Phosphatidylserine Containing Omega-3 Fatty Acids May Improve Memory Abilities in Non-Demented Elderly with Memory Complaints: A Double-Blind Placebo-Controlled Trial

Methods: 157 participants were randomized to receive either PS-DHA or placebo for 15 weeks. Efficacy measures, assessed at baseline and endpoint, included:

- The Rey Auditory Verbal Learning Test
- Rey Complex Figure Test
- And a computerized cognitive battery

Clinicians' Global Impression of Change was assessed following 7 and 15 weeks of treatment.

Results: 131 participants completed the study, although 9 were excluded from the efficacy analysis due to protocol violation.

- At endpoint, verbal immediate recall was significantly improved in the PS-DHA group compared to the placebo group.

- Post-hoc analysis revealed that a subset of participants with relatively good cognitive performance at baseline had significant treatment-associated improvements in:
  - Immediate and delayed verbal recall,
  - Learning abilities,
  - And time to copy complex figure.

These favorable results were further supported by responder analysis.

Conclusions:

The results indicate that PS-DHA may improve cognitive performance in non-demented elderly with memory complaints.

Post-hoc analysis of subgroups suggests that participants with higher baseline cognitive status were most likely to respond to PS-DHA.

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Phosphatidylserine Containing ω–3 Fatty Acids May Improve Memory Abilities in Non-Demented Elderly with Memory Complaints: A Double-Blind Placebo-Controlled Trial

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Key Words

Phosphatidylserine · ω–3 fatty acids · Docosahexaenoic acid · Cognitive decline · Memory · Elderly · Therapy · Double-blind study

Abstract

Background: Phosphatidylserine (PS) may have beneficial effects on cognitive functions. We evaluated the efficacy of a novel preparation of PS containing ω–3 long-chain polyunsaturated fatty acids attached to its backbone (PS-DHA) in non-demented elderly with memory complaints. ***Methods:*** 157 participants were randomized to receive either PS-DHA or placebo for 15 weeks. Efficacy measures, assessed at baseline and endpoint, included the Rey Auditory Verbal Learning Test, Rey Complex Figure Test, and a computerized cognitive battery. Clinicians' Global Impression of Change was assessed following 7 and 15 weeks of treatment. ***Results:*** 131 participants completed the study although 9 were excluded from the efficacy analysis due to protocol violation. At endpoint, verbal immediate recall was significantly improved in the PS-DHA group compared to the placebo group. Post-hoc analysis revealed that a subset of participants with relatively good cognitive performance at baseline had significant treatment-associated improvements in immediate and delayed verbal recall, learning abilities, and time to copy complex figure. These favorable results were further supported by responder analysis. ***Conclusions:*** The results indicate that PS-DHA may improve cognitive performance in non-demented elderly with memory complaints. Post-hoc analysis of subgroups suggests that participants with higher baseline cognitive status were most likely to respond to PS-DHA. The results of this exploratory study should be followed up by additional studies aimed at confirming the present tentative conclusions.

Introduction

Over the last century, life expectancy has risen dramatically, resulting in the aging of the population. Physicians and scientists have to face the medical challenges created by the increasing number of people reaching old age. One of these challenges derives from the high prevalence of diminished cognitive functioning and memory performance. Pharmaceutical research aimed at improving cognitive deficits has been actively engaged in finding both clinically active and well-tolerated substances. One treatment strategy is based on the association between

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aging and alterations in brain lipid composition [1], suggesting that phospholipids, which are fundamental components of neuronal membranes, may serve as effective treatment for cognitive deterioration.

Phosphatidylserine (PS) is the main acid phospholipid in the inner leaflet of mammalian plasma membranes, and it has been shown to play a key role in the functioning of neuron membranes, such as signal transduction, secretory vesicle release, cell-to-cell communication, and cell growth regulation [2].

Early observations associated the administration of PS extracted from bovine cortex (BC-PS) with positive effects on brain function. Supplementation of 300 mg/day BC-PS to subjects with age-associated memory impairment resulted in improved performance in tests related to attention, learning, and memory tasks of daily life [3]. Providing BC-PS to geriatric patients significantly enhanced behavioral and cognitive parameters [4]. Importantly, BC-PS supplementation to Alzheimer's disease patients had positive effects on their cognitive performance [5, 6].

Safety concerns of the risk for prion contamination in BC-PS limited its use and promoted the establishment of soybean-derived PS (SB-PS) as a safe alternative [7]. SB-PS was shown to attenuate both physical [8] and mental stress [9, 10]. However, inconclusive results have been obtained in clinical studies evaluating the ability of SB-PS to promote cognitive functioning in age-associated memory impairment subjects. An open-label study testing the effect of 300 mg/day of SB-PS on 18 healthy volunteers demonstrated a significant memory and learning improvement following 12 weeks of administration [11]. Nevertheless, no significant improvement in cognitive skills was observed in a double-blind study which evaluated the effect of 12 weeks' administration of SB-PS (300–600 mg/day) to 120 age-associated memory impairment subjects [12].

SB-PS differs considerably from BC-PS mainly in the absence of docosahexaenoic acid (DHA) which is the predominant ω–3 long-chain polyunsaturated fatty acid (LC-PUFA) in the mammalian central nervous system. Observational and epidemiological studies have associated ω–3 LC-PUFA consumption with a reduced risk of impaired cognitive function in middle-aged population [13], and with a reduced risk of dementia [14, 15]. Few interventional studies have supported this association; however, these studies involved a limited number of participants and short-term follow-ups [16, 17].

Another alternative to BC-PS is a safe-sourced PS with ω–3 LC-PUFA attached to its backbone (PS-ω–3). This compound was recently found to improve the symptoms of children with impaired visual sustained attention [18]. PS-ω–3 efficacy was further demonstrated in a pre-clinical study in middle-aged rats. The study results showed that PS-ω–3 consumption, rather than fish oil with or without SB-PS, has a significant impact on the brain fatty acid profile and protects from scopolamine-induced deleterious effects [19].

In the present double-blind placebo-controlled study, we evaluated for the first time the efficacy of a novel formulation of PS with ω–3 LC-PUFA, mainly DHA, attached to its glycerol backbone (PS-DHA), in treating cognitive decline in non-demented elderly with memory complaints.

Material and Methods

Subjects

Approximately 700 elderly were screened for enrollment to the study. Out of these, 157 non-demented participants with memory complaints met the inclusion criteria. Participants were recruited through advertisements in senior citizens homes, hospitals, and newspapers.

Participants eligible for enrollment were men or women between the ages of 50 and 90 years who met the following criteria:

(1) Complaints of memory loss in everyday life confirmed by a score of ≥25 on the Memory Complaint Questionnaire scale [20].

(2) Absence of dementia as determined by Mini-Mental State Examination (MMSE) score ≥27 for subjects with college education and ≥26 for all others, and Clinical Dementia Rating Scale score ≤0.5.

(3) Scores in NexAde™ computerized tests ≤ mean norm (±1.5 SD). In order to avoid a ceiling effect, a maximum of 4 subscores (out of 7 tests or 8 cognitive scores) above the norm was allowed.

Participants were ineligible for enrollment if any of the following conditions existed:

(1) Evidence of delirium, confusion, or other disturbances of consciousness.

(2) Any neurological disorder that could produce cognitive deterioration, including Alzheimer's disease, Parkinson's disease, stroke, normal pressure hydrocephalus, and other brain lesions including tumors.

(3) History of any infective or inflammatory brain disease including those of viral, fungal, or syphilitic etiologies.

(4) Significant head injury immediately preceding cognitive deterioration.

(5) Evidence of depression as determined by the Geriatric Depression Scale (short version) score of ≥5.

(6) Current psychiatric diagnosis according to DSM-IV criteria of depression, mania, or any other major psychiatric disorder.

(7) Current diagnosis or history of alcoholism or drug dependence.

(8) Any medical disorder that could produce cognitive deterioration, including renal, respiratory, cardiac, and hepatic disease, diabetes mellitus, endocrine, metabolic or hematological disturbances unless well controlled, and malignancy not in remission for more than 2 years.

(9) Use of psychotropic drug or any other drug or supplement that may significantly affect cognitive functioning during the month prior to psychometric testing.

(10) Use of any experimental medication within 1 month prior to screening or as concomitant medication.

(11) History of hypersensitivity or allergy to fish, fish oil, or soy.

The study was conducted according to the principles of the Declaration of Helsinki and good clinical practice. The protocol was approved by the Ethics Committee of the Sourasky Medical Center, Tel-Aviv, Israel, and all volunteers gave written informed consent prior to participation. (Trial registration: clinicaltrials.gov, identifier: NCT00437983).

Study Design

The study was designed as a single-center randomized double-blind placebo-controlled study. Duration of treatment was 15 weeks. Participants were randomized according to a computerized randomization process based on 6 and 8 blocks, in a 1:1 ratio stratified by gender, to receive 3 capsules per day of PS-DHA or a matched identically looking placebo (cellulose). The daily PS-DHA dosage provided 300 mg PS and 79 mg DHA+EPA (DHA/EPA ratio of 3:1). PS-DHA (Vayacog™) was supplied by Enzymotec Ltd., Migdal HaEmeq, Israel.

Efficacy measures were examined at baseline and endpoint (except for the Clinical Global Impression of Change (CGI-C) which was conducted at week 7 and at endpoint). Safety was assessed at baseline, week 7, and endpoint (except for the blood tests assessed only at baseline and endpoint). For treatment adherence monitoring, participants returned all treatment packs at each visit, and adherence was calculated using the number of capsules remaining.

Efficacy Measures

(1) Rey Auditory Verbal Learning Test (RAVLT). The Hebrew version of the RAVLT was used [21]. Administration was standardized, as described by Lezak [22]. Four different scores were derived from the test: immediate memory recall (trial 1 score), verbal total learning (sum of scores of trial 1 through 5), delayed recall (trial 8), and recognition (trial 9).

(2) Rey Complex Figure Test (RCFT). The RCFT measures visual-spatial perception/construction and memory. Test administration and scoring were according to Meyers [23]. Both the time to complete the task and the accuracy were used as measures for the analysis.

(3) Clinical Global Impression of Change. Global improvement score ranges from 1 = 'very much improved', through 4 = 'no change', to 7 = 'very much worse'. The interviewer was barred from knowledge of psychometric test scores and adverse event reports obtained as part of the protocol. Using the previous visit as reference, the evaluator interviewed the participant following 7 and 15 weeks of treatment to obtain an impression of change. To examine the differences between the treatment groups in the assessment of global change, participants who experienced an improvement (scores 1, 2 or 3) in at least 1 of the 2 visits (following 7 or 15 weeks of treatment) were classified as improved over the treatment period (with the exception of participants reporting improvement following 7 weeks and deterioration at endpoint, who were not rated as improved), otherwise participants were classified as 'unchanged' (score 4), or as 'worse' (score 5, 6, or 7).

(4) NexAde™ computerized cognitive assessment tool. This computerized neuropsychological assessment software consists of 7 separate tasks: symbol spotting, pattern identification, pattern recall, digit-symbol substitution, digit span forward, digit span backward and delayed pattern recall. Based on the results obtained in the single tasks, 8 cognitive composite scores are calculated, including focused attention, sustained attention, memory recognition and recall, visuospatial learning, spatial short-term memory, executive functions and mental flexibility. All tasks are computer-controlled [24].

Safety Measures

Safety was evaluated by means of physical examination, measuring of weight and vital signs (resting diastolic and systolic pressure and heart rate), and clinical laboratory assessments including clinical chemistry and hematology. Clinical chemistry consisted of glucose, sodium, potassium, chloride, calcium, phosphorus, blood urea nitrogen, creatinine, bilirubin, alanine-aminotransferase, aspartate-aminotransferase, alkaline phosphatase, total protein and lipid profile (total cholesterol, triglycerides, HDL, and LDL). Hematology consisted of red blood cell count, hemoglobin, hematocrit, MCV, MCH, and MCHC, white blood cell count and differential, and platelets. Samples were analyzed by the American Medical Laboratories, Herzliya, Israel. Adverse events were monitored and recorded at each visit and by telephone contact every other week.

Statistical Methods

Results are expressed as mean ± SE. Student's t test for independent samples was used to evaluate differences in demographic and baseline continuous variables. Pearson's χ^2 test was used for the analysis of categorical variables, CGI-C, and responder analysis.

The intervention group's effect was evaluated in an ANCOVA model. The main outcomes were change from baseline in RAVLT and RCFT scores. The covariates submitted to the model were demographics and baseline performance. Only significant covariates were included in the final model. Two covariates remained in the final model: MMSE score (26 and 26+) and baseline performance (score above or below mean ± 1 SD). Second order interactions were not significant, and therefore not included in the final model.

In addition, percentage of responders is also reported. Participants were considered as responders when their improvement in the RAVLT immediate recall task was at least 2 words (1 SD above baseline mean value) and when they had an overall improvement in the CGI-C.

All hypothesis tests were two-sided; $p < 0.05$ was considered significant, without correction for multiple comparisons.

The SPSS (version 17) statistical package was used for all analyses.

Results

Study Population

A flow diagram of the study participants is presented in figure 1. A total of 157 subjects underwent randomization and 131 completed the study. Dropouts were distributed equally over the two arms and reasons for discontinuation were generally similar across the treatment groups (fig. 1).

The treatment was generally well tolerated. Most subjects maintained good health throughout the study, and

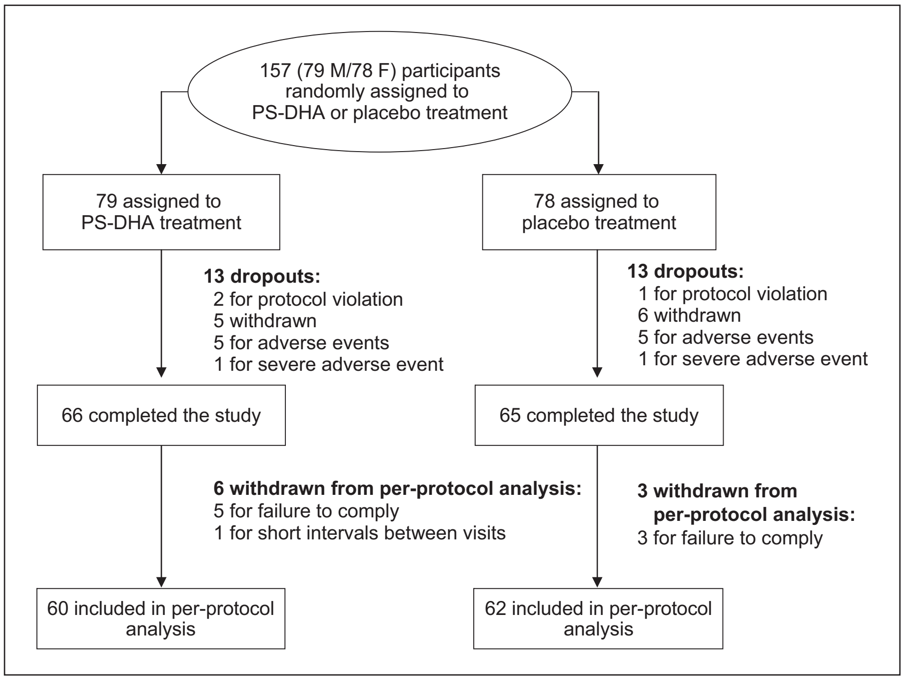

Fig. 1. Study flowchart. A total of 157 participants were randomized to receive PS-DHA or placebo treatment. Study completers (n = 131) included participants who completed 15 weeks of treatment. Participants who dropped out or failed to adhere to the study protocol were not included in the efficacy analysis.

Table 1. Baseline characteristics of study per-protocol subjects

	Placebo (n = 62)	PS-DHA (n = 60)	p
Age, years	73.01 ± 8.28	72.9 ± 8.20	0.632
Male gender, %	53.0	48.0	0.584
Married, %	77.0	67.0	0.222
Education, years	13.27 ± 3.62	13.5 ± 3.74	0.735
Education academic, %	45.2	51.7	0.476
Compliance, %	92.2 ± 9.67	91.92 ± 7.30	0.858
MAC-Q	29.15 ± 2.59	29.8 ± 2.87	0.188
MMSE	28.7 ± 1.13	28.4 ± 1.18	0.166
MMSE >28, %	66.1	50.0	0.104
CDR = 0, %	88.7	85.0	0.544
GDS	1.2 ± 1.17	1.3 ± 1.22	0.680
GDS >2, %	16.1	21.7	0.434

Data presented as means ± SD or %; p values derived from two-tailed Student's t test for continuous variables and Pearson's χ^2 test for categorical variables.

MAC-Q = Memory Complaints Questionnaire; CDR = Clinical Dementia Rating Scale; GDS = Geriatric Depression Scale (short version).

no major adverse events were classified by the study physicians as treatment related.

Overall adverse events were more common among PS-DHA-treated subjects (16 events in 10 participants: 13 consisting of gastrointestinal discomfort, 1 each of headache, weight loss, and rash) in comparison with placebo-treated subjects (11 events in 8 participants: 2 related to gastrointestinal discomfort, 2 headache cases, 2 dizziness cases, 1 each of increased weight and appetite, redness in mouth, mood swings, pruritus, and strange generalized feeling). Out of the 131 participants who completed the study, 9 were excluded from the per-protocol (PP) analysis (6 from the placebo group and 3 from the PS-DHA group), 1 due to short interval between visits and the rest failed to meet the post-specified compliance criteria (≥65%).

There were no significant differences between participants who were excluded from the PP analysis and those included in the PP group, except for the percentage of married participants (54 and 72%, respectively).

Baseline demographic characteristics of participants included in the PP analysis are described in table 1. No significant differences were observed between the 2 study groups.

Safety Measures

No serious adverse events were classified by the study physicians as treatment related.

There were no clinically meaningful differences between treatment groups on the tested blood parameters (data not shown). No significant findings were observed during physical examination or in vital signs or weight measurements (data not shown).

Table 2. Cognitive performance of per-protocol cohort at baseline and endpoint

	Placebo (n = 62)		PS-DHA (n = 60)		p
	baseline	endpoint	baseline	endpoint	
RAVLT score, number of words					
Immediate recall	4.74 ± 0.24	5.74 ± 0.23	4.52 ± 0.24	6.05 ± 0.26	0.041
Total learning	38.13 ± 1.28	42.15 ± 1.32	37.90 ± 1.30	43.20 ± 1.43	0.227
Delayed recall	6.77 ± 0.42	7.56 ± 0.42	6.95 ± 0.48	7.88 ± 0.44	0.640
Recognition, hits	11.69 ± 0.32	12.63 ± 0.28	12.07 ± 0.29	12.73 ± 0.29	0.689
RCFT score					
Copy time, s	211.3 ± 11.9	215.0 ± 16.4	219.9 ± 12.2	196.6 ± 9.6	0.079
Copy quality, points	28.15 ± 0.74	27.98 ± 0.85	29.20 ± 0.80	29.83 ± 0.68	0.413
Immediate recall, points	10.65 ± 0.81	12.00 ± 0.89	10.47 ± 0.78	13.19 ± 0.73	0.219
Delayed recall, points	9.72 ± 0.76	12.09 ± 0.83	10.13 ± 0.81	12.40 ± 0.76	0.916

Data presented as means ± SE; p values derived from two-tailed ANCOVA controlled for dichotomized baseline and MMSE values.

Cognitive Outcomes

PP Cohort

Rey Auditory Verbal Learning Test. Mean scores obtained at baseline and endpoint in the RAVLT are presented in table 2. At baseline, scores were similar in the PS-DHA and placebo groups. Following 15 weeks of treatment, a significant improvement was observed in the immediate recall trial in the PS-DHA group as compared to that of the placebo group (mean change ± SE: 1.53 ± 0.26 words and 1.00 ± 0.20 words, respectively, p = 0.041). No significant differences between groups were observed for the rest of the RAVLT tasks; however, improvement occurred more commonly in the PS-DHA group than in the placebo group in 2 of 3 items (table 2).

A further analysis of the immediate recall scores, which included all of the study completers (n = 131), revealed a trend toward improvement (p = 0.069) for the PS-DHA group, as compared to the placebo group (data not shown).

Rey Complex Figure Test. As indicated in table 2, PS-DHA tended (p = 0.079) to reduce the time in the copy task as compared to placebo (mean change ± SE: –23.27 ± 8.92 and 3.73 ± 12.44 s, respectively). No significant differences between groups were seen for the rest of RCFT tasks, although in all of them the PS-DHA group improved more (except in the delayed recall, where the 2 groups improved to a similar degree).

Global Impression of Change. A greater percentage of PS-DHA-treated participants (37%, 22 participants) were judged as clinically improved, by comparison with placebo (27%, 17 participants); however, the difference failed to reach statistical significance.

Table 3. Baseline characteristics of subset cohort

	Placebo (n = 38)	PS-DHA (n = 40)	p
Age, years	72.2 ± 8.34	71.8 ± 8.14	0.713
Male gender, %	44.7	37.5	0.338
Married, %	76.3	70.0	0.335
Education, years	14.6 ± 3.88	15.0 ± 3.45	0.636
Education academic, %	71.1	75.0	0.445
Compliance, %	90.9 ± 10.06	92.0 ± 7.15	0.559
MAC-Q	28.7 ± 2.10	29.5 ± 2.93	0.191
MMSE	28.9 ± 1.05	28.7 ± 1.07	0.309
MMSE >28, %	73.7	57.5	0.103
CDR = 0, %	94.7	87.5	0.237
GDS	1.1 ± 1.15	1.1 ± 1.19	0.937
GDS >2, %	13.2	15.0	0.537

Data presented as means ± SD or %; p values derived from two-tailed Student's t test for continuous variables and Pearson's χ^2 test for categorical variables.

MAC-Q = Memory Complaints Questionnaire; CDR = Clinical Dementia Rating Scale; GDS = Geriatric Depression Scale (short version).

Responder Analysis. At endpoint, a statistically significant association between responder status (yes/no) and treatment was obtained (p = 0.034). While the percentage of responders in the PS-DHA group was 22%, the percentage of responders in the placebo group was only 8% (13 and 5 participants, respectively). Similar percentages of responders were obtained in the study completer group (23% and 9% for the PS-DHA and placebo group, respectively, p = 0.035).

Table 4. Cognitive performance of subset cohort at baseline and endpoint

	Placebo (n = 38)		PS-DHA (n = 40)		p
	baseline	endpoint	baseline	endpoint	
RAVLT score, number of words					
Immediate recall	5.29 ± 0.30	6.08 ± 0.30	4.73 ± 0.32	6.70 ± 0.30	0.006
Total learning	42.71 ± 1.54	45.11 ± 1.62	40.55 ± 1.66	47.40 ± 1.66	0.002
Delayed recall	8.47 ± 0.46	8.42 ± 0.49	7.88 ± 0.64	8.90 ± 0.54	0.045
Recognition, hits	12.24 ± 0.41	12.97 ± 0.34	12.38 ± 0.37	13.20 ± 0.29	0.850
RCFT score					
Copy time, s	183.3 ± 11.8	182.9 ± 11.7	212.9 ± 16.0	181.9 ± 10.5	0.055
Copy, points	29.37 ± 0.84	29.55 ± 0.82	30.46 ± 0.85	30.39 ± 0.74	0.810
Immediate recall, points	11.66 ± 1.07	14.13 ± 1.13	11.10 ± 0.99	14.31 ± 0.90	0.551
Delayed recall, points	10.68 ± 0.99	13.68 ± 1.04	10.85 ± 1.02	13.39 ± 1.01	0.591

Data presented as means ± SE; p values based on two-tailed t test comparison of the mean difference from baseline for independent samples. Participants were included in this subset if they fulfilled 2 out of the 3 following criteria: (1) MMSE score >26; (2) baseline performance in the RAVLT delayed recall trial >7 words; (3) academic education (number of education years >12).

No significant differences between the groups were observed in any of the NexAde tasks (data not shown).

Subset Cohort

In order to identify participants' subgroups that might be differentially responsive to treatment, we defined a subset of subjects with relatively good cognitive performance at baseline. Participants were included in this selected subset if they fulfilled 2 out of the 3 following criteria: (1) score in the MMSE >26; (2) baseline performance in the RAVLT delayed recall trial above the PP group mean (7 words); (3) academic education (number of education years >12). This subset was composed of 78 participants (n = 38 placebo, n = 40 PS-DHA). Baseline demographic characteristics of participants included in the subset are described in table 3. No significant differences were observed between the 2 study groups.

Rey Auditory Verbal Learning Test. Table 4 presents the performance data on the RAVLT for the participants included in this subset cohort. Significant improvements were found for the PS-DHA group in both the immediate and delayed recall tasks (mean change ± SE: 1.98 ± 0.31 and 1.03 ± 0.36, respectively) in comparison with the placebo group (0.79 ± 0.28 and –0.05 ± 0.39, respectively). A statistically significant improvement in the PS-DHA group was also observed in the total learning score, as compared to placebo (mean change ± SE: 6.85 ± 0.99 and 2.39 ± 0.94, respectively).

Rey Complex Figure Test. A statistically significant improvement in the time needed to copy the complex figure was seen in the PS-DHA group, as compared to placebo (mean change ± SE: –31.00 ± 12.04 and –0.39 ± 10.00 s, respectively). The accuracy in the copy task remained almost unchanged in both groups indicating that the significant improvement observed in the time to complete the copy task was not at the expense of the quality of the copied figure.

Global Impression of Change. A greater percentage of PS-DHA-treated participants were judged as clinically improved in comparison with placebo-treated participants (40%, 16 participants, and 32%, 12 participants, respectively); however, the difference failed to reach statistical significance.

Responder Analysis. A similar pattern emerged as with the PP cohort. The percentage of responders in the PS-DHA group (25%, 10 participants) was significantly higher (p = 0.016) than that observed in the placebo group (5%, 2 participants).

No significant differences between the groups were observed in any of the NexAde tasks (data not shown).

Discussion

This exploratory study tested the effect of a novel PS-DHA compound on symptoms of cognitive decline in non-demented elderly. The key finding of this 15-week study indicates that PS-DHA treatment improves verbal immediate memory. Other parameters of RAVLT and RCFT were not significantly affected. The improvement in immediate memory is consistent with previous clinical studies in which administration of PS resulted in significant benefits on memory skills in a cognitively impaired population [25] and with recent studies which demonstrated the beneficial effects of PS with ω–3 LC-PUFA attached to its backbone [18, 19]. The efficacy of PS-DHA was further supported by a higher rate of participants who responded to treatment in the PS-DHA group in comparison with the placebo group. Response was defined by global and cognitive measure improvement; this stringent definition is of clinical significance since it implies both subjective and objective improvement.

Importantly, a subset of participants with higher cognitive status prior to treatment better demonstrated the effect of PS-DHA, with significant improvement in several cognitive parameters such as immediate memory, long-term memory and learning abilities. Additionally, a significantly higher response rate was obtained in the PS-DHA group in comparison with that of the control group. This subset of participants was defined using factors previously shown to be correlated with better cognitive status: MMSE score [26], delayed recall score [27], and education [28]. Influence of the abovementioned factors on responsiveness to interventions in cognitively impaired patients has barely been investigated, and results are inconclusive. For instance, Olazaran et al. [29] reported higher cognitive response in patients with fewer years of formal education, while an inverse correlation was found in a study evaluating the cognitive stimulation of dementia patients [30].

One possible explanation for PS-DHA showing a more profound effect in the above-mentioned subset is that the treatment reverses cognitive-related deficits; thus, participants experiencing a deeper cognitive decline, as compared to their performance in younger years, have a greater potential to improve following treatment. Since most of the participants in the subset had an academic education (73%), which is correlated with a better cognitive performance [28], it is very likely that they had a considerably better cognitive performance in earlier years and actually suffer from a deeper age-related cognitive deterioration and are therefore more likely to respond to treatment.

It is also possible that a longer treatment period and/or a higher treatment dose are required in order to cause a significant treatment effect in participants with severer cognitive impairment.

PS-DHA treatment was generally well tolerated, and no significant treatment-related adverse events were reported. Overall, slightly more adverse events were reported in the PS-DHA group (16 events) compared with the placebo group (11 events). Nonetheless, most adverse events in the PS-DHA group were related to occasional gastrointestinal discomfort which has been previously reported following PS consumption and can be minimized by consuming PS with food.

While the results of this study are encouraging, we acknowledge certain limitations in the study design. First, since this was an exploratory study, no primary endpoint was pre-determined and the selected subset and statistical plan were not pre-specified. Second, the inclusion criteria do not correspond to a single clinical entity, and thus the study population was probably not homogenous. However, the participants can be described as having either subjective cognitive impairment [31] or mild cognitive impairment [32].

At present, the exact mechanism of action of PS has not been established. In pre-clinical studies PS supplementation has been shown to affect multiple neurochemical systems, including the neuronal membranes [33], cell metabolism [34], and neurotransmitter systems including acetylcholine [35], norepinephrine [36], serotonin and dopamine [37].

To conclude, the current study shows that administration of PS-DHA may ameliorate cognitive deficits in a non-demented elderly population. Post-hoc analysis of subgroups suggests that, within the study sample, those with higher baseline cognitive status were more likely to respond to PS-DHA treatment. These results are promising and encourage further research in order to establish a safe and effective treatment solution for cognitive impairment of elderly population.

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References

1 Svennerholm L, Bostrom K, Helander CG, Jungbjer B: Membrane lipids in the aging human brain. J Neurochem 1991;56:2051–2059.
2 Vance JE, Steenbergen R: Metabolism and functions of phosphatidylserine. Prog Lipid Res 2005;44:207–234.
3 Crook TH, Tinklenberg J, Yesavage J, Petrie W, Nunzi MG, Massari DC: Effects of phosphatidylserine in age-associated memory impairment. Neurology 1991;41:644–649.

4 Cenacchi T, Bertoldin T, Farina C, Fiori MG, Crepaldi G: Cognitive decline in the elderly: a double-blind, placebo-controlled multicenter study on efficacy of phosphatidylserine administration. Aging (Milano) 1993;5:123–133.
5 Amaducci L: Phosphatidylserine in the treatment of Alzheimer's disease: results of a multicenter study. Psychopharmacol Bull 1988;24:130–134.
6 Crook T, Petrie W, Wells C, Massari DC: Effects of phosphatidylserine in Alzheimer's disease. Psychopharmacol Bull 1992;28:61–66.
7 Jorissen BL, Brouns F, Van Boxtel MP, Riedel WJ: Safety of soy-derived phosphatidylserine in elderly people. Nutr Neurosci 2002;5:337–343.
8 Jager R, Purpura M, Kingsley M: Phospholipids and sports performance. J Int Soc Sports Nutr 2007;4:5.
9 Benton D, Donohoe RT, Sillance B, Nabb S: The influence of phosphatidylserine supplementation on mood and heart rate when faced with an acute stressor. Nutr Neurosci 2001;4:169–178.
10 Hellhammer J, Fries E, Buss C, Engert V, Tuch A, Rutenberg D, Hellhammer D: Effects of soy lecithin phosphatidic acid and phosphatidylserine complex (PAS) on the endocrine and psychological responses to mental stress. Stress 2004;7:119–126.
11 Schreiber S, Kampf-Sherf O, Gorfine M, Kelly D, Oppenheim Y, Lerer B: An open trial of plant-source derived phosphatidylserine for treatment of age-related cognitive decline. Isr J Psychiatry Relat Sci 2000;37:302–307.
12 Jorissen BL, Brouns F, Van Boxtel MP, Ponds RW, Verhey FR, Jolles J, Riedel WJ: The influence of soy-derived phosphatidylserine on cognition in age-associated memory impairment. Nutr Neurosci 2001;4:121–134.
13 Kalmijn S, van Boxtel MP, Ocke M, Verschuren WM, Kromhout D, Launer LJ: Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. Neurology 2004;62:275–280.
14 Huang TL, Zandi PP, Tucker KL, Fitzpatrick AL, Kuller LH, Fried LP, Burke GL, Carlson MC: Benefits of fatty fish on dementia risk are stronger for those without APOE epsilon4. Neurology 2005;65:1409–1414.
15 Albanese E, Dangour AD, Uauy R, Acosta D, Guerra M, Guerra SSG, Huang Y, Jacob KS, Llibre de Rodriguez J, Noriega LH, Salas A, Sosa AL, Sousa RM, Williams J, Ferri CP, Prince MJ: Dietary fish and meat intake and dementia in Latin America, China, and India: a 10/66 Dementia Research Group population-based study. Am J Clin Nutr 2009;90:392–400.
16 Terano T, Fujishiro S, Ban T, Yamamoto K, Tanaka T, Noguchi Y, Tamura Y, Yazawa K, Hirayama T: Docosahexaenoic acid supplementation improves the moderately severe dementia from thrombotic cerebrovascular diseases. Lipids 1999;34(suppl):S345–S346.
17 Fontani G, Corradeschi F, Felici A, Alfatti F, Migliorini S, Lodi L: Cognitive and physiological effects of omega-3 polyunsaturated fatty acid supplementation in healthy subjects. Eur J Clin Investigation 2005;35:691–699.
18 Vaisman N, Kaysar N, Zaruk-Adasha Y, Pelled D, Brichon G, Zwingelstein G, Bodennec J: Correlation between changes in blood fatty acid composition and visual sustained attention performance in children with inattention: effect of dietary n-3 fatty acids containing phospholipids. Am J Clin Nutr 2008;87:1170–1180.
19 Vaisman N, Pelled D: n-3 Phosphatidylserine attenuated scopolamine-induced amnesia in middle-aged rats. Prog Neuropsychopharmacol Biol Psychiatry 2009;33:952–959.
20 Crook TH 3rd, Feher EP, Larrabee GJ: Assessment of memory complaint in age-associated memory impairment: the MAC-Q. Int Psychogeriatr 1992;4:165–176.
21 Vakil E, Blachstein H: Rey Auditory-Verbal Learning Test: structure analysis. J Clin Psychol 1993;49:883–890.
22 Lezak MD: Neuropsychological Assessment, ed 2. New York, Oxford University Press, 1983.
23 Meyers JE, Meyers KR: Rey Complex Figure and Recognition Trial: Professional Manual. Odessa, Psychological Assessment Resources, 1995.
24 Aharonson V, Korczyn AD: Human-computer interaction in the administration and analysis of neuropsychological tests. Comput Methods Programs Biomed 2004;73:43–53.
25 Pepeu G, Pepeu IM, Amaducci L: A review of phosphatidylserine pharmacological and clinical effects: is phosphatidylserine a drug for the ageing brain? Pharmacol Res 1996;33:73–80.
26 Folstein MF, Folstein SE, McHugh PR: 'Mini-Mental State': a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
27 Welsh K, Butters N, Hughes J, Mohs R, Heyman A: Detection of abnormal memory decline in mild cases of Alzheimer's disease using CERAD neuropsychological measures. Arch Neurol 1991;48:278–281.
28 Carrion-Baralt JR, Melendez-Cabrero J, Schnaider Beeri M, Sano M, Silverman JM: The neuropsychological performance of nondemented Puerto Rican nonagenarians. Dement Geriatr Cogn Disord 2009;27:353–360.
29 Olazaran J, Muniz R, Reisberg B, Pena-Casanova J, del Ser T, Cruz-Jentoft AJ, Serrano P, Navarro E, Garcia de la Rocha ML, Frank A, Galiano M, Fernandez-Bullido Y, Serra JA, Gonzalez-Salvador MT, Sevilla C: Benefits of cognitive-motor intervention in MCI and mild to moderate Alzheimer disease. Neurology 2004;63:2348–2353.
30 Breuil V, De Rotrou J, Forette F: Cognitive stimulation of patients with dementia: preliminary results. Int J Geriatr Psychiatry 1994;9:211–217.
31 Reisberg B, Shulman MB, Torossian C, Leng L, Zhu W: Outcome over seven years of healthy adults with and without subjective cognitive impairment. Alzheimers Dement 2010;6:11–24.
32 Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E: Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–308.
33 Calderini G, Aporti F, Bellini F, Bonetti AC, Teolato S, Zanotti A, Toffano G: Pharmacological effect of phosphatidylserine on age-dependent memory dysfunction. Ann NY Acad Sci 1985;444:504–506.
34 Pepeu G: The phosphatidylserine story. Nutrition 1999;15:789.
35 Vannucchi MG, Pepeu G: Effect of phosphatidylserine on acetylcholine release and content in cortical slices from aging rats. Neurobiol Aging 1987;8:403–407.
36 Leon A, Benvegnu D, Toffano G, Orlando P, Massari P: Effect of brain cortex phospholipids on adenylate-cyclase activity of mouse brain. J Neurochem 1978;30:23–26.
37 Argentiero V, Tavolato B: Dopamine (DA) and serotonin metabolic levels in the cerebrospinal fluid (CSF) in Alzheimer's presenile dementia under basic conditions and after stimulation with cerebral cortex phospholipids (BC-PL). J Neurol 1980;224:53–58.