



## Monograph

### Phosphatidylserine

#### Introduction

Phosphatidylserine (PS), a ubiquitous, endogenously-occurring phospholipid, is the major acidic phospholipid in the brain. PS is embedded in cell membranes, and along with other phospholipids, makes up the basic structural components of the cell membrane. These membrane phospholipids play an important role in cell-to-cell communication and transfer of biochemical messages into the cell, which trigger cellular responses. The proper functioning of these processes is of ultimate importance, especially in the central nervous system. It is theorized that PS enhances cellular metabolism and communication by influencing the fluidity of cell membranes.<sup>1-4</sup> Oral supplementation of PS has been shown to affect neuronal membranes, cell metabolism, and specific neurotransmitter systems, including acetylcholine, norepinephrine,

serotonin, and dopamine.<sup>1-4</sup> Numerous clinical trials have established that PS exerts significant benefit for cognitive functioning, especially those functions which tend to decline with age, including memory, learning, vocabulary skills, and concentration.<sup>5</sup>

PS is formed in the body from the amino acid L-serine, glycerophosphate, and two fatty acids. Some PS is converted to phosphatidylethanolamine, which is in turn converted to phosphatidylcholine. Phosphatidylethanolamine can also be enzymatically converted into phosphatidylserine; however, these conversions are energy costly.<sup>5</sup>

Aging is commonly associated with structural and biochemical changes in the brain, including derangement of neuronal membrane lipid composition and enzymatic activity, decreased neurotransmitter synthesis and metabolism, and/or decreased synaptic density.<sup>1-3</sup> Age-related alterations in neuronal membrane composition can cause neurochemical changes which can contribute to an increase in the viscosity of cellular membranes, thus reducing enzymatic activities that require optimum fluidity. These cell membrane changes can be indirectly responsible for alterations in enzymatic activities, receptor functions, membrane carriers, and neuronal electrical characteristics, resulting in impairments in behavior, memory, and learning.<sup>3</sup>

PS dosing in aged rats increases dopamine release from the striatum and stimulates acetylcholine release from the cerebral cortex, in addition to preventing age-induced loss of dendritic spines in the hippocampal pyramidal neurons and atrophy of cholinergic cells in the basal forebrain.<sup>6</sup>

Human studies using PET scanning to investigate brain glucose utilization in Alzheimer's patients noted increases in glucose utilization in PS-supplemented patients, especially in the temporoparietal areas which are specifically affected by Alzheimer's.<sup>7-10</sup>

PS may also protect cells from damage produced by free radicals. A significant decrease in damage to cultured human fibroblasts from the enzymatic oxidation of acetaldehyde by xanthine oxidase was noted in cultures pre-treated with PS.<sup>11</sup>

## Pharmacokinetics and Toxicity

Pharmacokinetic studies indicate exogenous PS crosses the blood-brain barrier, where it appears to have an affinity for the hypothalamus. Oral administration results in peak levels in one to four hours. The oral LD<sub>50</sub> in rats is >5 g/kg body weight, and no teratogenicity was noted in rats or rabbits. Mutagenic testing was negative.<sup>12</sup> In a tolerability and toxicity study of 130 patients, no significant changes were noted in CBC or serum chemistry results, except for a significant decrease in SGPT and uric acid levels.<sup>13</sup>

## Clinical Applications

**Age-Associated Memory Impairment/Cognitive Decline:** Studies of phosphatidylserine dosing in age-associated memory impairment indicate PS is an effective remedy for this common malady. The largest of these studies, a multi-center, placebo-controlled study of 494 elderly patients, resulted in significant improvements in behavioral alterations (loss of motivation, initiative, interest in the environment, and socialization), memory, and learning in the PS group (300 mg/day) compared to placebo.<sup>3</sup> At least a dozen other studies, most using 300 mg/day, note similar significant improvements in learning, memory, concentration, and recall.<sup>5</sup>

**Alzheimer's Disease:** Alzheimer's Disease (AD) is another clinical indication for which phosphatidylserine has received attention. Generally, PS produces significant improvement in anxiety, motivation, memory, and cognition.<sup>4,7-10,14,15</sup> In a placebo-controlled study of 142 AD patients, PS was given (200 mg/day) for three months, and the patients were followed for 24 months. In a subgroup of patients with severe cognitive impairment, significant improvements were noted on the Blessed Dementia Scale (activities of daily living, information processing, personal and non-personal memory) three months after treatment cessation.<sup>15</sup> In other studies, most using 300-400 mg/day, improvement tended to be the greatest in those with less severe cognitive impairment,<sup>4,8,9,14</sup> and in one study were transient, fading after 16 weeks.<sup>7</sup>

**Depression:** Maggioni and colleagues studied the effects of oral PS (300 mg/day) on depressed geriatric patients not exhibiting dementia and noted significant improvement in depressive symptoms after 30 days. Memory and behavioral symptoms were also improved compared to placebo.<sup>16-18</sup>

**Chronic Stress/Hypercortisolism:** It appears PS might modulate cortisol release in stressful situations. In a study of exercise-induced stress, both ACTH and cortisol were lower after exercise in healthy volunteers taking 800 mg/day PS versus placebo. It was thought that PS affected hypothalamic release of corticotropin-releasing factor, an activator of the hypothalamic-pituitary-adrenal axis in response to stress.<sup>19</sup> This may provide some insight into the effect of PS on depression, as hypercortisolism is a common finding in depression.

All of the aforementioned clinical studies utilized PS extracted from bovine brain. Since this is not a desirable commercial source due to the potential for transmission of slow-virus infection, phosphatidylserine derived from soybeans has been developed for oral supplementation, and has been in use approximately four years. Two studies utilizing soy-derived PS indicate it has similar therapeutic properties as bovine brain-derived PS.<sup>20,21</sup>

## References

1. Crook TH, Tinklenberg J, Yesavage J, et al. Effects of phosphatidylserine in age-associated memory impairment. *Neurology* 1991;41:644-649.
2. Amaducci L, Crook TH, Lippi A, et al. Use of phosphatidylserine in Alzheimer's Disease. *Ann NY Acad Sci* 1991;640:245-249.

3. Cenacchi T, Bertoldin T, Farina C, et al. Cognitive decline in the elderly: A double-blind, placebo-controlled multicenter study on efficacy of phosphatidylserine administration. *Aging Clin Exp Res* 1993;5:123-133.
4. Crook TH, Petrie W, Wells C, Massari DC. Effects of phosphatidylserine in Alzheimer's Disease. *Psychopharmacol Bull* 1992;28:61-66.
5. Kidd PM. Phosphatidylserine; membrane nutrient for memory. A clinical and mechanistic assessment. *Altern Med Rev* 1996;1:70-84.
6. Nunzi MG, Milan F, Guidolin D, et al. Effects of phosphatidylserine administration on age-related structural changes in the rat hippocampus and septal complex. *Pharmacopsychiat* 1989;22:S125-S128.
7. Heiss WD, Kessler J, Szelies B, Herholz K. Long-term effects of phosphatidylserine, pyritinol, and cognitive training in Alzheimer's Disease. *Dementia* 1994;5:88-98.
8. Heiss WD, Kessler J, Szelies B, Herholz K. Abnormalities of energy metabolism in Alzheimer's Disease studied with PET. *Ann NY Acad Sci* 1991;640:65-71.
9. Heiss WD, Kessler J, Slansky I, et al. Activation PET as an instrument to determine therapeutic efficacy in Alzheimer's Disease. *Ann NY Acad Sci* 1993;695:327-331.
10. Klinkhammer P, Szelies B, Heiss WD. Effect of phosphatidylserine on cerebral glucose metabolism in Alzheimer's Disease. *Dementia* 1990;1:197-201.
11. Latorraca S, Piersanti P, Tesco G, et al. Effect of phosphatidylserine on free radical susceptibility in human diploid fibroblasts. *Neural Transm Park Dis Dement Sect* 1993;6:73-77.
12. Heywood R, Cozens DD, Richold M. Toxicology of a phosphatidylserine preparation from bovine brain (BC-PS). *Clin Trials J* 1987;24:25-32.
13. Cenacchi T, Baggio C, Palin E. Human tolerability of oral phosphatidylserine assessed through laboratory examinations. *Clin Trials J* 1987;24:125-130.
14. The SMID Group. Phosphatidylserine in the treatment of clinically diagnosed Alzheimer's disease. *J Neural Transm* 1987;24:287-292.
15. Amaducci L, The SMID Group. Phosphatidylserine in the treatment of Alzheimer's Disease: results of a multicenter study. *Psychopharm Bull* 1988;24:130-134.
16. Maggioni M, Picotti GB, Bondiolotti GP, et al. Effects of phosphatidylserine therapy in geriatric patients with depressive disorders. *Acta Psychiatr Scand* 1990;81:265-270.
17. Brambilla F, Maggioni M. Blood levels of cytokines in elderly patients with major depressive disorder. *Acta Psychiatr Scand* 1998;97:309-313.
18. Brambilla F, Maggioni M, Panerai AE, et al. Beta-endorphin concentration in peripheral blood mononuclear cells of elderly depressed patients—effects of phosphatidylserine therapy. *Neuropsychobiology* 1996;34:18-21.
19. Monteleone P, Maj M, Beinat, et al. Blunting by chronic phosphatidylserine administration of the stress-induced activation of the hypothalamic-pituitary-adrenal axis in healthy men. *Eur J Clin Pharmacol* 1992;41:385-388.
20. Gindin J, Novikov M, Kedar D, et al. The effect of plant phosphatidylserine on age-associated memory impairment and mood in the functioning elderly. The Geriatric Institute for Education and Research, and Department of Geriatrics, Kaplan Hospital, Rehovot, Israel. Unpublished.
21. Sakai M, Yamatoya H, Kudo S. Pharmacological effects of phosphatidylserine enzymatically synthesized from soybean lecithin on brain functions in rodents. *J Nutr Sci Vitaminol* 1996;42:47-54.

# Abstracts

---

## Recently Published Abstracts

---

### **Effect of clozapine and adjunctive high-dose glycine in treatment-resistant schizophrenia.**

Potkin SG, Jin Y, Bunney BG, et al. *Am J Psychiatry* 1999;156:145-147.

**OBJECTIVE:** The focus of this study was the systematic evaluation of the clinical effects of glycine as an adjunct to the atypical antipsychotic clozapine in the treatment of schizophrenia. **METHOD:** In a double-blind, placebo-controlled study, 19 patients with chronic, treatment-resistant schizophrenia who were maintained on optimal doses of clozapine (400-1200 mg/day) were administered either 30 g/day of glycine (N=9) or placebo (N=10) for 12 weeks. Clinical evaluations with the Brief Psychiatric Rating Scale, the Scale for the Assessment of Negative Symptoms, and the Simpson-Angus movement scale were completed biweekly. **RESULTS:** The use of glycine as an adjunct to clozapine was not effective in decreasing positive or negative symptoms. In contrast, the patients treated with clozapine without glycine had a 35% reduction in positive symptoms. **CONCLUSIONS:** These preliminary data suggest that glycine may interfere with the antipsychotic efficacy of atypical neuroleptics such as clozapine.

### **Effect of niacin on atherosclerotic cardiovascular disease.**

Guyton JR. *Am J Cardiol* 1998;82:18U-23U.

Niacin has been studied in 6 major clinical trials with cardiovascular endpoints. The Coronary Drug Project (CDP) was the largest of these trials and the only one to use niacin monotherapy affecting cardiovascular outcomes: recurrent myocardial infarction and cerebrovascular events were significantly decreased. After long-term (15 years) follow-up, total mortality was also found to be decreased. The other 5 trials used varying combinations of niacin with other pharmacologic agents, examining coronary and total mortality, coronary events, and angiographic progression/regression. Significant benefit was found in all trials except for one in patients with normal cholesterol levels at entry. Thus, the use of niacin to prevent or treat atherosclerotic cardiovascular disease is based on strong and consistent evidence from clinical trials.