A Nutritional Formulation for Cognitive Performance in Mild Cognitive Impairment: A Placebo-Controlled Trial with an Open-Label Extension

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Accepted 22 June 2015

Abstract. Thirty-four individuals with mild cognitive impairment were randomized for 6 months to a nutraceutical formulation (NF: folate, alpha-tocopherol, B12, S-adenosyl methionine, N-acetyl cysteine, acetyl-L-carnitine) or indistinguishable placebo, followed by a 6-month open-label extension in which all individuals received NF. The NF cohort improved in the Dementia Rating Scale (DRS; effect size >0.7) and maintained baseline performance in CLOX-1. The placebo cohort did not improve in DRS and declined in CLOX-1, but during the open-label extension improved in DRS and ceased declining in CLOX-1. These findings extend prior studies of NF efficacy for individuals without cognitive impairment and with Alzheimer’s disease.

Keywords: Aging, Alzheimer’s disease, cognitive performance, dementia, mild cognitive impairment, nutraceutical

Mild cognitive impairment (MCI) is characterized by cognitive decline beyond that anticipated for an individual’s age demonstrated by neuropsychological examination, but not accompanied by functional impairment [1, 2]. Interventions to avoid or delay cognitive decline, including nutritional modifications, have the greatest potential for efficacy when initiated prior to cognitive decline [3-6]. This is in direct contrast with pharmacological interventions, which require prior cognitive decline for efficacy [4]. Consumption of a nutraceutical formulation [NF: folate, alpha-tocopherol, B12, S-adenosyl methionine (SAM), N-acetyl cysteine (NAC), and acetyl-L-carnitine (ALCAR)] improved cognitive performance and behavioral/mood complications for individuals diagnosed with varying stages of AD without serious adverse events in phase I and phase II trials. Greater efficacy was observed for individuals with less severe AD at the onset of the trial [7-9]. NF also significantly improved cognitive performance for community-dwelling individuals without cognitive difficulties in a placebo-controlled trial [10].
Herein, we report the effect of NF for individuals diagnosed with MCI.

INTERVENTION

NF consisted of 400 μg folic acid, 6 μg B12, 30 I.U. alpha-tocopherol, 400 mg SAM (200 mg active ion), 600 mg NAC, and 500 mg ALCAR, prepared by Nutricap Labs (Farmingdale, NY) at USP grade under FDA-approved, cGMP conditions, with 2 tablets/daily dose; placebo tablets consisted of the identically-appearing inert ingredients distinguishable only by lot number on otherwise identical bottles [9, 10]. Participants were advised to continue with their present diets and to continue any medications.

TRIAL REGISTRATION

This study was registered with ClinicalTrials.gov (NCT01320527 and NCT00903695) and the Alzheimer’s Association (http://alz.org/Trialmatch).

INCLUSION/EXCLUSION CRITERIA

Inclusion criteria were personal physician’s diagnosis of MCI and approval to participate, ability to swallow pills, 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

Community-dwelling individuals diagnosed with MCI (n = 34, 65.9 ± 11.3 years of age; 14.5 ± 2.4 years of education) and recruited from two test sites were randomized to NF or placebo and tested from March 2010–April 2012.

OUTCOME MEASURES

Participants completed the Dementia Rating Scale (DRS) and CLOX-1 at baseline, and at 3-month intervals until 12 months [7–10]. These instruments have established reliability and validity [12, 13]. DRS utilized to assay multiple cognitive domains. CLOX-1, which assesses executive function, was included since difficulties in executive dysfunction for individuals with MCI is associated has been associated with depression and anxiety [14, 15]. Intention-to-treat analysis was used to assess clinical effectiveness; all enrolled participants were included in analysis, regardless of attrition.

RANDOMIZATION AND MASKING

Participants selected a sealed bag containing NF or placebo; respective site coordinators recorded the lot number. Participant results were communicated to RR as two cohorts without revealing their distribution code. The protocol was approved by the New England IRB (Newton, MA) and by respective institutional IRBs for each site.

STUDY ENDPOINT

Based on prior efficacy of NF within 6 months for individuals with no known or suspected cognitive decline and for individuals with dementia [7–10], the New England IRB protocol specified randomization for a maximum of 6 months, after which code would be broken and all participants would receive NF in an open-label extension for the duration of the 12-month study (Fig. 1). Only one of the sites participated in this open-label extension; this site operated under its own IRB.

STATISTICAL ANALYSES

Data were independently analyzed by two statisticians (CM and RP) who were not involved in data acquisition. Statistical methods included Cohen’s effect size [16], paired Student’s t tests (2-tailed) of individual participant performance versus baseline, and unpaired 2-tailed t tests of NF and placebo cohorts. 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; effect sizes >0.2 were defined as a small effect, >0.6 as a moderate effect, and >0.8 as a large effect [16]. The number of participants completing each test varies both among tests and sampling intervals; see Figure legends.

Following randomization, NF (n = 22) and placebo (n = 12) cohorts were statistically identical (p > 0.05; Student’s t tests) in age (63 ± 12 versus 61 ± 11), years of education (15 ± 1.4 versus 14 ± 3), and baseline AEMSS (11 ± 4 versus 10 ± 4.2; NF versus
Fig. 1. Participant flow chart. Numbers refer to all cohorts (e.g., randomized AD and MCI participants and open-label AD participants). The first 6 months of randomization is considered "Allocation"; the 6-month open-label extension of the randomization protocol is considered as "follow-up." Only one of the two test sites participated in the open-label extension, resulting in loss of 9 participants in the NF cohort and 2 in the placebo cohort at 9 months. One additional participant withdrew from the placebo cohort at 6 months, and one from the NF cohort at 12 months. No withdrawals were due to adverse reactions with NF.

Participants receiving NF displayed a significant increase in performance on the DRS within 3 months (Cohen’s Effect Size 0.76), and maintained this level of improvement for the duration of the study (Fig. 2A).

Participants receiving placebo did not significantly improve during the randomization phase (i.e., the first 6 months). However, these individuals improved significantly within 3 months following transfer to NF during the open-label extension (Cohen’s Effect Size 0.35), and maintained this improvement for the duration of the study (Fig. 2A).

Participants receiving NF maintained their basal level of performance on CLOX.1 for the duration of the study, while those receiving placebo displayed a non-significant decline over the first 6 months (Fig. 2B). However, when the placebo cohort was transferred to NF during the open-label extension, no further decline was observed (Fig. 2B).
No serious adverse events were reported for any participants. At the end of the randomized phase (i.e., 6 months of receiving NF or placebo under double-blind conditions), 67% of the NF cohort that maintained or improved on AEMSS also maintained or improved on CLOX-1; by contrast, only 18% of the placebo cohort that maintained or improved in AEMSS also maintained or improved in CLOX-1. These studies demonstrate efficacy of NF for improvement in overall cognitive performance as quantified in the DRS [12], and maintenance of executive function as quantified by CLOX-1 [13] for as long as 1 year for individuals with MCI. The placebo cohort declined in executive function pending crossover to NF, at which point their executive function stabilized. While the DRS and CLOX-1 tests overlap, they quantify distinct aspects of cognitive performance [12, 13]. Identical baseline levels of performance and equivalent responses following the intervention were therefore not necessarily anticipated. However, since decline in executive dysfunction in MCI is associated with depression and anxiety [14, 15], the positive impact of NF on executive function may have implications for MCI prognosis; validation of this possibility will require longitudinal studies.

NF was well-tolerated here as in our prior studies. The impact of NF as observed herein for individuals with MCI is not unexpected, since prior studies demonstrate efficacy of NF for individuals with no known or suspected cognitive impairment, as well as for those diagnosed with mild-severe AD [7–10]. The long-term impact of NF may have been further highlighted had we maintained randomization for 12 months. However, we considered maintenance of individuals on placebo for such a protracted period to be inappropriate: since we observed statistical improvement for individuals with no cognitive impairment, as well as for those diagnosed with AD within 3–6 months of receiving NF [7–10]. Since MCI is a condition between normal cognitive performance and dementia, if NF were to be effective, improvement/maintenance versus placebo would be anticipated herein within 3–6 months, which was indeed the case.

As in these prior clinical studies, a limitation of the present analyses is that participants were not categorized according to prior or concurrent supplement/vitamin consumption, nor was baseline nutritional criteria considered. It is noteworthy that improvement was attainable herein despite these caveats. A second limitation is that we have no information of participant subtypes of MCI (e.g., amnestic, single/multiple domains). MCI is heterogeneous, and this variance may influence its progression. Individuals with amnesic or multi-domain MCI are more likely to progress to dementia; however, all subtypes can do so, and classification among subtypes can display instability over time [15, 17–20]. Comparison of MCI subtypes should be addressed in a larger study. Finally, additional test instruments, such as Trail-making and/or digit/word recall, may have been informative, since individuals with no cognitive compromise improved on these instruments following consumption of NF [10].

Fig. 2. Impact of NF on cognitive performance. Participants were randomized to NF or placebo for 6 months, after which all participants received NF under open label conditions as described in methods. The initial placebo cohort is therefore referred to as “Delayed Start.” Values represent the mean ± standard error of the mean total scores on the DRS (AEMSS: A) and CLOX-1 (B) for each cohort as indicated. Baseline values represent the mean ± standard error for the total participant pool. Subsequent values represent the mean ± standard error for NF and delayed-start cohorts, respectively. Participant numbers for Baseline, 3, 6, 9, and 12 months are as follows: AEMSS = 22, 14, 9, 5, and 10 for NF, and 12, 10, 9, 9, and 9 for Delayed Start, respectively; CLOX-1 = 21, 19, 19, 11, and 10 for NF, and 12, 13, 9, 9, and 9 for Delayed Start, respectively.
Our findings are consistent with the prior demonstration that nutritional modification, such as adherence to a Mediterranean-style diet or supplementation with B vitamins has been effective in reducing progression to AD [3–5, 17, 21, 22]. Physical exercise also improved global cognitive function, including a minor degree of impact on executive function [23]. Since many individuals with MCI will continue to decline in cognitive performance and display associated behavioral difficulties, eventually warranting a diagnosis of dementia, the findings presented here support including NF as part of a therapeutic approach to delay or minimize cognitive decline for individuals with MCI.

ACKNOWLEDGMENTS

Supported by an award to TBS and RR from the Alzheimer’s Association. No corporate funds were involved in these studies.

The nutraceutical formulation utilized herein is marketed by Sevo Nutraceuticals (Waltham, MA); TBS and UMass Lowell have a financial interest in this formulation and the company.

Authors’ disclosures available online (http://j-alz.com/manuscript-disclosures/15-0057r4).

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