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## Short Communication

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# Maintenance of Cognitive Performance and Mood for Individuals with Alzheimer's Disease Following Consumption of a Nutraceutical Formulation: A One-Year, Open-Label Study

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**Abstract.** Nutritional interventions have shown varied efficacy on cognitive performance during Alzheimer's disease (AD). Twenty-four individuals diagnosed with AD received a nutraceutical formulation (NF: folate, alpha-tocopherol, B12, S-adenosyl methionine, N-acetyl cysteine, acetyl-L-carnitine) under open-label conditions (ClinicalTrials.gov NCT01320527). Primary outcome was cognitive performance. Secondary outcomes were behavioral and psychological symptoms of dementia (BPSD) and activities of daily living. Participants maintained their baseline cognitive performance and BPSD over 12 months. These findings are consistent with improvement in cognitive performance and BPSD in prior placebo-controlled studies with NF, and contrast with the routine decline for participants receiving placebo.

**Keywords:** Alzheimer's disease, behavioral symptoms, cognitive performance, mood, nutraceutical formulation

Alzheimer's disease (AD) is characterized by progressive cognitive decline accompanied by mood and behavioral and psychological symptoms of dementia (BPSD) [1, 2]. To obtain maximal efficacy,

interventions must be initiated as early as possible [1–3]. In this regard, overt cognitive decline is required prior to initiation of current pharmacological agents [4]. A growing body of evidence points toward the efficacy of lifestyle modifications, including nutritional supplementation, in delaying cognitive decline and BPSD in AD [4, 5].

Consumption of a nutraceutical formulation [NF: folate, alpha-tocopherol, B12, S-adenosyl methionine (SAM) N-acetyl cysteine (NAC) and acetyl

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-L-carnitine (ALCAR)] improved cognitive performance and BPSD for individuals diagnosed with AD versus placebo without serious adverse events in phase I and phase II trials ranging from 9 months to 2.4 years, encompassing a total of 125 individuals [6–8]. NF also significantly improved cognitive performance during year-long trials for 34 community-dwelling individuals with mild cognitive impairment and for 93 individuals with no known or suspected cognitive difficulties [9, 10]. In all studies, individuals originally randomized to placebo demonstrated improvement following crossover to NF that was statistically identical to that of cohorts originally randomized to NF [8–10].

Herein, we report the findings for 24 individuals diagnosed with AD who initiated consumption of this formulation on their own or via caregiver/physician advice after publication of our phase I studies [6, 7], and who requested participation in our recent Phase II studies [8]. Since randomization of these individuals could result in temporary forced withdrawal of any benefit of NF, they were instead maintained in accordance with institutional review board (IRB) approval as a separate cohort that was provided NF under open label conditions for 12 months, during which they and their caregivers completed the same tests as randomized participants.

## INTERVENTION

As in prior studies [6–10], NF consisted of 400  $\mu$ g folic acid, 6  $\mu$ g B12, 30 IU alpha-tocopherol, 400 mg SAM (200 mg active ion), 600 mg NAC, and 500 mg ALCAR, prepared by Nutricap Labs (Farmingdale, NY 11735) at USP grade under FDA-approved, cGMP conditions, with 2 tablets/daily dose. Participants received NF under open-label conditions for 12 months.

## TRIAL REGISTRATION

This study was registered with ClinicalTrials.gov (NCT01320527) and the Alzheimer’s Association (alz.org/Trialmatch).

## INCLUSION/EXCLUSION CRITERIA

Inclusion criteria were personal physician’s diagnosis (probable AD and/or senile dementia of the Alzheimer type) and approval to participate, ability to swallow pills, availability of a personal or

professional caregiver, and signed consent from the participant or health-care proxy. Exclusion criteria were inability to swallow pills and known or suspected bipolar disorder (for which SAM is contraindicated) [11].

## PARTICIPANT DEMOGRAPHICS

Individuals diagnosed with AD ( $n=24$ ; aged  $78.4 \pm 5.7$  years,  $13.9 \pm 2.1$  years education, baseline MMSE  $19.6 \pm 6.0$ ).

## OUTCOME MEASURES

Primary outcome was defined as cognitive performance, ascertained by participant performance on Clox-1 and the Dementia Rating Scale [12, 13]. Secondary outcomes were defined as BPSD and daily function, ascertained by caregiver completion of the Neuropsychiatric Inventory (NPI) and the Alzheimer’s Disease Cooperative Study – Activities of Daily Living (ADL) [14, 15]. Tests were completed at baseline, and at 3-month intervals until 12 months. Primary analysis was Intention-To-Treat; all enrolled participants were included in analysis, subject to attrition. All instruments have established reliability and validity.

## RANDOMIZATION AND MASKING

The protocol was approved by the New England IRB (Newton, MA) and by respective IRBs.

## STUDY ENDPOINTS

Based on prior efficacy, the protocol specified that all participants would receive NF in an open-label extension for the duration of the 12-month study.

## STATISTICAL ANALYSES

Data were independently analyzed by statisticians (CM and RP) not involved in data acquisition. Statistical methods included paired Student’s  $t$  tests (2-tailed) of individual participant performance versus baseline, unpaired 2-tailed  $t$  tests of NF and placebo cohorts, and Cohen’s effect size. Effect size was calculated for each respective cohort according to the formula: [(cohort mean at treatment time) - (cohort mean at baseline)]/standard deviation at baseline of the entire participant pool;  $p$  values  $< 0.05$  and

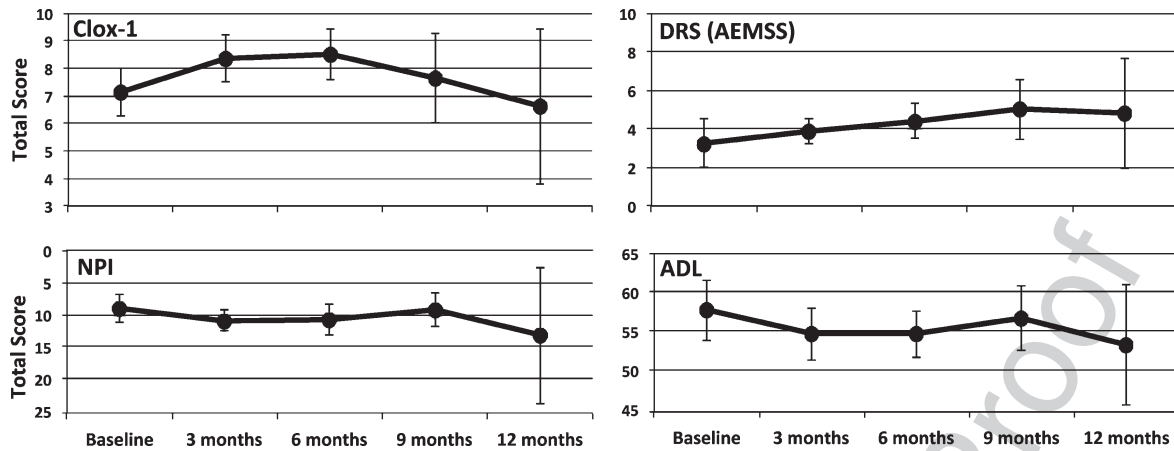


Fig. 1. Impact of NF on cognitive performance and BPSD for participants with AD under open-label conditions. Participants diagnosed with AD received NF in open-label conditions from baseline. Values represent the mean ( $\pm$ standard error of the mean) total scores of participants on Clox-1 and the DRS (AEMSS), and corresponding caregiver evaluations for the NPI and ADL as indicated. Participant numbers for Baseline, 3, 6, 9, and 12 months are as follows: Clox-1 = 24, 22, 22, 11, and 5; AEMSS = 121, 23, 20, 11, and 5; NPI = 12, 23, 20, 11, and 4; ADL = 13, 23, 22, 11, and 5.

effect sizes  $>0.2$  were considered significant [16]. Participants/caregivers completing each test varies both among tests and sampling intervals; see figure legends.

Participants did not display any significant or clinical change in cognitive performance over the course of 12 months. Caregivers reported no significant or clinical change in BPSD or daily function over the course of 12 months (Fig. 1). No serious adverse events were reported for any participants.

In prior studies where participants diagnosed with AD received NF *de novo*, participants randomized to NF improved in cognitive performance and BPSD within 3–6 months, and either maintained that improvement or displayed continued improvement over 12 months. Participants initially randomized to placebo did not improve or declined; however, following crossover to NF, these participants demonstrated improvement or maintenance paralleling that of participants initially randomized to NF [6–10].

The present study included a cohort with AD that had already been consuming NF prior to initiation of monitoring of cognitive performance and BPSD. Unlike individuals receiving NF *de novo*, participants in the present study did not display a significant change in cognitive performance or BPSD over 12 months. The lack of an increase may be anticipated, since any increase they might have displayed could have occurred prior to enrollment in this study. Notably, however, they displayed no significant decrease in cognitive performance or BPSD over the course of 12 months, which contrasts with the routine

decline observed for participants receiving a placebo for 12 months (Fig. 2) [8, 17–34]. It is recognized that this comparison is compromised since the participants in the present study were aware that they were receiving NF, while randomized participants did not share the same certainty.

These findings extend prior studies on the efficacy of NF in multiple studies from 2008 to 2015 [6–10]. A limitation of our analyses is that participants were not fully categorized according to prior or concurrent supplement/vitamin consumption or general nutritional intake. It is noteworthy that sustained cognitive and behavioral performance was maintained herein despite these caveats. The efficacy of NF may be maximized when combined with the so-called “Mediterranean diet,” which has beneficial effects [35] and other lifestyle modifications [4]. Maintenance of acetylcholine levels by NF components in murine models of AD neuropathology [36] holds the possibility that NF may augment acetylcholinesterase therapy. In this regard, administration of a combination of supplements may be essential to augment pharmacological approaches. Consistent with this possibility, a different antioxidant formulation provided significant improvement in cognitive function when administered in combination with donepezil versus donepezil alone [37]. In addition to providing benefit for cognitive performance, NF maintained and activities of daily living for as long as 28 months (the longest period tested thus far) [6], supporting the notion that nutritional approaches can positively impact the quality of life for individuals with AD.

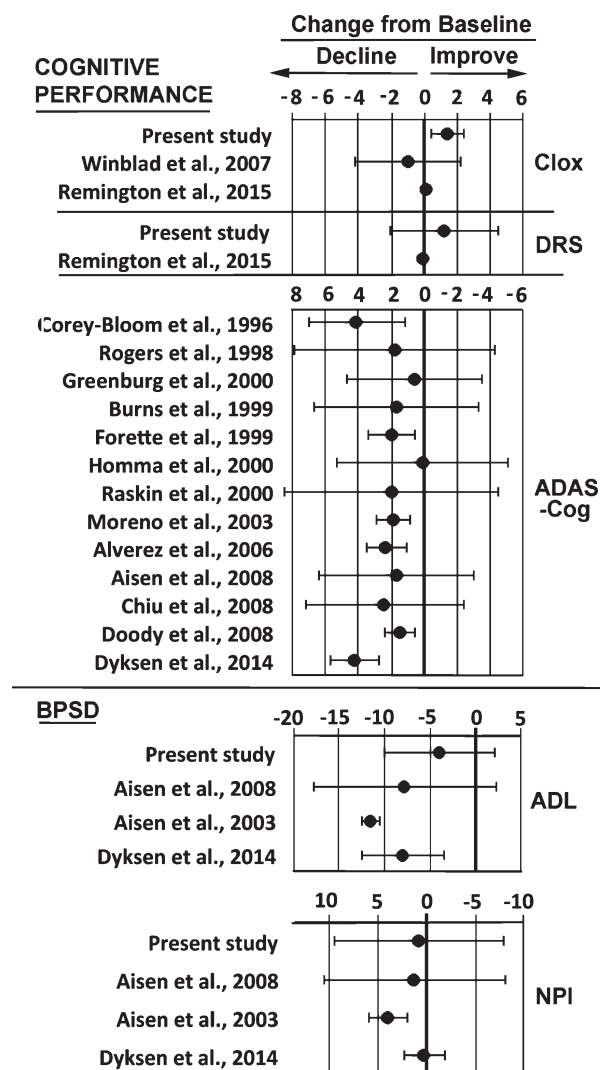


Fig. 2. Comparison of impact of NF on cognitive performance and BPSD in the present study with historical placebos. Upper panels (“Cognitive Performance”) compare values obtained for Clox and DRS for participants in the present study after consuming NF for 6 months with those of individuals randomized to placebo for 6 months from the indicated studies. Most prior studies utilized ADAS-cog rather than DRS, so historical placebo values for ADAS-cog are included for comparison. Lower panels (“BPSD”) compare values obtained in ADCS-ADL and NPI for participants in the present study after consuming NF for 12 months with those of individuals randomized to placebo for 12 months from the indicated studies. Intervals of 6 months for cognitive performance and 12 months for BPSD are presented due to maximal availability of historical placebo information at these respective intervals. Values represent the mean percent decline ( $\pm$  standard deviation) compared to respective baselines.

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The nutraceutical formulation utilized herein is marketed by Sevo Nutraceuticals (Watertown, MA); TBS and UMass Lowell have a financial interest in this formulation and the company. TBS is a consultant for Sevo Nutraceuticals. Study closure preceded any licensing agreements of this formulation to Sevo Nutraceuticals.

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