements are safe in elderly people with minimal side effects other than slightly reduced blood pressure, whether they are DHA-enriched or derived from soy. Longer studies in larger populations are unavailable, whether observational or randomized. Varied and very small clinical studies suggest a possible decrease in cortisol from bovine cortex PS-DHA.

- PS-DHA, eg. Viacog®: Over a 30-week clinical trial, 100-300 mg/d of Viacog® was well-tolerated with no serious adverse effects in elderly people with memory impairment reported. Resting diastolic blood pressure was decreased after 30 weeks in the open-label extension (3.1 mmHg,  $p=0.006$ ) and a slight weight gain was reported (0.7 kg,  $p=0.015$ ). A wide variety of biochemical parameters were unchanged (e.g. cholesterol, bilirubin, glucose, and others).
- PS-soy, in a handful of small clinical studies in elderly people at doses between 100-600 mg/day, had a good safety profile with no adverse effects. In one open-label trial, systolic and diastolic pressure was decreased [12]. Some evidence suggests that PS-soy in combination with exercise could reduce the cortisol response to overtraining or improve exercise capacity [20].

**Dosing and Sources:** Doses typically range from 100-500 mg/d. Many different formulations of PS are available, enriched with DHA and/or EPA to varying levels or enriched with omega-6 fatty acids and derived from soy. However, any type of PS in combination with DHA is likely to achieve the same effects given the expected pharmacokinetic properties.

- **Vayacog®** is a prescription medical food available in the United States for cognitive impairment, with phosphatidylserine enriched with DHA and EPA. The cognitive effects discussed above were observed with a dose between 100-300 mg/day. The 300 mg/d dose (100 mg t.i.d.) provided 300 mg PS and 79 mg of DHA and EPA (in a ratio of 3:1 DHA/EPA).
- **Sharp-PS gold** is also a PS enriched with either DHA or EPA/DHA. The clinical report of its use was at 300 mg PS, which includes 37.5 mg of EPA & DHA.
- PS derived from soy has been tested at doses from 300-600 mg/d in clinical trials.

- **Efalex Active 50+** contains 60 mg PS and fish oil 1g DHA, 160 mg EPA, 240 mg Ginkgo biloba, 20mg d-α tocopherol, 1mg folic acid, and 20 µg vitamin B12. Its use for 6 months was reported to improve some cognitive & mobility scores in high-performing elderly women [16].
- Ginkgo biloba complexed with PS was reported in a very small double-blind RCT in young adults to increase calm, memory performance, and speed of memory tasks. Investigators argued that the PS co-administration makes the active components of ginkgo biloba more bioavailable.

**Future research:** A 2-year clinical trial with DHA-enriched PS is planned in 360 patients with mild cognitive impairment, with outcomes including various cognitive tests, diagnosis of dementia, sleep, and anxiety. The trial is still recruiting now, 2 years into the study and the estimated date of completion has been pushed back from September 2017 to 2019. ([NCT02211560](https://clinicaltrials.gov/ct2/show/study/NCT02211560)). The company running the trial – Enzymotec Ltd was faced with two [class action lawsuits](#) still underway in 2016 around its marketing of infant formula.

## Search terms

Pubmed:

- phosphatidylserine + aging, brain, soy, positron emission tomography, PET, 'cancer and supplement'
- phosphatidylserine filtered by meta-analysis, systematic review, and clinical trial
- phosphatidylserine + cancer, cardiovascular, hypertension, heart failure with trials filter

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