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Efficacy of a Vitamin/Nutriceutical Formulation for Early-stage Alzheimer's Disease: A 1-year, Open-label Pilot Study With an 16-Month Caregiver Extension

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We examined the efficacy of a vitamin/nutriceutical formulation (folate, vitamin B6, alpha-tocopherol, S-adenosyl methionine, *N*-acetyl cysteine, and acetyl-L-carnitine) in a 12-month, open-label trial with 14 community-dwelling individuals with early-stage Alzheimer's disease. Participants improved in the Dementia Rating Scale and Clock-drawing tests (Clox 1 and 2). Family caregivers reported improvement in multiple domains of the Neuropsychiatric Inventory (NPI) and maintenance of performance in the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADL). Sustained performance was reported by caregivers for those participants who continued in an 16-month extension. Performance on the NPI was equivalent to published findings at 3 to 6 months for donepezil and exceeded that of galantamine and their historical placebos. Participants demonstrated superior performance for more than 12 months in NPI and ADL versus those receiving naproxen and rofecoxib or their placebo group. This formulation holds promise for treatment of early-stage Alzheimer's disease prior to and/or as a supplement for pharmacological approaches. A larger, placebo-controlled 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 for mild to moderate AD include acetylcholinesterase inhibitors and *N*-methyl-D-aspartic acid (NMDA) receptor antagonists. However, these approaches delay rather than prevent ultimate decline in cognitive and behavioral function, are costly, and are often accompanied by a host of adverse events.[3-7] Additional approaches, including anti-inflammatory agents, hold promise.[8] However, a considerable degree of cognitive decline must ensue before administration of pharmacotherapy, which by that time can be accompanied by irreversible functional decline.[9-11]

A growing body of research indicates that nutritional deficiencies contribute to AD onset and progression. Key genetic and/or environmental factors may remain latent pending age-related decline in nutrition.[12,13] This suggests the potential importance of early nutritional intervention, including preventative approaches prior to definitive

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diagnosis.[14,15] Oxidative stress is a pivotal factor in AD, and it is evident prior to cytopathological hallmarks of the disorder.[16] Antioxidants therefore represent a potential preventative approach.[17] Antioxidants such as vitamin E provide some, but not complete, neuroprotection in AD.[18-20] Limitations of vitamin E are likely to be due at least in part to its lipophilic nature and resultant inability to quench cytosolic oxidative species, including those resulting from antecedent membrane oxidation.[21] An additional approach may be to stimulate the production of endogenous antioxidants. The endogenous antioxidant, glutathione (GSH), and activity of its associated enzyme glutathione-S-transferase are reduced in AD.[22,23] Polymorphisms of this enzyme with diminished activity potentiate the impact of apolipoprotein E (ApoE) deficiency.[24,25] Strategies to maintain appropriate GSH production may be useful as part of a therapeutic approach to delay the onset or progression of AD. Glutathione itself cannot be taken up; however, the GSH precursor *N*-acetyl cysteine (NAC) increases GSH production, and demonstrated some efficacy in clinical trials.[26]

Folate deficiency contributes to many neurological and psychological disorders including AD.[13]Folate-dependent and B12-dependent reactions regenerate methionine from the neurotoxin homocysteine (which is related to the severity and progression of AD). The deleterious effects of folate deprivation are potentiated by deficiency in ApoE, which itself increases oxidative stress and is associated with AD.[27] Functional folate deficiency can also arise from polymorphisms in 5′,10′ methylene tetrahydrofolate reductase (MTHFR, the enzyme that uses folate), which represent synergistic AD risk factors along with ApoE deficiency.[28,29] Supplementation with folate and/or B12 in AD has generated conflicting results.[30-35]

Folate deficiency decreases S-adenosylmethionine (SAM), the major methyl donor, which declines in normal aging and AD and may underlie the gradual hypomethylation of DNA that accompanies aging.[36] Apolipoprotein E deficiency also fosters a critical reduction in SAM, and because SAM is an essential cofactor for glutathione-S-transferase, restricts the ability of GSH to quench cytosolic oxidative species.[29,37] Diminished SAM in AD may foster increased expression of presenilin (PS), leading to an increase in β-amyloid (Abeta), the pathological hallmark of AD, and β-secretase and γ-secretase activity, the enzymes responsible for the abnormal cleavage of the amyloid precursor protein.[38,39] Although SAM provided limited efficacy in clinical trials for depression,[40-42] its effect in AD remains unknown.

Quenching of oxidative species, including those generated by Abeta and homocysteine, and the increased DNA repair resulting from impaired DNA methylation (due to SAM depletion) can consume considerable energy and lead to ATP depletion, triggering neuronal apoptosis. Toward this end, acetyl-L-carnitine (ALCAR), which prevents mitochondrial degeneration, increases ATP, and supports GSH production,[21,43] was used in a clinical trial, but was ineffective against early-stage AD.[44]

Herein, we examined the efficacy of a combination of the compounds (folic acid, vitamin B12, vitamin E, NAC, ALCAR, and SAM) in early-stage AD. Preclinical studies from our laboratory and others demonstrate that the constituents of this formulation provide neuroprotection against oxidative stress, decrease PS-1 expression, γ-secretase activity, Abeta generation and tau phosphorylation, increase GSH, ATP, and acetylcholine, compensate for ApoE deficiency, prevent cognitive decline, and decrease aggression.[21,29,38,39,45-58] Moreover, our preclinical studies demonstrated synergistic neuroprotection by combining 2 or more of these constituents.[37,51,59,60] As presented herein, administration of the above constituents in combination maintained and/or improved cognitive performance, behavioral symptoms, and daily activities in an open-label, 12-month clinical trial, suggesting that they provide synergistic neuroprotection.

Methods

Preparation of Vitamin/Nutriceutical Formulation

Nutriceutical formulation (NF) 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).

Participants

Participants were recruited from community-dwelling patients of the Neurology Clinic at UMass

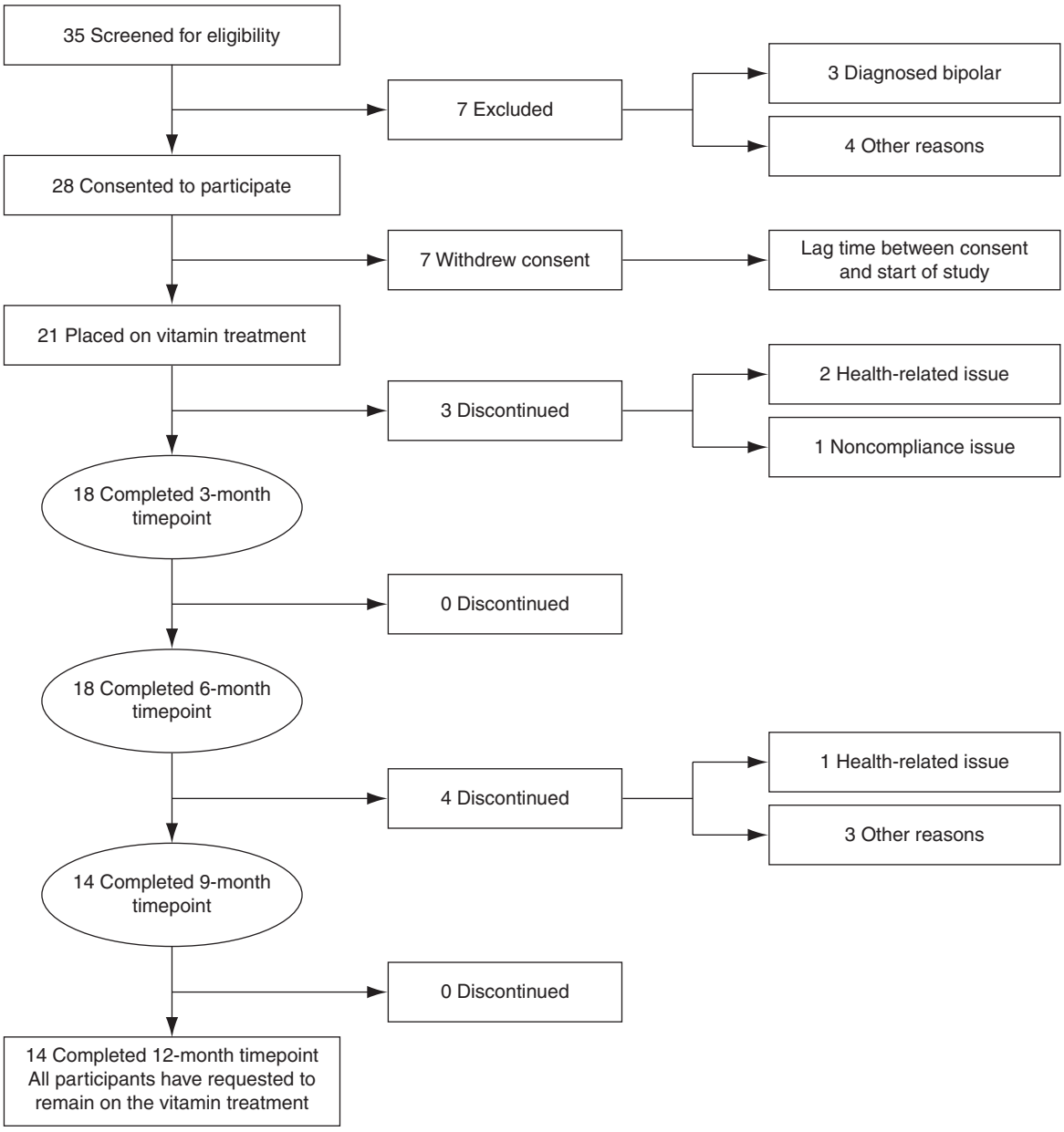

Figure 1. Participant flow.

Memorial Medical Center (Worcester, Mass). Inclusion criteria were as follows: (1) clinical diagnosis of early-stage AD [according to the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) criteria for probable AD[61]], (2) $\geq$50 years of age, (3) no history or diagnosis of bipolar disorder (because SAM is contraindicated for bipolar disorder[42]), and (4) ineffectiveness of and/or adverse events with certain prescribed AD pharmaceuticals (Figure 1). Dementia Rating Scale 2 (DRS-2) scores normalized for age and education level characterized participants as having mild to moderate AD (Mattis Dementia Rating Scale[62]). To encourage long-term compliance with this small population, we conducted an open-label study. Participants were asked to maintain their normal dietary regimen and vitamin/medication intake throughout the course of this study. Although not a specified inclusion criterion, all participants had at least 1 family member caregiver who provided evaluations. Participants and caregivers were informed that they would receive NF for 12 months, and could elect for continued participation beyond 12 months, and that only serious adverse events, rather than lack of efficacy, could prompt exclusion from the study.

Outcome Assessments

At baseline and at 3-month intervals for a total of 12 months, participants completed the DRS-2 and the Clock Drawing Tests (Clox 1 and 2)[63-65] each of which assess neuropsychological performance; caregivers completed the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL), which assesses ability to engage in day-to-day activities, and the 12-item Neuropsychiatric Inventory (NPI), which determines the degree to which abnormal behavior affects the patient's well-being, respectively.[66-68] Participants were offered the opportunity to continue with NF beyond the 12-month trial with a requirement for caregiver reports only. A subset (7) of these caregivers supplied ADCS-ADL and NPI information for their family members at 18 months. For statistical analyses, each participant's baseline score was subtracted from scores at subsequent intervals. Resultant paired differences were averaged and a 2-tailed t distribution was calculated for each interval versus baseline with 13 degrees of freedom (ie, $n - 1$); values were considered statistically significant if $P < .05$. The effect size was as 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.[69]

Results

Of the 21 participants who enrolled, 14 remained compliant and completed the year-long trial (Figure 1). Seven individuals withdrew during the course of the study for various personal reasons, although no withdrawals were because of adverse events.

Participant Performance

Participants demonstrated statistical improvement ($P < .02$) within 6 months in total performance on the DRS, with a trend toward statistical improvement ($P < .06$) by 3 months. Participants maintained statistical improvement until 12 months, with an overall improvement of 31% ± 8% (mean ± standard error) at 12 months (Figure 2). A clinically significant effect size for total performance was achieved within 3 months and was maintained for the duration of this trial (Table 1). Varying responses were observed for individual categories of this test. A statistically significant improvement in conceptualization ($P < .01$) and construction ($P < .03$) was observed within 3 months and was maintained for the duration of the study. A trend ($P < .06$) toward statistical significance in initiation/perseveration was observed within 9 months; statistical significance was achieved by 12 months ($P < .04$). A significant difference in attention ($P < .01$) was first observed at 12 months. No significant difference in memory ($P < .18$) was observed by 12 months, although limited improvement, with no evidence of decline was observed in this category (Figure 2).

Participants demonstrated a progressive increase, although not statistically significant, in performance in both Clox 1 and 2 over the 12-month trial ($P < .08$ and $P < .18$, 12 months vs baseline, respectively; Figure 3). Clinical significance was achieved within 3 months for Clox 1 and within 6 months for Clox 2, and was maintained for both tests for the duration of the trial (Table 1).

Caregiver Reports

A family caregiver completed the NPI for each participant; the same caregiver reported at each sample interval (Figures 4 and 5). A trend toward significance ($P < .07$) was observed for the total score at 3 months; significant improvement ($P < .02$) was observed at 6 months, and was maintained until 12 months ($P < .001$). A significant improvement ($P < .03$) in aggression was observed at 6 months; significance was maintained until 12 months ($P < .05$). A trend toward significance was observed for motor performance at 3 months and for depression at 6 months ($P < .07$, each) and were each maintained as such until 12 months. The remaining parameters did not demonstrate statistical change; however, none showed a decline for more than 12 months (Figure 2). A significant effect size (>0.8) was achieved within 3 months and was maintained for the duration of this trial (Table 1).

Caregivers also completed the ADCS-ADL. Participants demonstrated no mean change in their ability to carry out the day-to-day functions quantified by this test observed over the year-long trial (Figure 5). Varying responses were observed among participants in this caregiver test; 6/14 participants demonstrated an increased score (8.8 ± 1.9, mean ± standard deviation), 3 demonstrated no change, and the remaining 5 declined (−8.2 ± 6.7, mean ± standard deviation).

A subset (7) of these caregivers supplied NPI and ADCS-ADL information for their family members at 18 months, and 6 of these caregivers also supplied this information at 23 and 28 months, which revealed

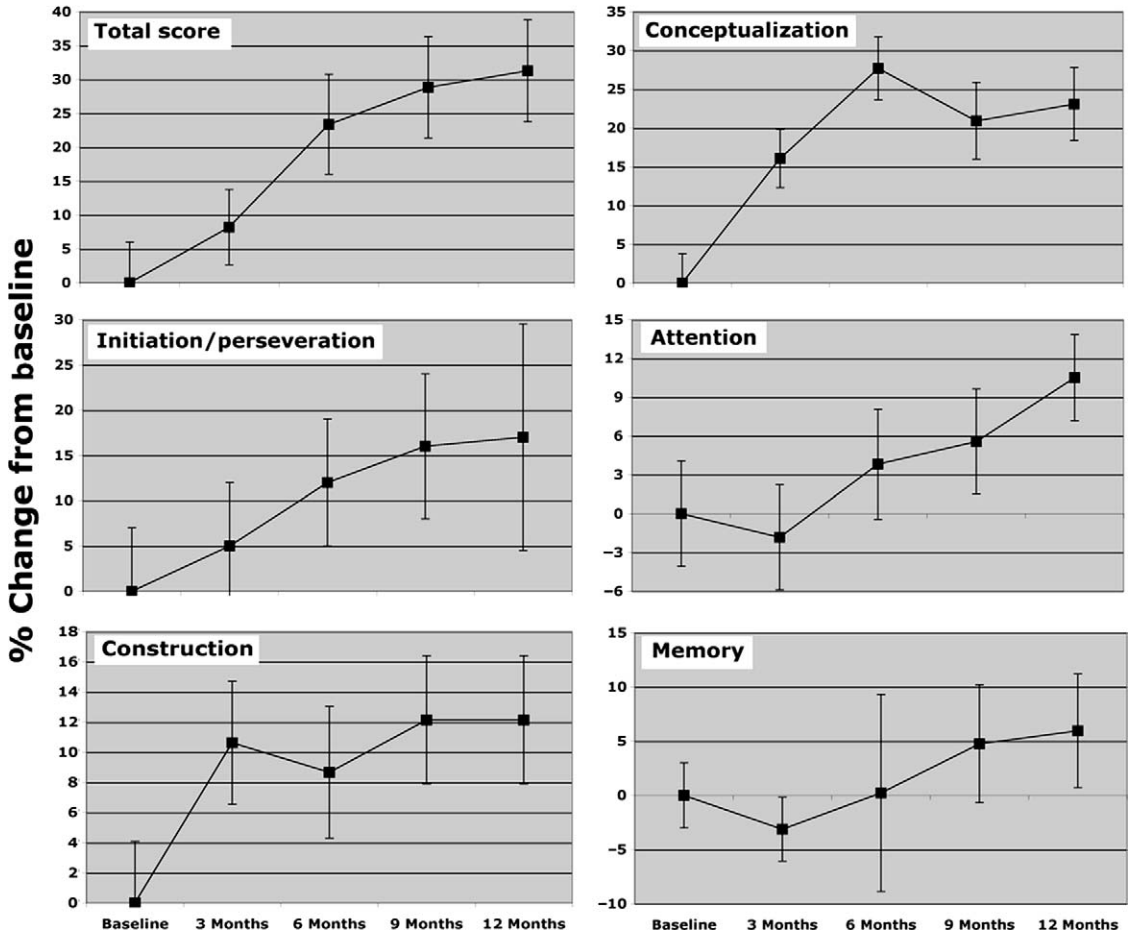

Figure 2. Nutriceutical formulation (NF) improves performance on the Dementia Rating Scale (DRS). Panels present performance on the individual parameters of the DRS and the total scores. Values in each panel represent mean raw scores for the total participants ± standard error of the mean; mean baseline scores were subtracted from all values to generate a baseline of 0 for clarity. All categories demonstrated improvement; see text.

Table 1. Effect Size of NF[a]

	3 Months	6 Months	9 Months	12 Months
DRS	0.35	1.17[b]	1.57[b]	1.66[b]
NPI	0.36	0.38	0.52	0.35
Clox 1	0.28	0.29	0.38	0.47
Clox 2	0[c]	0.44	0.33	0.41

Abbreviations: DRS, Dementia Rating Scale; NF, nutriceutical formulation; NPI, Neuropsychiatric Inventory.

[a] Values were calculated using raw scores at each time interval according to the formula: (mean at treatment time) − (mean at baseline)/standard deviation of baseline.[69]

[b] Large clinical significance (eg, >0.8), whereas all unlabeled values were clinically significant (>.2)[69]

[c] Nonsignificant.

Note that clinical significance was achieved for DRS, NPI, and Clox 1 within 3 months and for Clox 2 within 6 months. Note further that large clinical significance was achieved for 6 to 12 months for DRS.

sustained levels of performance in both tests (Figure 6).

To determine whether caregiver reports correlated with participant performance, we examined whether individual participant performance in the DRS correlated with respective caregiver reports in NPI. To accomplish this, participants were classified as "responders" if their total DRS score at 12 months exceeded that at baseline, and "nonresponders" if their total score at 12 months remained the same or declined versus baseline. Over the 12-month trial, 10/14 participants improved in DRS scores, 2 participants displayed no change, and 2 individuals declined slightly. The individuals demonstrating improved scores were defined as responders, and the remaining 4 individuals were defined as nonresponders (Table 2; Figure 7). Slight but nonsignificant differences were observed in mean baseline

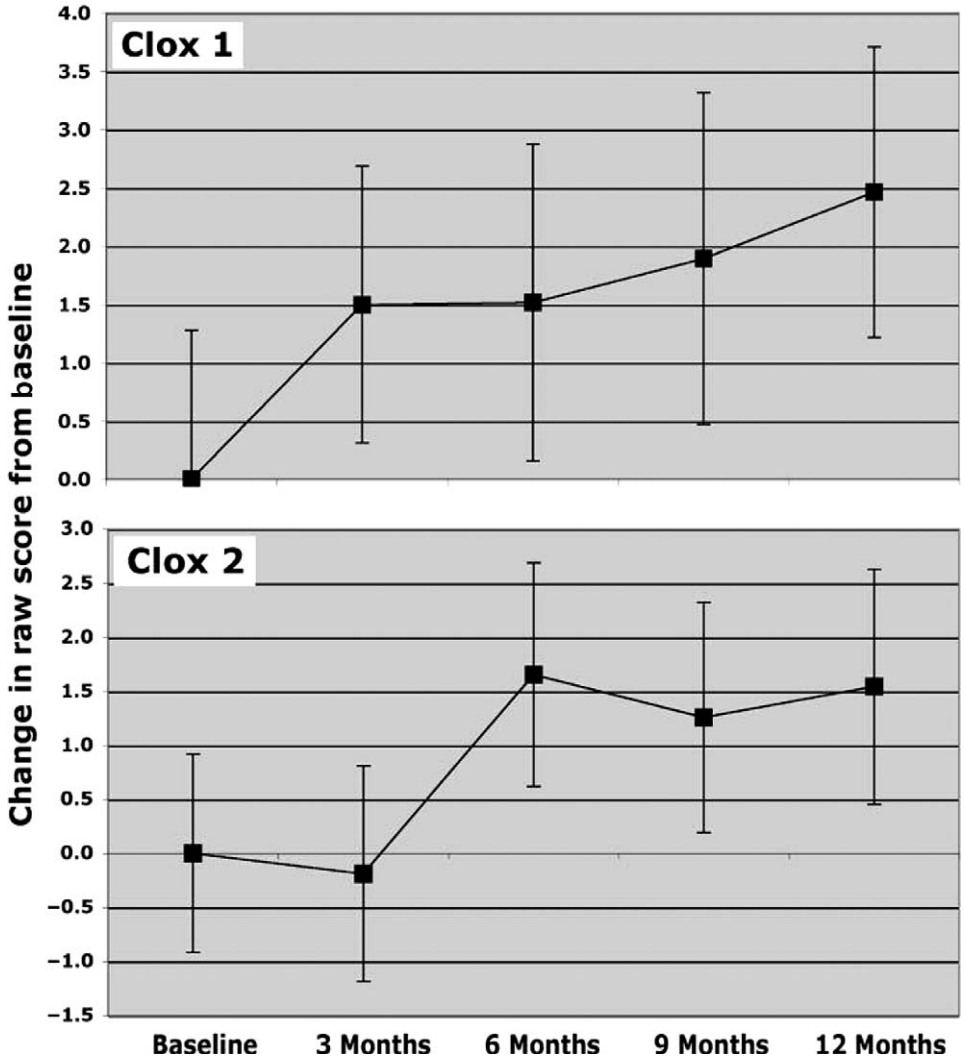

Figure 3. Nutriceutical formulation (NF) improves performance on Clox 1 and 2. Panels present performance on Clox 1 and 2 as indicated. Values in each panel represent mean total scores for the total participants ± standard error of the mean; mean baseline scores were subtracted from all values to generate a baseline of 0 for clarity. See text for further information and discussion.

scores for responders and nonresponders. The respective NPI scores for these participants were then examined; participants who demonstrated a decline in total NPI scores at 12 months versus baseline were defined as NPI responders (a decline in NPI constitutes improvement; see Methods). We observed that DRS performance was highly correlated with NPI performance; 8/10 DRS responders were also NPI responders, and 2/4 of DRS nonresponders were also NPI nonresponders. Identical results were obtained when participants were first grouped according to NPI performance; 8/10 NPI responders were also DRS responders, and 2/2 NPI nonresponders were also DRS nonresponders (not displayed but can be derived from values in Table 2). Because these are independent tests, one of which is completed by the participant without caregiver input and the other completed by the caregiver without participant input, there is no inherent reason to anticipate correlation of test results above that of chance (ie, 50%). The observed correlation of 10/14 participant scores for these independent tests (71%) provides internal support for test validity. We noted a much wider error range for NPI nonresponders than for responders; the standard error was approximately 60% of the mean overall time points, whereas that of responders was only approximately 30% (Table 2; Figure 7).

Our participants demonstrated improved performance over several historical placebo groups in both the NPI and ADSC-ADL[70-72] (Figures 8 and 9). The preliminary findings with our small participant

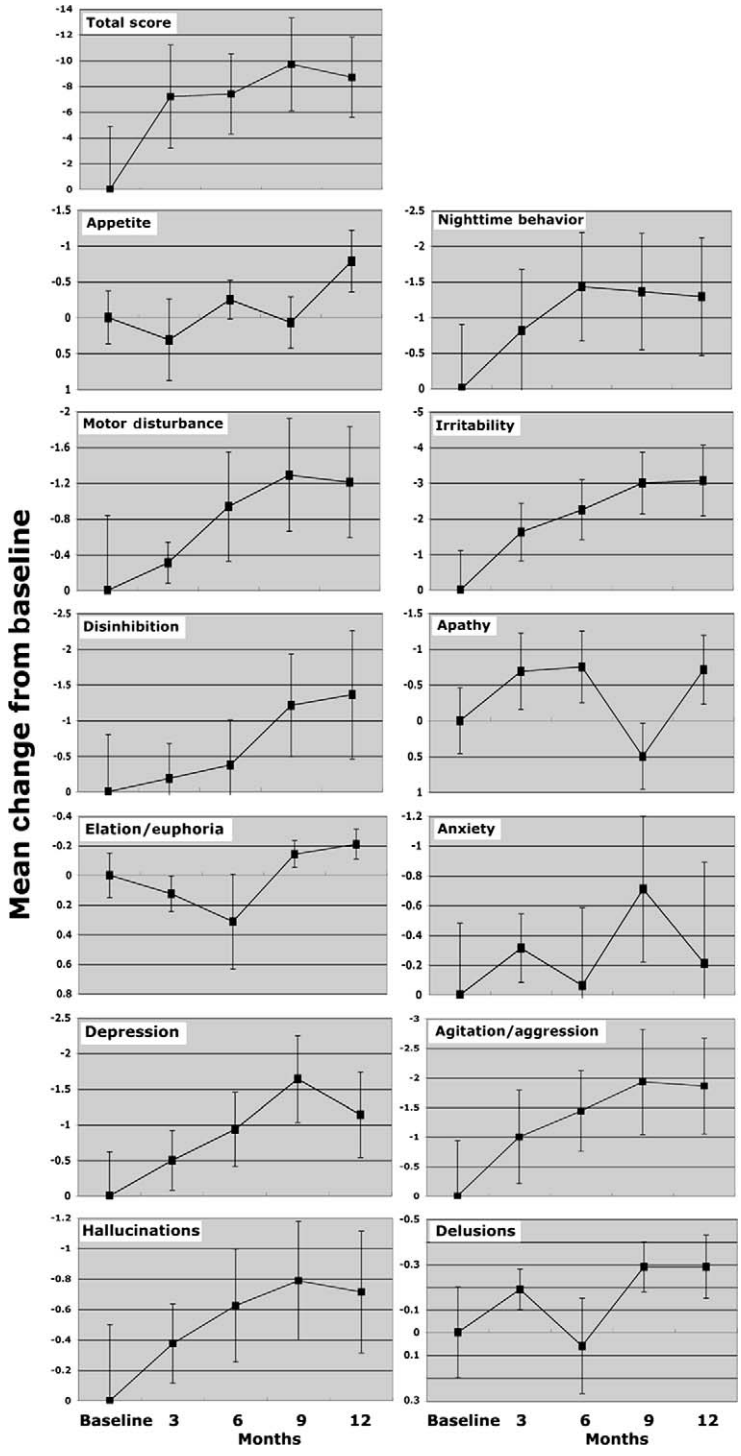

Figure 4. Nutriceutical formulation (NF) improves performance in Neuropsychiatric Inventory (NPI). Panels present the mean change in scores for each domain measured by the NPI, and the total score at baseline and more than 12 months. Values in each panel represent mean raw scores for the total participants ± standard error of the mean; for presentation of total scores, mean baseline scores were subtracted from all values to generate a baseline of 0 for clarity. Because a decrease in score denotes improvement, the y-axis has been inverted for clarity. See text for further information and discussion.

population also demonstrated performance in the NPI apparently equivalent to that of individuals receiving donepezil and apparently superior to that for individuals receiving galantamine or placebo for more than 3 to 6 months[70,71] (Figure 8). Our participants also demonstrated apparent superior

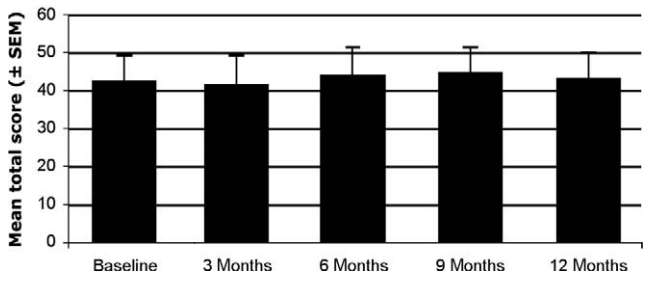

Figure 5. Nutriceutical formulation (NF) maintains performance in the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL). The graph presents total scores (mean ± standard error) in ADCS-ADL as reported by caregivers. Note the maintenance of identical performance over the 12-month trial.

performance for more than 12 months in both the NPI and the ADCS-ADL than did individuals receiving the anti-inflammatory agents, naproxen and rofecoxib[72] (Figure 9). Extrapolation of our findings with this limited participant population must, however, be made with caution.

Discussion

The present study provides evidence that NF can maintain or improve both cognitive and behavioral performance in mild-to-moderate AD. Clinical and statistical significance was achieved in several parameters as quantified by participant performance and caregiver evaluations. Although the present study suffers from the lack of a placebo, NF efficacy over the course of 12 months exceeded that of historical placebos from 3 studies on mild-to-moderate AD.[70-72] In addition, correlation of responders on the DRS (a participant test) with responders in NPI (a caregiver report) provided an internal control for NF efficacy. Differential responses of caregivers to the various domains of the NPI, and the report of a decline in some participants in ADL, were inconsistent with the possibility that caregivers were reporting false-positive performance.

Alzheimer's disease is accompanied by behavioral and psychological symptoms of dementia (BPSD) that do not necessarily correlate with cognitive performance.[73,74] Behavioral and psychological symptoms of dementia are associated with caregiver distress and increased likelihood of institutionalization, and much less affected by cognitive performance.[74-79] A deleterious feedback burden can ensue, because caregivers in some cases fail to appreciate that BPSD are a manifestation of cognitive impairment and therefore maintain hope for improvement, which increases caregiver distress,[80] and caregiver distress may in some cases potentiate BPSD.[81] Following institutionalization, BPSD present a unique challenge to caregiver staff.[82,83] Treatments to alleviate the BPSD severity therefore remain important independently of any efficacy on cognition.

Behavioral parameters are directly addressed by the NPI, and their relative presence, progression, and efficacy of therapy can be ascertained by comparison of performance on individual NPI domains.[74,84,85] The most burdensome BPSD parameter can vary; for example, 1 study reported agitation/aggression and irritability to induce the largest caregiver distress,[77] although another reported that apathy, depression, and anxiety invoke the largest distress.[86] Nevertheless, improved total performance in NPI correlates with reduced caregiver distress.[87]

Nutriceutical formulation had the maximum effect for the participant pool on irritability and agitation/aggression domains of the NPI (Figure 5). Moderate efficacy was observed for nighttime behavior, motor disturbance, disinhibition, and depression. Although negligible effects were observed on the remaining domains, these latter domains were markedly less evident at baseline, precluding evaluation of NF efficacy in these domains for the total participant population. However, 1 participant had baseline evaluations of 6, 4, and 2 for hallucinations, apathy, and appetite, respectively, but by 12 months these domains were evaluated at 0. Another participant declined from 6 to 4 for hallucinations for more than 12 months, another declined from 4 to 2 for apathy and 2 to 1 for appetite, and a third declined from 2 to 0 for appetite. The extent of improvement for these participants in these individual domains rivals or exceeds the overall efficacy observed for irritability and agitation/aggression, underscoring that NF is apparently effective for a wider range of domains than is revealed by this limited study. It further remains possible that NF may have delayed manifestation of behavioral issues over the course of the 12-month trial for those not exhibiting these behavioral problems at baseline.

The beneficial effect on irritability and agitation/aggression in the NPI is likely to be derived principally from SAM, which reduced aggression in transgenic mice harboring the ApoE4[59]; the underlying biochemical mechanism is not clear but may relate to restoration/improved neurotransmitter balance, as SAM restored acetylcholine levels in mice, including that resulting from folate deficiency.[48] Nutriceutical formulation may therefore potentiate

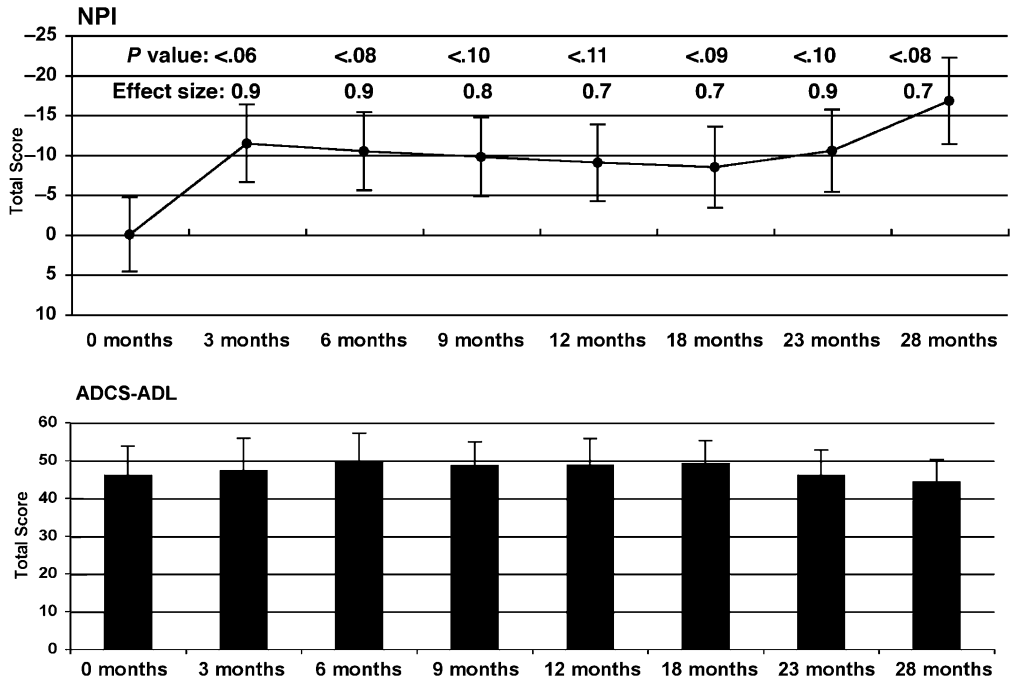

Figure 6. Nutriceutical formulation (NF) maintains performance levels in Neuropsychiatric Inventory (NPI) and Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL): caregiver reports from a 16-month extension. A subset of participants (7) continued NF for an additional 16 months. Caregivers provided NPI and ADCS-ADL scores at 18, 23, and 28 months after initiation of the study. Panels present scores from baseline for these individuals only. *P* values and effect size are noted at each time point for the NPI; these are diminished as compared with the starting population because of the smaller participant number in this subset (7 vs 14). Note that this subset of participants achieved statistical significance and a large effect size in NPI within 3 months and did not decline only slightly for more than a total of 28 months. No decline in ADCS-ADL performance for more than 28 months was observed.

acetylcholinesterase efficacy. In this regard, clinical improvement in mild to moderate AD has been observed following treatment with the acetylcholine precursor choline alfoscerate.[88] Notably, SAM has multiple additional neuroprotective effects directly relevant to AD progression, including suppression of PS-1 overexpression, reduction in γ-secretase activity, Abeta generation and tau phosphorylation, and promotion of GSH efficacy.[54]

Our preclinical studies in normal, aged, and transgenic mice and in cultured neurons have demonstrated that the constituents of NF potentiate the efficacy of each other against neuronal oxidative stress derived from dietary deficiency, Abeta, and/or homocysteine both by direct quenching of reactive oxygen species (folate, vitamin E, and ALCAR) and by increasing GSH levels and efficacy (NAC, SAM), suppressing PS-1 expression and resultant increased γsecretase activity and Abeta generation (SAM), reducing homocysteine (folate, B12, SAM) maintaining neuronal energy by protecting mitochondria (ALCAR), and improving cognition and reducing aggression by maintaining neurotransmitter balance (SAM[21,29,38,39,45-58]). Although each agent demonstrated a degree of efficacy in isolation, the impact of simultaneous administration of multiple agents provided superior neuroprotection.[37,51,59,60] Similarly, the above agents demonstrated limited efficacy in prior clinical trials[18-20,26,30-35,40-42,44] as compared to the degree of cognitive and behavioral improvement observed herein.

Our findings provide direct support that nutritional intervention can have a positive effect on progression of early-stage AD. They further suggest that a combinatorial approach can provide superior neuroprotection than individual supplements and suggest that NF may potentiate pharmacological approaches. In 1 study, folic acid, B12, and B6 combined with donepezil lowered homocysteine in AD patients but did not improve cognition over that of donepezil alone.[89] However, a second study reported that folic acid supplementation improved response to cholinesterase-inhibitor treatment.[90] Supplementation of cholinesterase-inhibitor therapy with the

Table 2. Total DRS Scores of Responders and Nonresponders[a]

Participant[b]	Baseline	3 Months	6 Months	9 Months	12 Months
Total DRS score of responders[c]					
1	2	2	2	3	5
2	6	7	9	9	9
3	3	4	5	6	6
4	3	5	9	9	9
5	5	6	8	8	7
6	2	5	6	6	6
7	2	2	3	4	4
8	5	5	9	7	7
9	5	5	7	8	8
10	3	4	6	6	6
Mean ± SEM	3.6 ± 0.5	4.5 ± 0.5	6.4 ± 0.8	6.6 ± 0.6	6.7 ± 0.5
P value[d]	–	.13	.02	.00	.00
Total DRS score of nonresponders					
11	3	2	2	2	2
12	2	2	2	2	2
13	2	2	2	2	2
14	5	5	5	5	5
Mean ± SEM	3.0 ± 0.7	2.8 ± 0.8	2.8 ± 0.8	2.8 ± 0.8	2.8 ± 0.8
P value	–	.81	.81	.81	.81
Total NPI score of responders					
1	1	0	0	0	1
2	2	4	2	0	0
3	19	3	15	5	17
4	39	1	0	4	2
5	13	8	8	9	5
6	12	6	3	4	2
7	8	32	14	14	15
8	18	7	6	5	12
9	18	1	2	1	1
10	8	6	2	14	2
Mean ± SEM	13.8 ± 3.4	6.8 ± 2.9	5.2 ± 1.7	5.6 ± 1.6	5.7 ± 2.0
P value	–	.23	.06	.07	.07
Total NPI score of nonresponders[d]					
11	1	0	0	0	0
12	1	3	4	4	6
13	28	27	17	14	18
14	39	34	44	40	42
Mean ± SEM	17.3 ± 9.6	16.0 ± 8.5	16.3 ± 9.9	14.5 ± 9.0	16.5 ± 9.3
P value	–	.93	.94	.84	.96

Abbreviations: DRS, Dementia Rating Scale; NPI, Neuropsychiatric Inventory.

[a] Participants were classified as "responders" if their total DRS score at 12 months exceeded that at baseline and "nonresponders" if their total score at 12 months remained the same or declined versus baseline. The mean ± standard error was calculated for responders and nonresponders at each time point and statistically compared to baseline. The respective NPI scores for these participants were then examined; participants who demonstrated a decline in total NPI scores at 12 months versus baseline were defined as NPI responders (note: a decline in NPI constitutes improvement; see Methods). Note that 8/10 DRS responders were also NPI responders, and 2/4 of DRS nonresponders were also NPI nonresponders.

[b] Arbitrary code numbers assigned for this table only; numbers refer to same participants in both DRS and NPI tabulations.

[c] Values represent raw total scores for DRS and NPI; participants sorted according to responders and nonresponders as described in Methods.

[d] 2-Tailed Student's *t* test versus baseline score.

metabolic antioxidant alpha-lipoic acid also slowed disease progression.[91]

The findings of the present study warrant more extensive clinical investigation, including the use of larger participant populations from multiple sites as well as placebo groups. Such larger studies should also encompass comparison of the relative efficacy of this formulation for participants with balanced and deficient diets; key dietary deficiencies may exacerbate the need for 1 or more constituents of

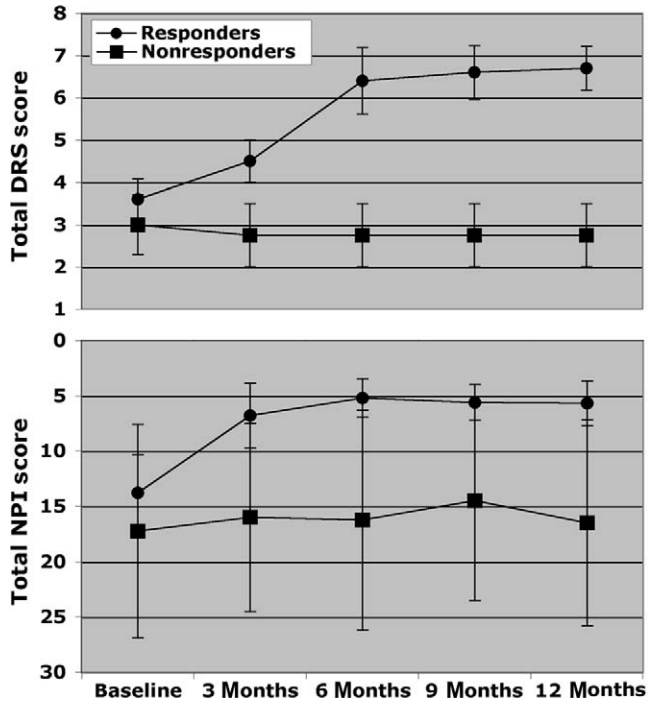

Figure 7. Performance in Dementia Rating Scale (DRS) is correlated with performance in Neuropsychiatric Inventory (NPI). Graphs present the mean ± SEM of participant scores in DRS and NPI following grouping of participants into responders or nonresponders according to their DRS performance as described in Methods; see also Table 2). Note that participants classified as responders according to DRS scores are also responders according to NPI scores. Note that because a decline in NPI score constitutes improvement, the y-axis of the NPI graph is inverted as in Figure 5 to facilitate comparison between DRS and NPI performance. Note the wide standard errors for NPI nonresponders as opposed to responders.

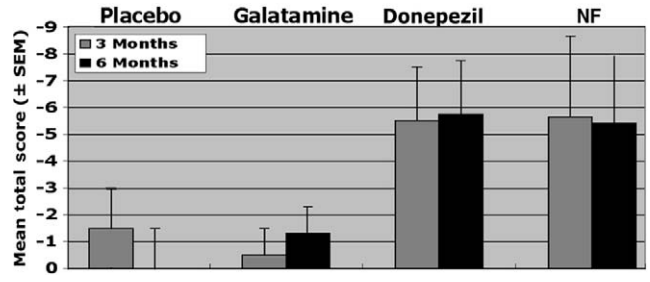

Figure 8. Comparison of nutriceutical formulation (NF) efficacy with that of donepezil, galantamine, and their respective placebo groups. Total Neuropsychiatric Inventory (NPI) scores of participants from the present study after 3 and 6 months along with those from published studies for galantamine and donepezil (see text for references) and scores averaged from the placebo groups of both studies, following 3 and 6 months of treatment. Note that individuals receiving NF performed as well as those receiving donepezil and exceeded the performance of those receiving galantamine or placebo, at both time points.

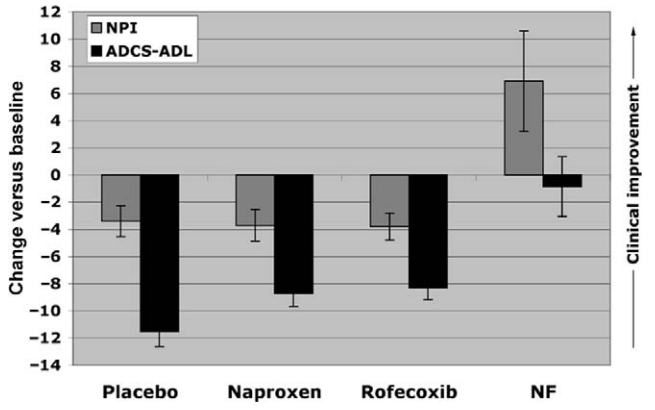

Figure 9. Comparison of nutriceutical formulation (NF) efficacy with that of naproxen, rofecoxib, and their respective placebo groups. Total Neuropsychiatric Inventory (NPI) and Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) scores of participants from the present study after 12 months along with those from a prior study where participants received naproxen (n = 118), rofecoxib (n = 122), or placebo (n = 111) for 12 months. Positive values correspond to improvement; negative values correspond to decline. The drugs neither statistically improved performance on the NPI nor prevented decline in ADCS-ADL; however, a trend toward diminished decline was observed ($P < .10$ and .097 vs placebo, respectively). Note that individuals receiving NF markedly exceeded the performance of those receiving either drug or placebo in both NPI and ADCS-ADL.

NF, whereas a balanced diet may minimize or lessen the need for certain constituents. The findings of the present study should be interpreted with caution pending completion of larger, placebo-controlled studies. The apparent efficacy of NF for early-stage AD coupled with the demonstration that NF improves cognitive response in nondemented adults[92] suggests that NF may also be useful in efforts to delay progression of MCI (mild cognitive impairment) to AD. Pending the outcome of further such studies, it will also be useful to determine whether the preclinical effects of NF on other hallmarks of AD (eg, PS-1 expression, γ-secretase activity, Abeta generation, tau phosphorylation[47,59]) hold true for clinical participants.

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