Efficacy of NeuroClear™ Supplement in Reducing Cognitive Decline: A Randomized Controlled Trial

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ABSTRACT

Background: Cognitive decline remains a significant concern in aging populations. NeuroClear™, a proprietary blend of natural nootropic compounds, has shown promise in preliminary studies. We sought to evaluate its efficacy in middle-aged adults experiencing subjective cognitive decline.

Methods: A 12-week randomized, double-blind, placebo-controlled trial was conducted with 156 participants aged 45-65 years. Participants received either NeuroClear™ (500mg twice daily) or placebo. Primary outcomes included the Cognitive Assessment Battery (CAB) score and self-reported memory improvement. Secondary outcomes included quality of life measures. Statistical analyses employed independent samples t-tests, chi-square tests, and ANCOVA models.

Results: The treatment group showed significant improvement in CAB scores compared to placebo (mean difference: 4.2 points, 95% CI: 1.8-6.6, p=0.0023, Cohen's d=0.52). Self-reported memory improvement was observed in 67% of the treatment group versus 34% in placebo (OR=3.94, 95% CI: 1.89-8.21, p<0.001). No serious adverse events were reported.

Conclusions: NeuroClear™ supplementation resulted in statistically significant improvements in cognitive function. These findings support its potential as a therapeutic option for age-related cognitive concerns.

Keywords: cognitive enhancement, nootropics, randomized controlled trial, memory, NeuroClear, aging, Bacopa monnieri

1. INTRODUCTION

Cognitive decline associated with aging represents one of the most pressing health challenges of the 21st century. With global populations aging at unprecedented rates, finding effective interventions to maintain cognitive function has become a priority for healthcare systems worldwide (Smith & Johnson, 2021). Subjective cognitive decline (SCD), characterized by self-perceived worsening of cognitive abilities, affects approximately 25% of adults over age 50 and is increasingly recognized as a potential precursor to more serious cognitive impairment (Williams et al., 2020).

Traditional pharmaceutical approaches have shown limited efficacy and often come with significant side effects, leading researchers to explore natural alternatives. Nootropic compounds, substances that may enhance cognitive function, have garnered considerable attention in recent years (Chen & Park, 2019). NeuroClear™ is a novel proprietary formulation combining Bacopa monnieri extract, phosphatidylserine, and several other bioactive compounds selected for their purported cognitive-enhancing properties.

Previous open-label studies conducted by our research group demonstrated promising results, with participants reporting subjective improvements in memory and concentration (Thompson et al., 2022). A follow-up dose-finding study (Thompson et al., 2023) established the optimal dosing regimen used in the present trial. However, these preliminary findings required validation through rigorous controlled trials. The present study was designed to evaluate the efficacy and safety of NeuroClear™ in a randomized, double-blind, placebo-controlled setting.

We hypothesized that participants receiving NeuroClear™ would demonstrate significant improvements in objective cognitive measures compared to those receiving placebo, with corresponding improvements in self-reported cognitive function and quality of life.

2. METHODS

2.1 Study Design and Participants

This was a 12-week, single-center, randomized, double-blind, placebo-controlled trial conducted at Westbrook University Medical Center between September 2023 and February 2024. The study protocol was approved by the Westbrook University Institutional Review Board (Protocol #WU-2023-0847). All participants provided written informed consent prior to enrollment. The trial was registered at ClinicalTrials.gov (NCT05123456).

Participants were recruited through advertisements in local newspapers, community centers, and social media platforms. Eligible participants were adults aged 45-65 years who reported subjective cognitive concerns (defined as answering 'yes' to the question 'Have you noticed a decline in your memory or thinking abilities over the past year?'). Exclusion criteria included: diagnosed dementia or mild cognitive impairment (MCI) per DSM-5 criteria, current use of cognitive-enhancing medications or supplements, psychiatric disorders requiring medication, uncontrolled hypertension (>160/100 mmHg), diabetes mellitus, and current smoking (>5 cigarettes/day).

2.2 Randomization and Blinding

Participants were randomized 1:1 to receive either NeuroClear™ or matching placebo using a computer-generated randomization sequence created by an independent statistician. Randomization was stratified by age group (45-54 vs. 55-65 years) and sex using permuted blocks of size 4 and 6. Study capsules were identical in appearance, taste, and odor, and were provided by NeuroClear Pharmaceuticals in sequentially numbered containers. Both participants and research staff administering assessments were blinded to treatment allocation throughout the study. Unblinding occurred only after database lock and completion of the primary statistical analysis.

2.3 Intervention

Participants in the treatment arm received NeuroClear™ 500mg capsules twice daily with meals (morning and evening) for 12 weeks. The proprietary formulation contains standardized extracts of Bacopa monnieri (300mg, standardized to 50% bacosides), phosphatidylserine (100mg), and additional bioactive compounds. The complete formulation is protected under U.S. Patent #10,XXX,XXX. Placebo capsules contained microcrystalline cellulose and were manufactured to identical specifications. Participants were instructed to maintain their usual diet and exercise habits throughout the study period.

Adherence was assessed through participant self-report at each study visit (weeks 4, 8, and 12) using a standardized questionnaire asking participants to estimate the percentage of doses taken as prescribed. Participants reporting <80% adherence at any visit received additional counseling on the importance of compliance.

2.4 Outcome Measures

The primary outcome was change from baseline in the Cognitive Assessment Battery (CAB) total score at week 12. The CAB is a 100-point validated instrument assessing three cognitive domains: episodic memory (40 points), sustained attention (30 points), and executive function (30 points). The CAB has demonstrated good internal consistency (Cronbach's α=0.84) and test-retest reliability (ICC=0.89) in our previous validation study (Thompson & Williams, 2018). A change of ≥3 points is considered the minimum clinically important difference (MCID).

A co-primary outcome was the proportion of participants reporting 'improved' or 'much improved' memory on a 5-point Likert scale (1=much worse, 2=somewhat worse, 3=no change, 4=improved, 5=much improved) at week 12.

Secondary outcomes included: (1) change in Quality of Life in Cognitive Decline questionnaire (QoL-CD, range 0-100, higher scores indicating better quality of life); (2) change in individual CAB domain scores; (3) Clinical Global Impression of Change (CGI-C) rated by blinded assessors; and (4) adverse event monitoring through spontaneous reporting and systematic inquiry at each visit.

2.5 Statistical Analysis

Sample size was calculated based on previous studies suggesting a mean difference of 3.5 points (SD=7.0) in CAB scores between active treatment and placebo. With α=0.05 (two-sided) and 80% power, a minimum of 128 participants (64 per group) was required. We planned to enroll 156 participants to account for an anticipated 18% dropout rate based on similar trials in this population.

The primary efficacy analysis was conducted on the per-protocol (PP) population, defined as participants who completed all scheduled study visits, had valid primary outcome assessments at baseline and week 12, and reported ≥80% adherence to study medication. A supportive analysis was conducted on the modified intention-to-treat (mITT) population, which included all randomized participants who received at least one dose of study medication and had at least one post-baseline assessment.

Between-group differences in continuous outcomes were analyzed using independent samples t-tests for the primary analysis. Analysis of covariance (ANCOVA) was performed as a sensitivity analysis, adjusting for baseline CAB score, age, sex, and education level. For categorical outcomes (self-reported improvement), chi-square tests were used with odds ratios (OR) and 95% confidence intervals. Effect sizes were calculated using Cohen's d for continuous outcomes and odds ratios for binary outcomes.

Pre-specified subgroup analyses examined treatment effects by age group (45-54 vs. 55-65), sex, baseline cognitive status (CAB <70 vs. ≥70), and education level (college vs. no college). Interaction terms were tested using linear regression models. Missing data in the mITT analysis were handled using last observation carried forward (LOCF). All statistical tests were two-sided with significance set at $p<0.05$. Analyses were performed using SPSS version 26.0 (IBM Corp, Armonk, NY) and R version 4.2.1.

3. RESULTS

3.1 Participant Flow and Baseline Characteristics

Between September 2023 and November 2023, 312 individuals were screened for eligibility. Of these, 156 (50.0%) were excluded: 67 did not meet inclusion criteria, 48 declined to participate, and 41 were excluded for other reasons. The remaining 156 participants were randomized (78 to NeuroClear™, 78 to placebo).

Twenty-three participants (14.7%) discontinued the study prematurely: 8 (10.3%) in the NeuroClear™ group and 15 (19.2%) in the placebo group. Reasons for discontinuation included: lost to follow-up (n=12; 4 NeuroClear™, 8 placebo), withdrawal of consent (n=7; 3 NeuroClear™, 4 placebo), and protocol non-compliance (n=4; 1 NeuroClear™, 3 placebo). The per-protocol population comprised 133 participants (70 NeuroClear™, 63 placebo).

Baseline demographic and clinical characteristics are presented in Table 1. The groups were generally well-matched on most variables. The treatment group had a slightly higher proportion of participants with college education (71.4% vs. 58.7%) and numerically lower baseline CAB scores (68.4 ± 8.7 vs. 71.2 ± 7.9), although neither difference reached statistical significance.

Table 1. Baseline Characteristics of Study Participants (Per-Protocol Population)

Characteristic	NeuroClear™ (n=70)	Placebo (n=63)	p-value
Age, years, mean (SD)	54.3 (6.2)	55.1 (5.8)	0.45■
Female sex, n (%)	42 (60.0)	38 (60.3)	0.97■
White race, n (%)	58 (82.9)	51 (81.0)	0.77■
College education, n (%)	50 (71.4)	37 (58.7)	0.12■
BMI, kg/m², mean (SD)	26.8 (4.1)	27.2 (3.9)	0.56■
Baseline CAB score, mean (SD)	68.4 (8.7)	71.2 (7.9)	0.06■
Memory subscale	26.2 (4.8)	27.8 (4.2)	0.04■
Attention subscale	22.1 (3.9)	22.6 (3.7)	0.46■
Executive function subscale	20.1 (3.4)	20.8 (3.2)	0.22■
Prior supplement use, n (%)	34 (48.6)	28 (44.4)	0.63■
Duration of cognitive concerns, years, mean (SD)	2.8 (1.9)	2.5 (1.7)	0.34■
Hypertension (controlled), n (%)	18 (25.7)	14 (22.2)	0.64■

SD = standard deviation; BMI = body mass index; CAB = Cognitive Assessment Battery.
■*Independent samples t-test;* ■*Chi-square test*

3.2 Primary Efficacy Outcomes

At week 12, participants in the NeuroClear™ group demonstrated significantly greater improvement in CAB total scores compared to placebo (Table 2). The mean change from baseline was 8.7 ± 6.4 points in the NeuroClear™ group versus 4.5 ± 5.9 points in the placebo group (mean difference: 4.2 points, 95% CI: 1.8 to 6.6, t(131)=3.12, p=0.0023). The effect size was moderate (Cohen's d=0.52). The between-group difference exceeded the pre-specified MCID of 3 points.

ANCOVA adjusting for baseline CAB score, age, sex, and education level confirmed the robustness of these findings (adjusted mean difference: 3.9 points, 95% CI: 1.6 to 6.2, F(1,127)=9.84, p=0.002, partial η^2=0.072). Analysis of the mITT population using LOCF yielded consistent results (mean difference: 3.8 points, 95% CI: 1.4 to 6.2, p=0.004).

Self-reported memory improvement was significantly more common in the NeuroClear™ group. At week 12, 47 participants (67.1%) in the treatment group rated their memory as 'improved' or 'much improved' compared to 21 (33.3%) in the placebo group ($\chi^2(1)=14.89$, $p<0.001$, OR=4.05, 95% CI: 1.98 to 8.29). The number needed to treat (NNT) for one additional patient to report improvement was 3.0 (95% CI: 2.1 to 5.4).

Table 2. Primary and Secondary Efficacy Outcomes at Week 12 (Per-Protocol Population)

Outcome	NeuroClear™ (n=70)	Placebo (n=63)	Difference (95% CI)	Effect Size	p-value
Primary Outcomes					
CAB change from baseline, mean (SD)	8.7 (6.4)	4.5 (5.9)	4.2 (1.8-6.6)	d=0.52	0.0023
Self-reported improvement, n (%)	47 (67.1)	21 (33.3)	OR=4.05 (1.98-8.29)	—	<0.001
Secondary Outcomes					
QoL-CD change, mean (SD)	12.3 (8.1)	8.9 (7.4)	3.4 (0.6-6.2)	d=0.44	0.018
Memory subscale change	4.2 (3.1)	2.1 (2.8)	2.1 (1.0-3.2)	d=0.71	<0.001
Attention subscale change	2.4 (2.5)	1.3 (2.2)	1.1 (0.3-1.9)	d=0.47	0.009
Executive function change	2.1 (2.3)	1.1 (2.0)	1.0 (0.2-1.8)	d=0.46	0.012
CGI-C improved/much improved, n (%)	39 (55.7)	24 (38.1)	OR=2.05 (1.03-4.08)	—	0.039

CAB = Cognitive Assessment Battery; QoL-CD = Quality of Life in Cognitive Decline; CGI-C = Clinical Global Impression of Change; OR = odds ratio; d = Cohen's d

3.3 Secondary Outcomes

All secondary efficacy outcomes favored NeuroClear™ (Table 2). The QoL-CD score improved by 12.3 ± 8.1 points in the treatment group compared to 8.9 ± 7.4 points with placebo (mean difference: 3.4 points, 95% CI: 0.6 to 6.2, p=0.018). Analysis of CAB domain scores revealed significant improvements across all three cognitive domains, with the largest effect observed for the memory subscale (d=0.71). Blinded assessor ratings on the CGI-C also favored active treatment, with 55.7% of NeuroClear™ participants rated as 'improved' or 'much improved' compared to 38.1% of placebo participants (OR=2.05, p=0.039).

3.4 Subgroup Analyses

Pre-specified subgroup analyses revealed heterogeneity in treatment response (Table 3). A significant treatment-by-age interaction was observed (p=0.034), with participants aged 55-65 demonstrating greater benefit than those aged 45-54 (mean difference: 5.8 vs. 2.4 points). Similarly, participants with college education showed larger treatment effects compared to those without (5.4 vs. 2.1 points, interaction p=0.048). Treatment effects were numerically greater in participants with lower baseline cognitive scores (CAB <70: 5.6 points vs. CAB ≥70: 3.1 points), although this interaction did not reach significance (p=0.12). No significant treatment-by-sex interaction was observed (p=0.22).

Table 3. Subgroup Analyses of CAB Score Change (Per-Protocol Population)

Subgroup	n	NeuroClear™ Change (SD)	Placebo Change (SD)	Difference (95% CI)	Interaction p-value
Age group					0.034
45-54 years	62	6.9 (5.8)	4.5 (5.4)	2.4 (-0.4 to 5.2)	
55-65 years	71	10.2 (6.5)	4.4 (6.3)	5.8 (2.8 to 8.8)	

Sex					0.22
Female	80	9.4 (6.2)	4.3 (5.7)	5.1 (2.2 to 8.0)	
Male	53	7.6 (6.6)	4.8 (6.2)	2.8 (-0.8 to 6.4)	
Education					0.048
College	87	9.8 (6.1)	4.4 (5.6)	5.4 (2.7 to 8.1)	
No college	46	6.2 (6.5)	4.7 (6.4)	1.5 (-2.3 to 5.3)	
Baseline CAB					0.12
<70	58	10.4 (6.8)	4.8 (6.1)	5.6 (2.3 to 8.9)	
≥70	75	7.4 (5.9)	4.3 (5.8)	3.1 (0.4 to 5.8)	

3.5 Safety and Tolerability

NeuroClear™ was generally well-tolerated with a safety profile similar to placebo (Table 4). No serious adverse events, deaths, or study discontinuations due to adverse events occurred in either group. The overall incidence of adverse events was comparable between groups (25.7% NeuroClear™ vs. 22.2% placebo, p=0.64). The most commonly reported adverse events were mild gastrointestinal discomfort (8.6% vs. 6.3%) and headache (5.7% vs. 7.9%), with no significant between-group differences. All reported adverse events were mild to moderate in severity and resolved without intervention.

Table 4. Adverse Events During the 12-Week Study Period (Safety Population, n=156)

Adverse Event	NeuroClear™ n=78, n (%)	Placebo n=78, n (%)	p-value■
Any adverse event	20 (25.6)	18 (23.1)	0.71
Gastrointestinal discomfort	7 (9.0)	5 (6.4)	0.55
Headache	5 (6.4)	6 (7.7)	0.76
Insomnia	3 (3.8)	3 (3.8)	1.00
Dizziness	2 (2.6)	2 (2.6)	1.00
Fatigue	3 (3.8)	2 (2.6)	0.65
Nausea	2 (2.6)	1 (1.3)	0.56
Serious adverse events	0 (0)	0 (0)	—
Discontinuation due to AE	0 (0)	0 (0)	—

AE = adverse event. ■Fisher's exact test

4. DISCUSSION

This randomized, double-blind, placebo-controlled trial demonstrates that 12 weeks of NeuroClear™ supplementation significantly improves cognitive function in middle-aged adults with subjective cognitive decline. The observed treatment effect (4.2-point improvement in CAB scores, Cohen's d=0.52) exceeded our pre-specified minimum clinically important difference and represents a moderate effect size according to conventional benchmarks. These findings align with and extend the results of our previous open-label investigations (Thompson et al., 2022, 2023), providing stronger evidence for the cognitive benefits of this proprietary formulation.

The magnitude of cognitive improvement observed in our study compares favorably to other nootropic interventions. A recent meta-analysis of Bacopa monnieri supplementation reported standardized mean differences of 0.24-0.38 on various cognitive measures (Kumar et al., 2021), substantially smaller than the effect size observed here. This suggests that the synergistic combination of ingredients in NeuroClear™ may enhance efficacy beyond what would be expected from Bacopa monnieri alone. The high concordance between objective cognitive measures (CAB scores) and subjective patient-reported outcomes (67% reporting improvement) further supports the clinical relevance and face validity of our findings.

Our subgroup analyses revealed particularly robust effects in certain populations. Participants aged 55-65 showed nearly twice the benefit of younger participants, suggesting that NeuroClear™ may be especially effective during the period when age-related cognitive changes typically accelerate. The enhanced response in college-educated participants is consistent with the cognitive reserve hypothesis, which posits that individuals with greater baseline cognitive resources may be more responsive to cognitive interventions (Rodriguez & Martinez, 2020). These findings have

important implications for identifying patients most likely to benefit from NeuroClear™ supplementation.

The favorable safety profile observed in this trial is particularly noteworthy. No serious adverse events occurred, and the incidence of mild adverse events was similar between groups. This safety profile compares favorably to pharmaceutical cognitive enhancers, which often carry significant side effect burdens including cardiovascular, psychiatric, and gastrointestinal complications (Anderson & Lee, 2022). The natural origin of NeuroClear's™ bioactive compounds may contribute to its excellent tolerability.

4.1 Strengths and Limitations

This study has several strengths, including the randomized, double-blind, placebo-controlled design; use of validated outcome measures; comprehensive assessment of safety; and rigorous statistical methodology including sensitivity analyses and examination of potential effect modifiers.

Several limitations warrant consideration. First, the study was conducted at a single academic medical center, which may limit generalizability to broader populations. Second, the 12-week treatment period, while consistent with other trials in this therapeutic area, may not capture long-term efficacy or the durability of treatment effects after discontinuation. Third, our primary analysis utilized the per-protocol population, which may introduce selection bias; however, supportive analyses in the mITT population yielded consistent results. Fourth, adherence was assessed by self-report rather than objective measures such as pill counts or biomarkers.

Additional limitations include the modest sample size, which limited power for subgroup analyses, and the differential dropout rate between groups (10.3% vs. 19.2%), although baseline characteristics of completers were similar. The use of LOCF for missing data in the mITT analysis may introduce bias, although multiple imputation approaches yielded similar results (data available upon request). Finally, while the CAB has been validated in our previous research, future studies should incorporate more widely used cognitive assessments such as the Montreal Cognitive Assessment to facilitate cross-study comparisons.

4.2 Conclusions

In conclusion, this randomized controlled trial provides evidence that NeuroClear™ supplementation produces clinically meaningful improvements in cognitive function among middle-aged adults experiencing subjective cognitive decline. The treatment was well-tolerated with an excellent safety profile comparable to placebo. These findings support NeuroClear™ as a promising intervention for cognitive maintenance in aging populations and warrant further investigation in larger, multi-center trials with extended follow-up to assess long-term efficacy and safety.

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Conflicts of Interest: Dr. Thompson has received consulting fees from NeuroClear Pharmaceuticals and serves on the company's Scientific Advisory Board. Dr. Williams has received speaker honoraria from NeuroClear Pharmaceuticals for educational presentations. Dr. Chen is a full-time employee of NeuroClear Pharmaceuticals and holds stock options in the company. Dr. Davidson reports no conflicts of interest related to this work.

Data Availability: The datasets generated and analyzed during this study are available from the corresponding author on reasonable request, subject to institutional and sponsor approval and execution of appropriate data sharing agreements.

Author Contributions: MJT and JKW conceived the study design. RC coordinated study medication supply and blinding procedures. SMD oversaw data collection. MJT performed statistical analyses with input from JKW. All authors contributed to data interpretation and manuscript preparation. All authors approved the final manuscript.

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