American Journal of Alzheimer's Disease & Other Dementias®
Volume 24 Number 1
March 2009 27-33

10.1177/1533317508325094
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Efficacy of a Vitamin/Nutriceutical Formulation for Moderate-stage to Later-stage Alzheimer's disease: A Placebo-controlled Pilot Study

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Recent studies demonstrated efficacy of a vitamin/nutriceutical formulation (folate, vitamin B12, alpha-tocopherol, S-adenosyl methionine, *N*-acetyl cysteine, and acetyl-L-carnitine) for mild to moderate Alzheimer's disease. Herein, we tested the efficacy of this formulation in a small cohort of 12 institutionalized patients diagnosed with moderate-stage to later-stage Alzheimer's disease. Participants were randomly separated into treatment of placebo groups. Participants receiving the formulation demonstrated a clinically significant delay in decline in the Dementia Rating Scale and clock-drawing test as compared to those receiving placebo. Institutional caregivers reported approximately 30% improvement in the Neuropyschiatric Inventory and maintenance of performance in the Alzheimer's Disease Cooperative Study–Activities of Daily Living for more than 9 months. This formulation holds promise for delaying the decline in cognition, mood, and daily function that accompanies the progression of Alzheimer's disease, and may be particularly useful as a supplement for pharmacological approaches during later stages of this disorder. A larger trial is warranted.

Keywords: cognition; behavioral response; vitamin; nutriceutical; supplement

Introduction

Alzheimer's disease (AD) is characterized by a progressive loss of memory and decline in cognitive function. Although the onset, advancement, and severity of these conditions are highly variable in nature, the types of symptoms are common, including behavioral changes and the loss in ability to carry out activities of daily living.[1] As the disease becomes progressively more severe, caregiver burden and health care costs concurrently increase.[2]

Current pharmacological treatments reduce symptoms of AD rather than prevent ultimate decline in cognitive and behavioral function, are costly, and are often accompanied by a host of adverse events. Moreover, a considerable degree of cognitive decline must ensue before administration of pharmacotherapy, which by that time can be accompanied by irreversible functional decline.[3-10]

The decline in nutrition that often accompanies age can exacerbate otherwise latent AD risk factors, which highlights the potential importance of nutritional intervention.[11-14] Herein, we examined the efficacy of treatment with a nutriceutical formulation (NF) consisting of folic acid, vitamin B12, vitamin E, *N*-acetyl cysteine (NAC), acetyl-L-carnitine (ALCAR), and S-adenosyl methionine (SAM) for individuals with moderate-stage to late-stage AD, which improved cognition and behavioral symptoms for mild to moderate AD.[15] Preclinical studies demonstrate that the constituents of this formulation provide neuroprotection against multiple factors that contribute to AD, including reducing oxidative stress, decreasing PS-1 expression, gamma-secretase activity, Abeta generation, and tau phosphorylation, increasing glutathione, ATP, and acetylcholine, compensating for apolipoprotein E deficiency,

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preventing cognitive decline, and decreasing aggression.[16-32] Preclinical studies further demonstrate that synergistic neuroprotection can be achieved by combining 2 or more of these constituents.[21,25,33,34]

Methods

Preparation of Vitamin/Nutriceutical Formulation

Nutriceutical formulation consisted of folic acid (400 μg), vitamin B12 (6 μg), vitamin E (as alpha-tocopherol; 30 IU), SAM (400 mg), NAC (600 mg), and ALCAR (500 mg). Nutriceutical formulation was prepared at *United States Pharmacopeia* (*USP*) grade under Food and Drug Administration (FDA)-approved, cyclic guanosine monophosphate (cGMP) conditions in tablet form, with 2 tablets constituting a daily dose, by Nutricap Labs (Farmingdale, NY).[15]

Participants

Twelve participants were recruited from residents of a Massachusetts nursing home. Participants were clinically diagnosed with moderate to late-stage AD according to the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) criteria for probable AD[35] and had an average Mini-Mental State Examination (MMSE) score of 11.9 $\pm$ 2.5 (Mattis Dementia Rating Scale[36]). Participants were randomly assigned to treatment or placebo groups and maintained their normal dietary regimen and vitamin/medication intake throughout the course of this study.

Outcome Assessments

At baseline and at 3-month intervals for a total of 9 months, participants completed the Dementia Rating Scale 2 (DRS-2) and the Clox Drawing Test (CLOX-1[37-39]) each of which assess neuropsychological performance. Institutional caregivers completed the 12-item Neuropsychiatric Inventory (NPI), which determines the degree to which abnormal behavior affects the patient's well-being and the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL), which assesses ability to engage in day-to-day activities, respectively.[40-42]

Treatment and placebo groups were statistically compared at 3 months using Student's *t* test. In addition, each participant's baseline score was subtracted from scores at subsequent intervals, and resultant paired differences were averaged and a paired *t* distribution was calculated for each interval versus baseline. Values in both tests were considered statistically significant if $P < .05$. The effect size was calculated using raw scores at each time interval according to the formula: (mean at treatment time) − (mean at baseline)/standard deviation of baseline. Values >.2 were considered clinically significant; values >.8 were considered to have large clinical significance.[43]

Results

Informed consent was sought from the health care proxy of 19 residents of a dementia unit. Twelve consented to their family member's participation and were enrolled. At 3 months, 1 participant within the treatment group had refused to take all medications and 1 participant receiving the placebo died; these participants were not included in baseline calculations. By 6 months, 5 additional subjects withdrew: 1 participant had all unnecessary medications stopped due to advanced disease, 2 participants had refused all medications, and 2 participants could only take medications in crushed form because of swallowing difficulties; these withdrawals resulted in elimination of the placebo group, which is therefore only represented at 3 months. By 9 months, 1 participant had all medications stopped and the remaining 4 participants would only take medications in crushed form; because the constituents of NF as prepared and used in this study were incompatible with crushing, the study was halted at 9 months.

NF delayed the decline in DRS and CLOX-1 versus placebo (Figure 1). Clinical significance (0.9 and 0.38) was attained for the treatment group within 3 months versus baseline as ascertained by DRS and CLOX-1, respectively. The relatively small participant pool in each population precluded statistical significance between treatment and placebo groups at 3 months, although a trend toward statistical significance was observed in a 1-tailed, nonpaired *t* test ($P < .1$ and .06 for DRS and CLOX-1, respectively). Paired *t* tests for individual participants indicated that treatment groups did not decline significantly from baseline in DRS performance for 6 months ($P < .86$); however, the decline exhibited between 6 and 9 months displayed a trend toward a significance ($P < .07$). Both treatment and participant groups declined in performance in CLOX-1, but the treatment group displayed a slower decline (Figure 1).

Institutional caregivers reported that participants receiving NF demonstrated a moderate, steady (30%) improvement in the NPI for more than 3 months,

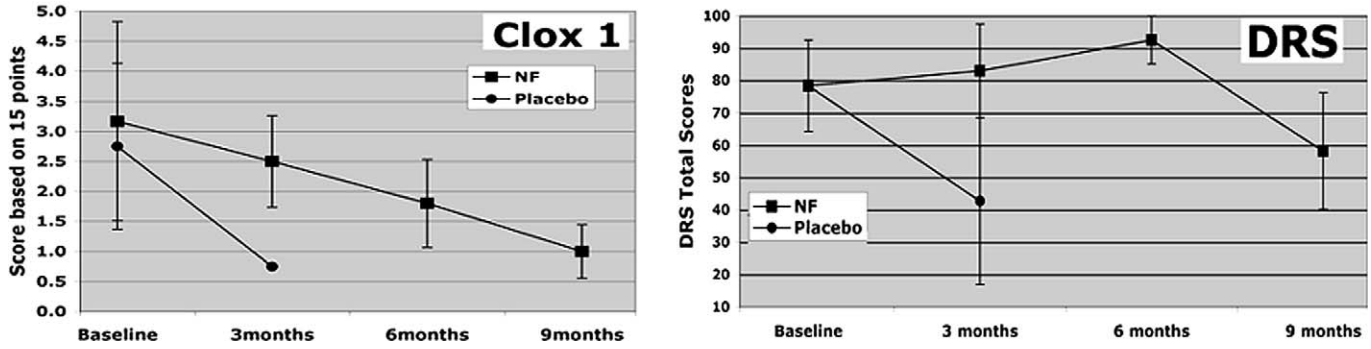

Figure 1. Nutriceutical formulation delays the decline in cognitive performance in moderate-stage to late-stage AD. Panels present performance on the DRS and CLOX-1 as indicated. Values in each panel represent mean total scores for the total 12 participants ± standard error of the mean; mean baseline scores were subtracted from all values to generate a baseline of 0 for clarity. Note that participants receiving NF maintained performance on the DRS for an additional 6 months, after which they underwent a similar decline as did placebo at 3 months. Note also the delay in decline in performance on CLOX-1 versus placebo. AD indicates Alzheimer's disease; CLOX-1, Clox Drawing Test; DRS, Dementia Rating Scale; NF, nutriceutical formulation.

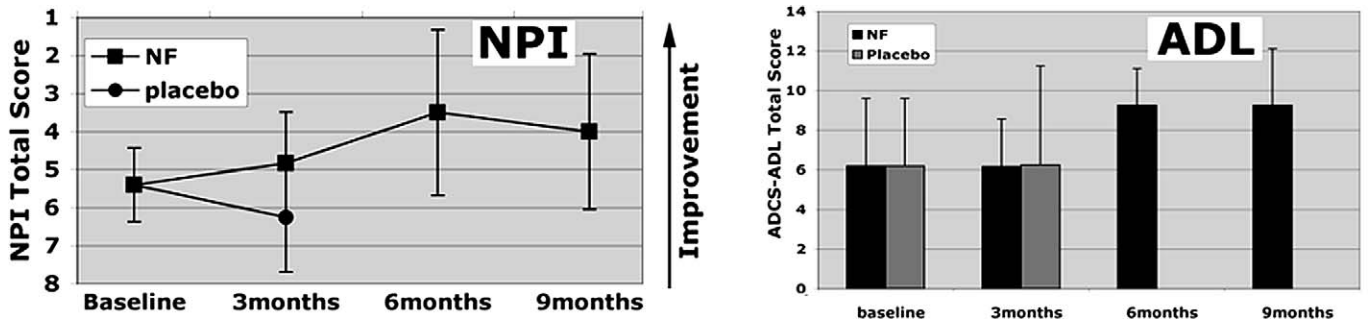

Figure 2. NF improves BPSD and ability to carry out daily activities. Panels present institutional caregiver reports for 12 participants for the NPI and ADCS-ADL as indicated. Values in each panel represent mean total scores for the total participants ± standard error of the mean; mean baseline scores were subtracted from all values to generate a baseline of 0. Since a decrease in score denotes improvement, the y-axis has also been inverted for clarity. ADCS-ADL indicates Alzheimer's Disease Cooperative Study–Activities of Daily Living; BPSD, behavioral and psychological symptoms of dementia; NPI, Neuropsychiatric Inventory.

whereas the placebo group declined (Figure 2); however, these differences were not statistically or clinically significant ($P < .78$, NF vs baseline at 6 months). Neuropsychiatric Inventory scores remained elevated at 9 months. Participants demonstrated a similar improvement in ADCS-ADL at 6 and 9 months (Figure 2). Elimination of the placebo group precluded caregiver comparison of NF versus placebo beyond 3 months. Nevertheless, reporting of improvement in performance in both tests supports the notion that this formulation can improve mood, behavior, and support continued performance of daily activities.

Discussion

As in our prior study with mild to moderate AD,[15] NF had a positive impact on cognitive performance, behavioral and psychological symptoms of dementia (BPSD) and activities of daily living in moderate-stage to later-stage AD. Participants receiving the placebo exhibited a decline in cognitive performance as ascertained by both the DRS and clock-drawing tasks. Unlike the placebo group, participants receiving NF maintained performance on the DRS for 6 months equivalent to that observed at baseline. The eventual decline in DRS between 6 and 9 months (37%) mirrored that observed for the placebo group between 3 months (45%). This finding indicates that NF delayed cognitive decline as monitored by the DRS for approximately 6 months. NF also delayed the decline in cognitive performance as indicated by CLOX-1. Participants receiving NF displayed only a 20% decline by 3 months, as opposed to the 72% decline observed in the placebo group by this time. Notably, participants receiving NF underwent

a linear, continuous decline, reaching a total decline of 68% by 9 months. The correspondence of this total decline at 9 months to that of the placebo group at 3 months corresponds temporally to the 6-month delay in decline of performance on the DRS for participants receiving NF versus those receiving placebo.

Institutional caregiver reports were somewhat more positive than the above cognitive tests, in that participants receiving NF were reported to have improved in both NPI and ADCS-ADL within 6 months and were reported to have sustained this improvement until termination of the study at 9 months. Notably, this sustained improvement in caregiver reports exceeds by at least 3 months the maintenance of cognitive performance in participants receiving NF. This observation is consistent with the notion that BPSD that accompany AD do not necessarily correlate with cognitive performance[44-47]; treatments to alleviate the BPSD severity therefore remain important independently of any efficacy on cognition. Following institutionalization, BPSD present a unique challenge to caregiver staff, and improved total performance in NPI correlates with reduced caregiver distress.[48-56] The efficacy of NF in BPSD may therefore represent an important aspect of its usefulness following institutionalization. However, the possibility remains that any alleviation of institutional caregiver burden in participants receiving NF may inadvertently foster additional enthusiasm in their reporting of NPI and ADCS-ADL, which may or may not have contributed to the apparent more prolonged efficacy of NF in NPI and ADCS-ADL (which are caregiver reports) as opposed to DRS and clock-drawing (which are direct assessment of participant cognitive performance).

We have previously reported clinical and statistical improvement in both cognitive performance as well as BPSD following administration of this formulation to individuals with mild to moderate AD.[15] The findings presented herein add to the growing body of evidence that nutritional intervention can have a positive effect on progression of AD even at advanced stages. Preclinical studies demonstrate that the constituents of NF boost acetylcholine production, glutathione efficacy, maintain ATP production, and provide antioxidant protection.[16-34] We have not examined the underlying mechanisms in clinical studies; however, the delay of cognitive decline and improvement in BPSD versus placebo observed herein, coupled with improvement in both criteria in mild to moderate AD coupled with the lack of adverse events,[15] suggests that the constituents of NF are likely to provide multiple mechanisms of neuroprotection similar to those observed in our preclinical studies.

The small participant populations in both of these studies suggest that the efficacy of NF be interpreted with caution. Nevertheless, they support more extensive clinical investigation, including comparison of the relative efficacy of this formulation for participants with balanced versus deficient diets; key dietary deficiencies may exacerbate the need for 1 or more constituents of NF, whereas a balanced diet may minimize or lessen the need for certain constituents. The apparent efficacy of NF for early-stage AD, coupled with the demonstration that NF improves cognitive response in nondemented adults[57] suggests that NF may also be useful in efforts to delay progression of MCI to AD. It will eventually be useful to determine whether the preclinical effects of NF on other hallmarks of AD (eg, PS-1 expression, gamma-secretase activity, Abeta generation, tau phosphorylation[22,23]) hold true for clinical participants.

The decision to continue therapeutic approaches in severe/late-stage AD presents a unique challenge; however, certain approaches have demonstrated efficacy in both patient quality of life and reduction of caregiver burden.[58] Donepezil fostered improvement in cognition and some parameters of global function in patients with severe AD,[58,59] but was not effective for BPSD as ascertained by the ADCS-ADL or NPI.[59] The findings of the present study, which demonstrated improvement in both of these latter parameters as well as a delay in cognitive decline, supports administration of this formulation in combination with ongoing or de novo pharmacological approaches. In this regard, memantine, which improved activities of daily living in moderate to severe AD,[60,61] potentiated the efficacy of donepezil treatment in severe AD.[62]

Although a growing body of evidence supports the usefulness of nutritional approaches in delaying the onset and progression of AD even in the face of known genetic risk factors,[15,63-65] the findings of the present study underscore long-term usefulness of nutritional approaches even during the late stages of this disorder.

Acknowledgments

We are grateful for internal financial support from UMass Lowell Chancellor Hogan.

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