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Effectiveness of NADH in Alleviating Effects of Acute Sleep Deprivation in Healthy Middle-Aged Adults

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This study involved the investigational use of a nutritional supplement available commercially over-the-counter.

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ABSTRACT

Study Objectives: To test the ability of oral stabilized NADH (ENADAlert®) to improve alertness, mood, and performance on cognitive tasks in middle-aged subjects after one night of total sleep deprivation.

Design: Randomized, crossover, placebo-controlled clinical trial of sublingual NADH.

Setting: Sleep laboratory.

Participants: 25 healthy male and female subjects ages 40-59.

Interventions: Administration of sublingual NADH 20 mg following one night of total sleep deprivation.

Measurements and Results: Subjects underwent baseline cognitive assessment with placebo, then two sessions with enforced nocturnal wakefulness, followed by morning consumption of NADH (ENADAlert 20 mg) or placebo. During the day, cognitive testing, mood, subjective/objective sleepiness (MSLT) were performed. CogScreen-Aeromedical Edition computerized cognitive battery assessed attention, memory, and reaction time among other domains. CogScreen-AE subtests were analyzed by throughput (correct responses/minute), accuracy, and speed.

Overall throughput was significantly better following NADH than placebo, after adjusting for baseline performance. Accuracy and speed were not different between conditions, although improvement in reaction time with NADH was noted on one subtest. Subjective and objective measures of sleepiness and mood did not differ. Although several subjects reported typical effects of total sleep deprivation, no adverse effects were reported.

Conclusions: This study is among the first evaluating a non-prescription substance aside from stimulants for sleep deprivation. NADH is the first non-stimulant to show increased aspects of cognitive performance, despite subjective reports of increased fatigue following sleep deprivation. NADH may have an important role in mitigating the effects of unavoidable sleep deprivation.

Key Words: sleep deprivation, alertness, nutritional supplement, cognitive performance

INTRODUCTION

Chronic sleep deprivation is very common in the general population, leading to well-described difficulties in concentration and cognitive performance and increases in irritability and malaise, among other symptoms (1). Acute sleep deprivation, when an individual must forgo most or all of a night's sleep can also lead to immediate daytime consequences. To combat the effects of sleep loss, several types of strategies have been recommended, including the consumption of alertness-promoting pharmaceuticals (2) or nutraceuticals, the latter comprised of nutritional, over-the-counter types of products (3).

Until the last few years, typical prescription medications to promote alertness included adrenergic drugs such as amphetamine, methylphenidate, and pemoline (2,4). Given its FDA-approved use for sleepiness with patients with narcolepsy, such attention has also been placed on modafinil as a wake-promoting agent following sleep deprivation (5). Wesensten and colleagues (5) showed that modafinil use maintained performance and alertness during a sustained wakefulness paradigm, but was comparable to a caffeine group.

Caffeine has been studied extensively as a countermeasure for sleepiness resulting from sleep deprivation (see for example 6,7). In addition, there has been recent interest in the "functional energy drinks" (8) such as Red Bull (T), that contain caffeine as well as taurine, glucuronolactone, glucose, and B vitamins. Such an energy drink has been shown to improve scores on a simulated driving test following restricted sleep on the previous night (8,9). When tested early in the subjective night, young subjects performed better on cognitive tests following a taurine-caffeine beverage (10).

Ginseng and ephedrine are also available over-the-counter as agents that allegedly promote increased energy and performance (3). However, Lieberman (3) reports that the data on effectiveness of ginseng are not definitive, and studies have had questionable control groups and definitions that render interpretation difficult. Ephedrine, while appearing similar to caffeine in some protocols, nevertheless can lead to serious and life-threatening cardiovascular effects that render its use inadvisable.

Finally, another approach to improving energy and well-being is the oral stabilized supplement of nicotinamide adenine dinucleotide (NADH), marketed as ENADA or ENADAlert. NADH is a co-enzyme that is involved in cellular production of ATP (11). This product was reported to improve symptoms of patients with chronic fatigue syndrome (12). In addition, in a jet lag paradigm involving actual travel, subjects treated with 20 mg of sublingual stabilized NADH performed better on four cognitive test measures and reported less sleepiness at the time of testing at the destination than those who had received placebo (13,14). In a chronic toxicity study in rats, no treatment-related adverse events were reported (15).

To further explore the potential effectiveness of NADH as a countermeasure for sleepiness, we tested 20 mg sublingual NADH in a double-blind placebo-controlled cross-over design of healthy middle-aged adults following one night of acute sleep deprivation. This research has been presented in abstract form (16).

METHODS

OVERALL DESIGN: The study used a randomized, crossover, placebo-controlled design following a baseline assessment. Thirty-five male and female subjects were enrolled and 25 subjects completed the study. An initial cognitive assessment established the baseline of the subject on the cognitive testing battery for comparison to the sleep-deprived state with and without NADH. Subjects then participated in two laboratory sessions at least 10 days apart, one including the consumption of 20 mg sublingual NADH (4 tablets of 5 mg each) and the other with 4 matching placebo tablets. During each laboratory session, subjects underwent complete sleep deprivation for one night, verified by polysomnography, followed by subjective ratings of alertness and mood, cognitive assessment, and objective sleepiness measurements using a modified multiple sleep latency test. The study was reviewed and approved by the Committee on Human Rights in Research and conformed to the Declaration of Helsinki.

SUBJECT RECRUITMENT: Subjects were recruited by advertisement to participate in a screening phase followed by two overnight plus daytime sessions in the Sleep Center. After giving informed consent, subjects underwent the screening, consisting of a brief physical examination, sleep and medical history, determination of habitual daily caloric consumption, psychological interview via the Structured Clinical Interview for DSM-IV (SCID), and visit to the Sleep Center to see the environment of the study. A urine pregnancy test was performed for female subjects. Subjects meeting criteria for entry (See Table 1) were provided with a sleep log to be kept for one week and scheduled for baseline cognitive assessment.

BASELINE ASSESSMENT: After keeping the sleep log for at least one week after screening, subjects returned to the laboratory for baseline assessment. The assessment was conducted at the same time of day as the cognitive testing was to be administered during the laboratory sessions. Prior to testing, subjects knowingly consumed 4 placebo tablets sublingually to control for tablet taking and to practice the sublingual route of administration. They were administered the battery of cognitive tests of attention, executive function, memory, mood and subjective alertness that were used during the experimental sessions (see description below). The sleep log ensured that the subject was not sleep-deprived prior to the baseline assessment. In order to control for any impact of the electrodes on performance on the testing battery, electrodes were applied to subjects in the same fashion as during the laboratory sessions, but polysomnography was not performed.

On the days of the baseline and laboratory assessments, subjects were advised to avoid caffeinated beverages and strenuous exercise. Subjects were also advised to avoid taking NADH on their own until they completed the study.

LABORATORY SESSIONS: Following the baseline assessment, subjects were scheduled for two overnight sessions at the Center (Figure 1). Subjects arrived at the laboratory at least one hour before their usual bedtime at which time electrodes and sensors were applied for polysomnography. The standard montage for a Multiple Sleep Latency Test (without respiratory or limb electrodes) was used. Wakefulness was enforced by technologists to ensure that the subjects did not sleep except when scheduled during the MSLT. Subjects were recorded via polysomnography from their habitual bedtimes through the end of the session the following day. At 30 minutes past their usual wake times as determined by the sleep log, subjects consumed either NADH (4 sublingual tablets of 5 mg each) or placebo (4 tablets matching NADH tablets) in sublingual form. Subjects then consumed breakfast consisting of approximately 25% of their habitual daily caloric intake. Sixty minutes post-NADH or placebo, they were tested with the cognitive battery. Following the battery, a Multiple Sleep Latency Test, modified to comprise only three nap opportunities that were terminated upon sleep onset, was performed. Subjects were asked to report any side effects and whether they could determine whether

they had consumed active substance or placebo. Testing was repeated with the opposite substance on a second visit at least 7 days later.

COGNITIVE BATTERY: A well-validated instrument designed to detect subtle changes in cognitive functioning across a broad range of clinically meaningful domains (including attention, executive function and memory) was used. This instrument, distributed as CogScreen-Aeromedical Edition (CogScreen-AE), assesses deficits or changes in attention, immediate- and short-term memory, visual-perceptual functioning, sequencing functions, logical problem solving, calculation skills, reaction time, simultaneous information processing abilities, and executive functions (see Table 2). It consists of a series of computerized cognitive tasks, each self-contained and presented with instructions and a practice segment. Requiring 45-60 minutes to complete, the battery comprises multiple subtests, each generating measures representing response, speed, response accuracy, and response "throughput" (number of correct responses per minute). Up to 12 alternate test forms are automatically generated for repeated test administration to the same individual. A light pen serves as the primary response input device to reduce a potential advantage of having prior computer and keyboard experience. The light pen further allows the respondent to maintain focus on the screen at all times. Criterion-related studies have shown this computer-administered and scored cognitive-screening instrument to have high levels of sensitivity and specificity in comparison to conventional (i.e., non-computerized) neuropsychological instruments (17).

CogScreen has been used in a variety of relevant biomedical research applications, including studies of initial and steady-state effects of diphenhydramine and loratadine on sedation, cognition, mood, and psychomotor performance (18), the effects of normal aging on cognition and flight performance (19), the effects of low-dose alcohol on cognition and pilot flight performance (20), other uses in aviation (21).

ALERTNESS AND MOOD MEASUREMENT: Alertness was assessed by the modified Multiple Sleep Latency Test that followed the cognitive test battery. Subjects were allowed to try to sleep in a dark and quiet room. Nap opportunities occurred every 2 hours and were terminated after three epochs of Stage 1 or one epoch of Stage 2 scored by conventional methods. Latency to sleep onset for each nap and a mean sleep latency were calculated. Subjective sleepiness was assessed by the Stanford Sleepiness Scale and modified Epworth Sleepiness Scale administered to the subjects just prior to the naps. Mood was assessed by Profile of Mood States (POMS) (22) completed during the baseline and once each session one hour after consuming NADH or placebo and before the first napping opportunity.

DATA ANALYSIS: MANOVA was used to compare baseline and the two conditions (NADH, placebo) on the data from the POMS and cognitive tests. Prior to analysis, POMS data were grouped by convention into 6 categories (fatigue, tension, depression, anger, vigor, confusion), and a global score (total emotional disturbance) (22). Global analysis of all speed, throughput and accuracy variables was performed after controlling for each individual subject's baseline performance and after excluding the Dual Task. This task was not performed at acceptable levels by many subjects, leading to incomplete data. Contrasts were performed when the main effect of session was statistically significant.

Objective and subjective sleepiness data were compared across experimental sessions.

SUBJECT COMPENSATION: Subjects were compensated for their participation and were offered a six-month complimentary supply of NADH by Menuco Corporation if they so desired.

RESULTS

Thirty-five subjects signed consent and were enrolled in the study (Table 3). Twenty-five subjects completed the study; the other ten were ruled out during the screening/baseline (4 subjects), had scheduling difficulties (5 subjects), or were unable to complete the laboratory session due to illness (1 subject). Of the completers, 15 were female and 10 were male. The mean age was 49.6 years (SD 5.8 years).

SELF-REPORT MEASURES: Six factor scores and a total mood disturbance score were computed from the subjects' responses to the POMS questionnaire (Table 4). Subjects reported significantly reduced levels of vigor and increased levels of fatigue, confusion, and total mood disturbance during both laboratory sessions compared to baseline. Substance consumed (NADH or placebo) did not affect the scores on these factors. Anxiety, depression, and anger did not change from baseline. These results are consistent with the effects of sleep deprivation in that the study paradigm induced changes in variables related to alertness, but not to those related to negative mood.

Average sleepiness scores reported by subjects on the Stanford Sleepiness Scale increased but not significantly from baseline to the times just prior to each nap opportunity on the MSLT (Table 5). Scores on the Epworth Sleepiness Scale were not different following sleep deprivation (Table 6)

OBJECTIVE SLEEPINESS: Average sleep latency scores on the Multiple Sleep Latency Test were in the sleepy range (6.3 ± 3.1 minutes after NADH compared to 6.1 ± 4.3 minutes after placebo), but were not affected by the substance consumed (Table 7).

COGNITIVE TESTING: Overall speed and accuracy on the Cogscreen-AE test battery were not affected by the substance consumed. However, throughput (number of correct answers per minute), a combined accuracy-speed metric, was significantly better after consumption of NADH than after placebo, when controlling for baseline performance (increase from baseline of 7.1% . ± 13.9% for NADH versus an increase of 2.1% ± 11.6% for placebo, $p < 0.02$; Table 8). Examples of specific tests that were significantly improved with NADH (compared to placebo) can be found in Figures 2 and 3.

SUBJECT PREFERENCE & SIDE EFFECTS: Subjects were asked at the completion of each laboratory session whether they thought they had consumed placebo or active substance (Table 9). Of the 25 subjects who completed the study, only 36% were able to correctly identify the order of administration.

Only two of the completing subjects reported physical symptoms during the laboratory sessions. In each case, the onset of the symptoms occurred prior to consumption of placebo or NADH. Other than reporting symptoms of sleepiness, as was expected following sleep deprivation, subjects did not report any side effects following drug or placebo administration.

DISCUSSION

This study is among the first to rigorously evaluate a non-prescription substance that is not known to have a stimulant effect in order to counteract the effects of acute sleep deprivation. The study paradigm successfully induced daytime sleepiness as measured both by the multiple sleep latency tests and by self-reports. Despite the level of sleepiness detected, subjects taking NADH demonstrated superior cognitive test performance without noted side effects. This is an important consideration for individuals who could benefit from the use of an alertness-promoting substance but who are sensitive to the effects of caffeine or concerned about the expense of a prescription medication.

Results in the current study are markedly similar to those previously observed in a study measuring jet lag and the use of NADH as a jet lag countermeasure (13,14). Following a "red-eye" flight subjects reported sleepiness and demonstrated declines in vigilance, working memory, divided attention and visual perceptual speed. Subjects who received NADH performed significantly better than subjects who received placebo on measures of cognitive and psychomotor functioning. On the other hand, NADH had no significant effect on mood or self-reported sleepiness.

It is important that nutritional products undergo the same type of rigorous scientific scrutiny as other types of drugs so that claims can be substantiated or refuted by data. In this case, the positive effects on performance without adverse side effects suggest that additional research be performed to further explore the potential use of NADH as an alerting substance.

REFERENCES

(1) Dinges DF, Kribbs NB. Performing while sleepy: effects of experimentally-induced sleepiness. In: Monk TH (ed) Sleep, Sleepiness and Performance. Wiley, New York, pp 97-128.

(2) Akerstedt T, Ficca G. Alertness-enhancing drugs as a countermeasure to fatigue in irregular work hours. Chronobiology International 1997; 14(2):145-158.

(3) Lieberman HR. The effects of ginseng, ephedrine, and caffeine on cognitive performance, mood and energy. Nutr Rev 2001; 59(4):91-102.

(4) Oken BS, Kishiyama SS, Salinsky MC. Pharmacologically induced changes in arousal: effects on behavioral and electrophysiologic measures of alertness and attention. Electroencephalogr Clin Neurophysiol 1995; 95:359-371.

(5) Wesensten NJ, Belenky G, Kautz MA, Thorne DR, Reichardt RM, Balkin TJ. Maintaining alertness and performance during sleep deprivation: modafinil versus caffeine. Psychopharmacology (Berl) 2002;159(3)238-47.

(6) De Valck E, Cluydts R. Slow-release caffeine as a countermeasure to driver sleepiness induced by partial sleep deprivation. J Sleep Res 2001; 10(3):203-209.

(7) Beaumont M, Batejat D, Pierard C, Coste O, Doireau P, Van Beers P, Chauffard F, Chassard D, Enslen M, Denis JB, Lagarde D. Slow release caffeine and prolonged (64-h) continuous wakefulness: effects on vigilance and cognitive performance. J Sleep Res 2001; 10(4):265-276.

(8) Reyner LA, Horne JA. Efficacy of a 'functional energy drink' in counteracting driver sleepiness. Physiol Behav 2002; 75(3):331-5.

(9) Horne JA, Reyner LA. Beneficial effects of an "energy drink" given to sleepy drivers. Amino Acids 2001; 20:83-89.

(10) Seidl R, Peyrl A, Nicham R, Hauser E. A taurine and caffeine-containing drink stimulates cognitive performance and well-being. Amino Acids 2000; 19:635-642.

(11) Pelzmann B, Hallstron S, Schaffer P, et al. NADH supplementation decreases pinacidil-primed $I_{K(ATP)}$ in ventricular vadiomyocytes by increasing intracellular ATP. Br J Pharmacol 139:749-754, 2003.

(12) Forsyth LM, Preuss HG, MacDowell AL, Chiazze L Jr, Birkmayer GD, Bellanti JA. Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome. Ann Allergy Asthma Immunol 1999; 82(2):185-191.

(13) Birkmayer GD, Kay GG, Virre E. Stabilized NADH (ENADA) improves jet lag-induced cognitive performance deficit. Wien Med Wochenschr 2002; 152(17-18):450-4.

(14) Kay, G.G., Viirre, E., & Clark, J. Stabilized NADH as a countermeasure for jet lag. Paper presented at the 48th International Academy of Aviation and Space Medicine, Rio de Janeiro, Brazil, September, 2000.

(15) Birkmayer JG, Nadlinger K. Safety of stabilized, orally absorbable, reduced nicotinamide adenine dinucleotide (NADH): a 26-week oral tablet administration of ENADA/NADH for chronic toxicity study in rats. Drugs Exp Clin Res 2002; 28(5):185-92.

(16) Moline ML, Rebeta JL, Flye BL, Broch L, Ford T, Zendell SM, Kay GG. Effectiveness of NADH in alleviating effects of acute sleep deprivation in healthy middle-aged adults. Sleep 2002; 25(Supplement):A208.

(17) Kane RL, Kay GG. Computerized assessment in neuropsychology: a review of tests and test batteries. Neuropsychol Rev1992; 3:1-117.

(18) Kay GG, Berman B, Mockoviak SH, Morris CE, Reeves D, Starbuck V, Sukenik E, Hariis AG. Initial and steady-state effects of diphenhydramine and loratadine on sedation, cognition, mood, and psychomotor performance. Arch Int Med 1997; 157:2350-6.

(19) Taylor, J.L., O'Hara, R., Mumenthaler, M.S., & Yesavage, J.A. (2000) Relationship of CogScreen-AE to Flight Simulator Performance and Pilot Age. Aviation, Space, and Environmental Medicine, 71:373-380.

(20) Hyland, D.T., Kay, E.J., Deimler, J.D. Age 60 study, Part IV: Experimental evaluation of pilot performance. Washington, DC: Office of Aviation Medicine, 1994; DOT/FAA/AM-94/23.

(21) Callister, J.D., King, R.E., Retzlaff, P.D. (1996) Cognitive assessment of USAF pilot training candidates. Aviation, Space, and Environmental Medicine, 67:1124-1129.

(22) McNair DM, Lorr M, Droppleman LF. EITS Manual for the Profile of Mood States. San Diego: Educational and Industrial Testing Service, 1971.

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. Age 40-59, male or female.	1. Any unstable clinically significant medical condition or one that might interfere with interpretation of study results.
2. No acute medical illness.	2. Any major psychiatric illness within the past 6 months.
3. No current significant psychiatric disorder or substance abuse disorder	3. Use of any medication acutely or chronically that can enhance alertness, cause sleepiness, or interfere with motor activity. This list would include, but is not limited to, sedative-hypnotics, stimulants, psychotropic medication, and analgesics.
4. No history of psychiatric disorder that might be exacerbated by sleep deprivation (particularly bipolar disorder).	4. Shiftworker, habitually keeps an irregular schedule (time of sleep onset varies by more than one hour from one night to the next), or frequent traveler across time zones.
5. No current significant sleep disorder.	5. Previous use of NADH.
6. Able to follow instructions and complete all tests.	6. Frequent consumer of herbal medication.
7. Fluent in English.	7. Habitually obtains less than 6 or more than 9 hours of sleep per night as determined by clinical sleep history and by sleep log.
8. Habitually consumes no more than 3 cups of coffee or equivalent caffeine per day.	8. Participation in other clinical trial within the past 30 days.
9. Non-smoker.	9. Subject is pregnant or likely to become pregnant during the study.
10. Able and willing to give informed consent.	

Table 2. Components of CogScreen-AE Battery

Test	Description	Domain(s)
Backward Digit Span	Requires recall of a sequence of visually presented digits in reverse order	Visual attention, working memory, verbal-sequential processing
Math	Asks traditional math word problems in a multiple choice format	Computational math skills, attention, concentration, working memory, reading comprehension, logical reasoning
Visual Sequence Comparison	Asks the respondent to compare two simultaneously presented series of letters and numbers	Visual attention, working memory, verbal-sequential processing, visual-perceptual speed
Symbol Digit Coding	Requires substitution of digits for symbols using a key, and assesses immediate and delayed recall of symbol-digit pairs	Attention, visual scanning, working memory, speed of information processing, immediate/delayed visual paired-associate memory
Matching to Sample	Entails identification of matching patterns following brief presentation of a four-by-four colored square grid	Visual-perceptual speed, spatial processing, visual working memory
Manikin Test	Requires the person to identify the hand in which a rotated human figure is holding a flag	Visual-spatial perception, spatial orientation, ability to mentally rotate visual images
Divided Attention Test	Requires the monitoring of a bar within a circle either alone or in combination with the Visual Sequence Comparison task	Visual monitoring, choice visual reaction time, impulsivity, divided attention, working memory, verbal-sequential processing, visual-perceptual speed, capacity for multitasking
Auditory Sequence Comparison	Requires the respondent to compare two series of tone sequences	Auditory attention, working memory, sound pattern discrimination
Pathfinder	Involves the sequencing of numbers alone, letters alone, and an alternating sequence of numbers and letters	Number and letter sequencing skills, ability to systematically apply an organizing principle, immediate memory, motor coordination, visual scanning, ability to shift mental set
Shifting Attention Test	Presents three response rules, each practiced in isolation, that are then applied; the respondent must deduce the rule in force and adapt to programmed changes as they subsequently occur	Concept formation, mental flexibility, sustained attention, deductive reasoning, vulnerability to response interference, working memory, application of novel rules, visual scanning, choice visual reaction time, perseverative tendencies
Dual Task	Presents two tasks, a visual-motor tracking task and a continuous memory task involving recall of the previously presented number. Each is presented first alone and then together as a simultaneous task.	Sustained attention, visual-motor tracking, divided attention, working memory

Table 3. Demographic Characteristics of the Subject Sample

GENDER AND ETHNICITY			
	F	M	Total
African-American	20%	12%	**32%**
Asian	4%	0%	**4%**
Hispanic	0%	4%	**4%**
Caucasian	36%	24%	**60%**
Total	**60%**	**40%**	**100%**

AGE RANGE	Total
40-44	20%
45-49	32%
50-54	24%
55-59	24%
Total	**100%**

Table 4. Profile of Mood States

	COMPARISON	BASELINE	NADH	PLACEBO
			VIGOR	
MEAN	BL-A p<0.02	17.2	14.68	14.48
STD DEV	BL-B p<0.01	5.11	6.48	6.08
N	A-B NS	25	25	25
			FATIGUE	
MEAN	BL-A p<0.02	2.72	4.64	4.92
STD DEV	BL-B p<0.03	2.59	3.96	4.80
N	A-B NS	25	25	25
			CONFUSION	
MEAN	BL-A p<0.01	-2.04	-0.28	-0.48
STD DEV	BL-B p<0.01	1.14	3.17	2.62
N	A-B NS	25	25	25
			TENSION-ANXIETY	
MEAN	NS	-0.46	0.33	0.42
STD DEV		3.09	2.63	3.82
N		24	24	24
			DEPRESSION-DEJECTION	
MEAN	NS	1.16	0.8	1.12
STD DEV		1.86	1.12	1.30
N		25	25	25
			ANGER-HOSTILITY	
MEAN	NS	1.75	1.33	1.08
STD DEV		2.64	2.04	1.53
N		24	24	24
			TOTAL MOOD DISTURBANCE	
MEAN	BL-A p<0.03	-13.61	-7.39	-6.30
STD DEV	BL-B p<0.01	12.99	15.27	14.65
N	A-B NS	23	23	23

Table 5. Stanford Sleepiness Scale

	BASELINE	NADH			PLACEBO		
		1	2	3	1	2	3
MEAN	1.28	3.25	3.20	3.08	3.44	3.56	3.48
SD	0.46	1.15	1.22	1.15	1.29	1.26	1.16
N	25	24	25	25	25	25	25
OVERALL MEAN	1.28	3.17			3.49		
OVERALL SD	0.46	0.99			0.99		

NOTES:
Scale range is 1 – 7, with 7 being sleepiest. Scores over 4 are considered "sleepy."

Table 6. Epworth Sleepiness Scale

	BASELINE	NADH	PLACEBO
MEAN	6.04	6.36	5.52
STD	2.68	2.29	2.57
N	25	25	25

NOTES:
Scale range is 0-24, with 6 being normal, 12 reported by patients with sleep apnea, and 18 by patients with narcolepsy.

Table 7. MSLT Sleep Latency (min)

SUBSTANCE:	NADH			PLACEBO		
NAP OPPORTUNITY:	1	2	3	1	2	3
MEAN	6.00	6.69	6.14	6.20	5.48	6.72
STD DEV	4.72	3.97	4.57	5.18	4.22	5.48
N	24	24	25	25	25	25
OVERALL MEAN	**6.33**			**6.13**		
OVERALL STD DEV	3.10			4.28		

NOTE:
No sleep counted as latency of 20 min

Table 8. Cognitive Performance

PARAMETER			BASELINE	NADH	PLACEBO
SPEED	Variables	NS	15		
	Mean		49.5	45.96	43.79
	SD		13.5	11.66	9.15
	N		17	17	17
ACCURACY	Variables	NS	17		
	Mean of summed variables		1416.35	1478.8	1451.7
	SD		121.71	96.82	99.85
	N		20	20	20
THROUGHPUT	Variables	$p < 0.02$	14		
	Mean		598.84	633.21	605.94
	SD		129.77	123.43	128.05
	N		18	18	18

Table 9. Subject Identification of Substance

ACCURACY	SUBJECTS	%
Correct	9	36%
Incorrect	3	12%
Both Active	2	8%
Both Placebo	11	44%
TOTAL	**25**	**100%**

Figure 1. Schematic Protocol

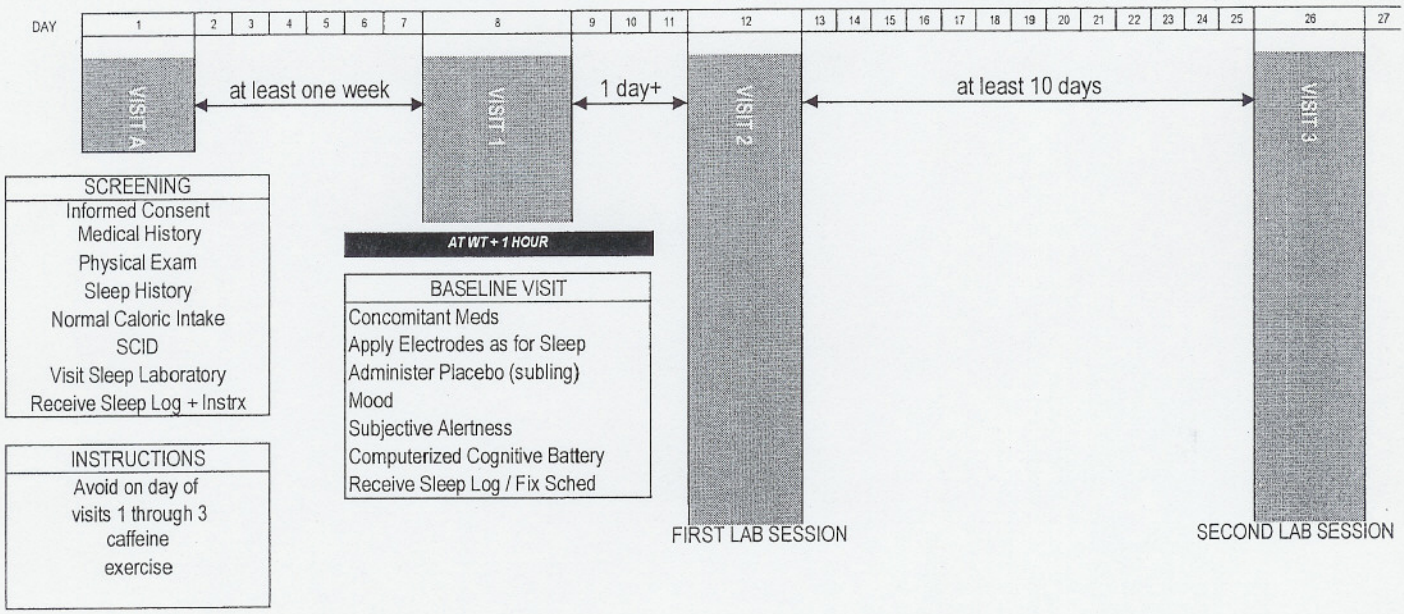


Figure 2. Visual sequence comparison throughput.

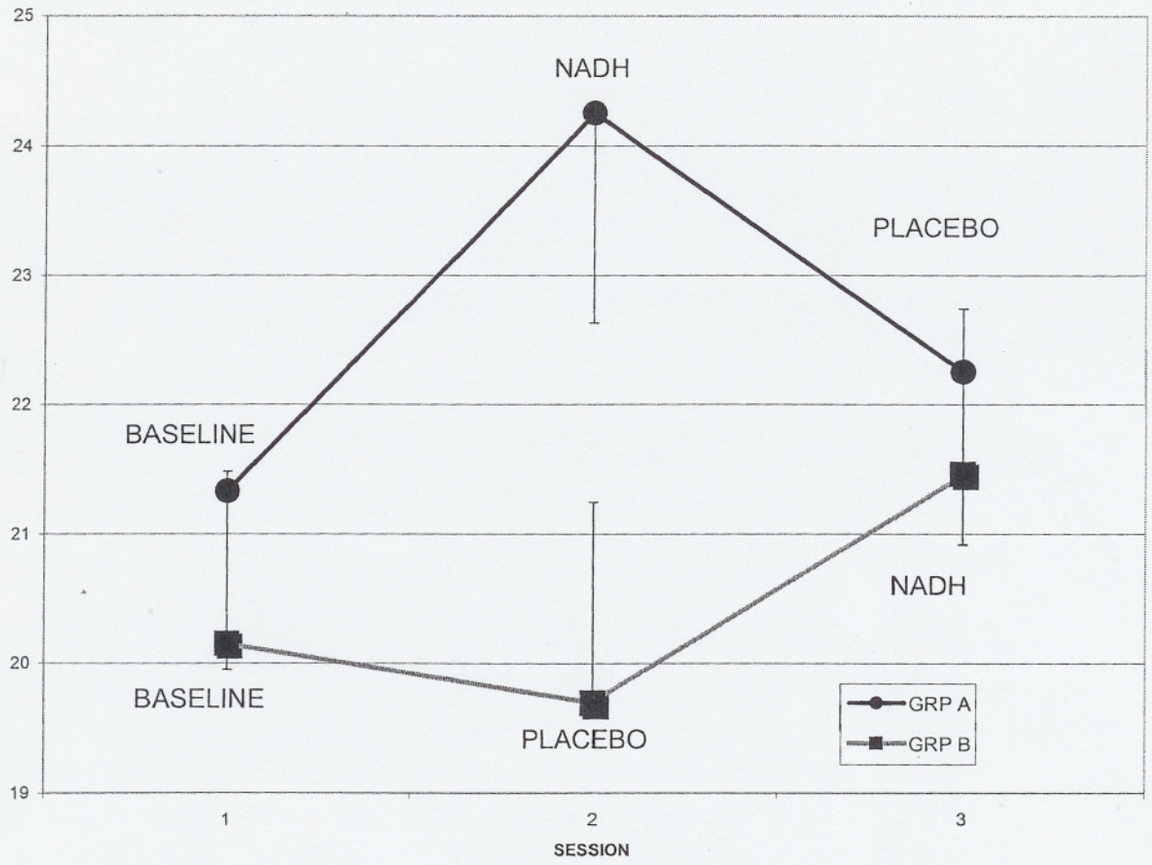
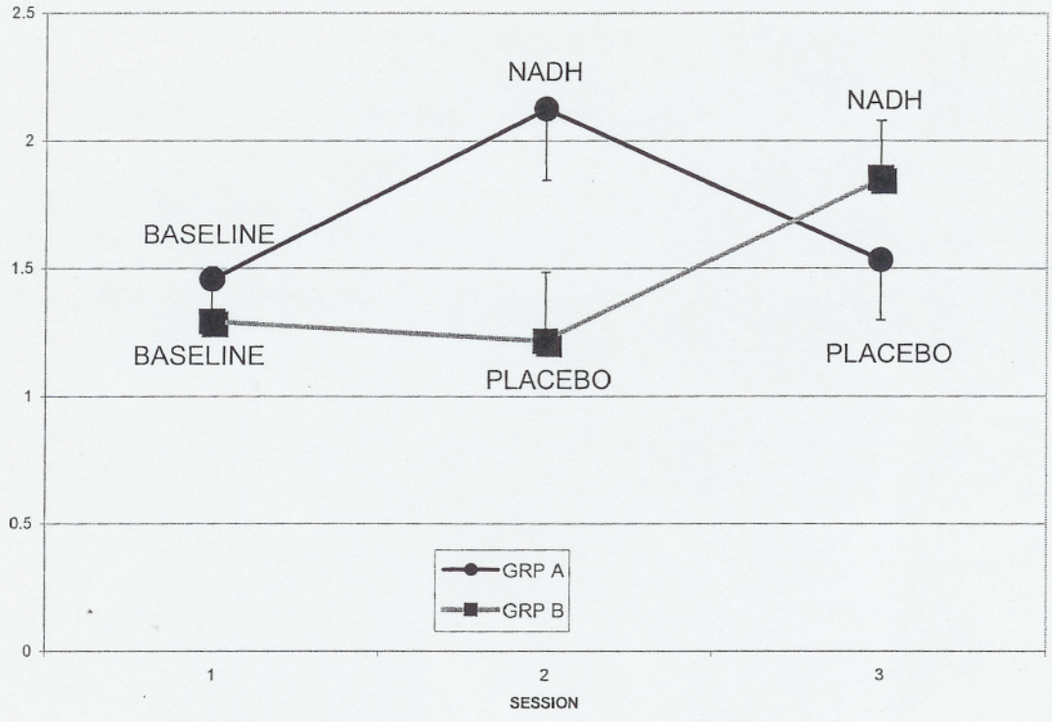


Figure 3. Math throughput.



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