A Nutritionally Based Approach for Functional Mental Enhancement Assessment Using a Double-Blind, Placebo-Controlled, Randomized Clinical Trial

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Abstract

Background: Consumers are using a number of alternative therapies for a variety of health issues. There is frequently no sound information discussing efficacy or toxicity upon which to base a sound decision regarding proposed therapies.

Aim of the Study: To help address these concerns, a group of nutrients with potential efficacy in improving mental function was evaluated in a clinical setting.

Material and Methods: A prospective, double-blind, randomized, placebo-controlled 3-month duration human clinical trial was performed to test a nutrient formulation for impact on parameters of mental function. Forty-one subjects were studied. Age ranged from 35-70 years. Two-thirds were from 40-60 years old which is considered middle age. This is a time when certain aspects of mental function decline. Subjects underwent baseline neuropsychological testing and were then randomized to receive placebo or active product. After three months, repeat testing was then performed and inter-group comparisons were analyzed.

Results: Baseline profiles and neuropsychological test results were similar between groups. There was no toxicity associated with use of the nutritional formulation. Subjects receiving active product demonstrated statistically significant improvements on numerous clinical endpoints of the testing protocol.

Conclusions: In this contingent of subjects, nutritional enhancement over a 3-month interval improved performance on various components of the brain testing protocol. This approach may be useful for functional mental enhancement during the mid-life period. The results need to be confirmed in a larger study.

INTRODUCTION

Convincing evidence implies that degenerative disorders manifesting as slow, progressive loss of brain function are associated with specific physiologic changes, alterations in functional signaling pathways and risk factors that cumulatively impair normal neuronal function. [1] It is noteworthy that clinical symptoms are generally present before frank neuronal loss is observed. This suggests the presence of a window of opportunity for reversal, or slowing, of the process or for potential functional enhancement. [2]

Based on this type of observation, many individuals currently use alternative therapies for a range of conditions including brain health. The safety and efficacy of these products are rarely substantiated. This creates a confusing marketplace for consumers seeking such approaches.

The present clinical trial was conducted to evaluate the efficacy of a combination of nutrients on parameters of cognitive function in an aging but otherwise cognitively healthy group of humans. One group of subjects took a placebo product and one group took an active product for a three-month period. Depression and anxiety scales and two panels that tested various mental functions were administered at baseline and after three months in both groups. Inter-group comparisons were studied as a function of time.

MATERIAL AND METHODS

PARTICIPANTS

Subjects were recruited from the general population of Bangor, Maine. Telephone interviews were used to screen potential participants. They then had an on-site interview with a registered nurse. At their initial visit with the nurse, each potential subject answered questions about medical history, medications, current medical conditions and therapy, dietary supplement use, habits, work environment and living conditions.

Mild chronic medical conditions, such as treated hypertension, were permitted. Excluded conditions are listed in Table 1.

Table 1: Medically Excluded Conditions

- Severe cardiovascular, hepatic, renal or pulmonary disease
- Insulin-dependent diabetes
- Prevalent cancer
- Immune dysfunction
- Head or spinal injury
- Mental illness
- Excessive alcohol intake (*7 drinks per week) or addiction
- Women who were nursing, pregnant, or attempting to become pregnant

Allowed medication for pre-existing conditions was not discontinued. Attempts were made to exclude the use of medications that impacted cognitive function. These medications are listed in Table 2. Their use precluded participation in the clinical trial.

Figure 1

Table 2: Excluded Categories of Medication

Category of Drug	Name (examples)
Anti-anxiety	Xanax, Valium, Ativan
Anti-depressant	Elavil, Zoloft, Prozac
Antihistamine	Benadryl
Anti-nausea	Antivert, Reglan
Beta-blocker	Inderal
Narcotic pain medication	Codeine, Vicodin, Percocet
Seizure medication	Phenobarbital, Dilantin, Depakote
Stimulant	Dexedrine, Ritalin
Psychotropic	Risperidone
Sleeping medication	Lunesta, Ambien

Study participants were between 35 and 70 years of age. The mean age was 46.6 years and two-thirds of the subjects were between 40 and 60 years of age. This is considered middle age and represents a period of life when certain aspects of cognitive processing decline. All those included had the ability to tolerate the product or placebo and completed compliance testing. After reading and signing the consent form, subjects were informed how to report adverse events and were randomized according to protocol. The clinical study was reviewed and approved by the Asentral Human Institutional Review Board in Salisbury, Massachusetts. Subjects were treated equally and were free to withdraw from the study at any time. Baseline characteristics were not significantly different. Data are shown in Table 3.

Figure 2

Table 3: Baseline Characteristics*

(Percentages unless marked.)

Parameter	Placebo Group	Treatment Group
Mean Age	47.6 years	45.7 years
Mean Weight	78.3 kg	85 kg
Female	63	69
Diabetic	0	3
Hypertension	6	0
Asthma	0	10
Elevated Cholesterol	19	17
Mean Caffeine cups/day	1.6	1.6
Mean Alcohol oz/week	1.6	1.4
Current Smoker	19	14
High School Education	50	52
Bachelor's or above	37	38

* No differences were statistically significant at the p=0.05 level.

EXPERIMENTAL DESIGN AND PROCEDURES

A three-month, double-blind, fixed-dose, placebo-controlled, randomized, parallel-group experimental design was used. Individuals meeting inclusionary criteria were randomly assigned to either the placebo or active product group in an enrollment ratio of 2:3, respectively. The active product and the placebo were similar in appearance, number, smell and taste. Ingredients for the active product are listed in Table 4. The placebo consisted of cellulose.

Figure 3

Table 4: Ingredients in One Day Dosing of Active Product

Vitamins and Minerals	% Daily Value*
Vitamin C (ascorbic acid and ascorbyl palmitate)	125
Vitamin D3	25
Vitamin E (D-α tocopheryl succinate)	50
Thiamin	1333
Riboflavin	1176
Niacin	125
Vitamin B6	2500
Folate	200
Vitamin B12	2083
Biotin	100
Pantothenic Acid	250
Magnesium	20
Zinc	100
Selenium	285
Chromium	333
Potassium	1

Antioxidants

Beta carotene, alpha carotene, lutein, zeaxanthin, cryptoxanthin, Gingko biloba, green tea, vinpocetine, bilberry, grape seed, maritime pine bark, lycopene, resveratrol

Antireductants

Choline, inositol, trimethylglycine
Calcium modulators
Taurine
Cholinergic neuromodulators
DMAE (dimethylaminoethanol), Huperzine A
Cellular energizers
Creatine, alpha ketoglutarate, N-acetyl L-tyrosine, acetyl L-carnitine, PABA, glutamine, L-pyroglutamic acid
Phosphatidyl serine
Soy bean oil
Modulators of glycosaminoglycans
Chondroitin, glucosamine
Insulin sensitizers
Vanadium

Mitochondrial cofactors

Acetyl L-carnitine, alpha lipoic acid, coenzyme Q10

Neurotrophins
Soy isoflavones

*Based upon a 2000 calorie diet

To assess treatment changes, enrolled participants were administered the following series of standardized neuropsychological tests during pretreatment baseline evaluations, and again, after three months of randomized treatment: Vigil Continuous Performance Test (Vigil); California Verbal Learning Test-version II (CVLT-II); and Beck Depression and Anxiety Scales.

Noncompliance was defined as a deviation of greater than 10 percent from the optimum treatment regimen. Adverse events and protocol compliance were assessed at each biweekly contact period, at the end of the study and on an as-needed basis.

STATISTICAL METHODS

Z scores for the Vigil and the CVLT-II were obtained from the computerized testing procedures. Differences of Z scores between baseline and end-of-study testing were the primary outcome measures. The responses for the two groups (placebo and treatment) for each parameter were compared. Differences in the means between the treatment and placebo groups were analyzed using the t-test.

SPSS software (version 12.0) was used to analyze the results. Paired t tests were used to examine differences between groups. All p values were two-tailed and the level of significance was set at 0.05.

The other primary outcome measures consist of intergroup comparisons of the changes in the means of raw data for the Beck Depression and Beck Anxiety scales between baseline and off-study (3-month) time points.

RESULTS

After obtaining informed consent, 43 subjects who met the inclusion criteria and were assessed as being able to comply with the test protocol were randomized (26 and 17 in the treatment and placebo groups, respectively). Of these 43, there were 2 who failed to complete the trial. Loss-to-follow-up was the reason for dropout. Thus, the data from 41 subjects are included in the trial; 25 in the treatment group and 16 in the placebo group.

Baseline cognitive status of the study population was not statistically different between groups. (Data not shown.) The subjects reported no serious adverse events. Mild nausea was noted in 6 of the subjects on product and 5 on placebo. This was transitory in all cases and did not require removal from the trial..

One of the primary outcomes, summarized in Table 5, was from the computerized version of the Vigil Continuous Performance Test. The active product produced an improvement (Z=0.55) which was significant (p*0.01) in commission error (extra hits) testing.

Figure 4

Table 5: Vigil: Mean Differences of Z Scores (Age and Gender-Adjusted) from Baseline (a positive mean number indicates improvement)

Parameter	Group	Mean	Std. Dev.	P Value
Hit Rate	Placebo	0.39	1.6	
	Product	0.88	2.2	
	Difference	0.49		0.45
Omissions	Placebo	0.16	1.1	
	Product	0.82	1.95	
	Difference	0.66		0.17
Commissions	Placebo	-0.05	0.45	
	Product	0.50	0.85	
	Difference	0.55		0.01
Speed	Placebo	0.06	1.0	
	Product	0.54	1.35	
	Difference	0.48		0.2

The second set of outcomes came from the California Verbal Learning (CVLT-II) tool. The primary responses are shown in Table 6.

Figure 5

Table 6: CVLT-II: Mean Differences of Z Scores (Age and Gender-Adjusted) from Baseline (a positive mean number indicates improvement)

Parameter	Group	Mean	Std. Dev.	P Value
Total Response	Placebo	0.26	0.7	
	Product	0.91	0.8	
	Difference	0.65		0.01
Trial 1	Placebo	0.41	1.7	
	Product	1.74	1.3	
	Difference	1.33		0.006
Trial 5	Placebo	0.06	0.8	
	Product	0.33	0.7	
	Difference	0.27		0.25
Slope	Placebo	0.28	1.4	
	Product	1.04	1.3	
	Difference	0.76		0.085
Trial B	Placebo	-0.03	0.8	
	Product	0.30	1.1	
	Difference	0.33		0.32

Among these five variables, a beneficial effect due to active product was seen in Total Response and Trial 1 with differences that were significant at $p<0.01$ and $p<0.006$, respectively. Learning Slope showed a difference between groups that represented a trend ($p<0.085$). No other CVLT-II variables were statistically different.

As depicted in Table 7, the third group of end points-the Beck Depression and Beck Anxiety scales-demonstrated improvements between the groups that were statistically significant at $p<0.05$ and $p=0.009$, respectively.

Figure 6

Table 7: Mood Rating Scales (a positive mean number indicates improvement)

Scale	Group	Mean	Std. Dev.	P Value
Beck Depression	Placebo	0.69	5.0	
	Product	4.31	6.2	
	Difference	3.62		0.05
Beck Anxiety	Placebo	-2.44	8.0	
	Product	5.74	10.2	
	Difference	8.18		0.009

DISCUSSION

The Vigil test is the most popular clinic-based measure of sustained attention and vigilance. [3] It has also been described as being the most sensitive measure for evaluating therapeutic efficacy in these domains. [4] In the Vigil testing, all of the individual parameters were improved. The subjects on product were more alert than the group on placebo, missing far fewer of the target stimuli. They could also focus and sustain their attention better. The group on product gave fewer false-positive responses. This suggests they were better able to inhibit the impulse to respond inappropriately. This was statistically significant ($p=0.01$). The group on product had a tendency to respond more quickly, indicating greater activation and more efficient information processing. When evaluated for a 30-millisecond improvement in cognitive processing speed, those on product outperformed those on placebo by 30.4 percent (42.9 percent v. 12.5 percent, $p=0.049$).

Improvements of attention and impulsivity with psychostimulants are well documented. [5] Attention, concentration and processing speed also respond to stimulant medications. Moderate effect sizes have been noted in various meta-analyses with Z-score improvements in the 0.3 to 0.5 range. [6] In the present trial, the nutritional product produced an improvement in the commission rate parameter of $Z=0.55$ ($p=0.01$). The comparable improvements for hit rate, omissions and reaction rate were $Z=0.49$, $Z=0.66$ and $Z=0.48$, respectively.

Results on the CVLT-II Total Response score indicate overall cumulative learning (information that can be stored and retrieved from short-term storage, while being actively processed) was better for those on product. This difference was large ($Z=0.65$) and significant (p