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Stabilized NADH as a Countermeasure for Jet Lag

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Running Head:

Stabilized NADH and Jet Lag

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Abstract

Background: Current remedies for jet lag (phototherapy, melatonin, stimulant, and sedative medications) are limited in efficacy and practicality. The cognitive effects of jet lag have not been well established. We examined the efficacy of a stabilized, sublingual form of reduced nicotinamide adenine dinucleotide (NADH, ENADAlert®, Menuco Corp.) as a countermeasure for jet lag. ***Hypothesis:*** Administration of sublingual NADH to travelers would result in a reduction of the impact of jet lag on cognitive functioning and sleepiness. ***Methods:*** Thirty-five healthy subjects participated in this double-blind, placebo-controlled study. Training and baseline testing were conducted in San Diego, California, before subjects flew overnight to Baltimore, Maryland (a 3-hour time difference). Upon arrival, individuals were randomly assigned to receive either 20 mg of sublingual stabilized NADH (n=18) or identical placebo tablets (n=17). All participants completed computer-administered tests (e.g., CogScreen7) to assess changes in cognitive functioning, mood, and sleepiness in the morning and afternoon. ***Results:*** Jet lag resulted in increased sleepiness for over half the participants and deterioration of cognitive functioning for approximately one third. Cognitive changes were evident in vigilance, working memory, divided attention, and visual perceptual speed. Subjects who received NADH performed significantly better ($P<.05$) on the primary outcome measure (KCPT Total Errors), a measure of vigilance. On 3 of the 7 secondary cognitive and psychomotor test measures subjects who received NADH also performed significantly ($P<.05$) better than those who received placebo and showed a trend ($P\leq.10$) for better performance on the other 4 measures. The effect of NADH on mood and sleepiness was non-significant. No adverse effects were observed with NADH treatment. ***Conclusions:*** Stabilized NADH significantly reduced jet lag-induced disruptions of cognitive functioning, was easily administered, and was found to have no adverse side effects.

Keywords: jet lag, cognitive testing, fatigue countermeasures, NADH

Jet lag is a constellation of symptoms that occur after flying across time zones. It affects a large number of travelers and aircrew (23). These symptoms include: general malaise and fatigue, disrupted sleep, gastrointestinal distress, and memory loss (5,16,19,20,24). Rosekind (15) estimates that jet lag can degrade decision-making abilities, communication, and memory by 30% to 70%. The disruption of the body's entrainment of internal 24-hour cycles of temperature, sleep initiation and other activities to the day-light cycle is believed to be the trigger for jet lag (6). Today's modern jet traveler (soldier, businessperson, athlete, or tourist) often is required to perform at a high functional level upon reaching their destination. Furthermore, the problems of jet lag have been compounded in recent years because business travelers are taking more international trips and staying fewer days at their destination.

Research on the mitigation of jet lag has emphasized methods to speed the entrainment of the circadian rhythm to the new time zone. These methods include sleep scheduling, phototherapy, and administration of sedative and/or stimulant medications (10,14,22). Each of these methods has been found to have some merit, though each has potential adverse side effects and some are considered impractical (4).

An alternative approach to countering the effects of jet lag is to provide the traveler with a nutritional supplement that may help restore the loss of energy and alertness that occur while readjusting to a new time zone. One potential agent is the energy producing coenzyme NADH (ß-nicotinamide adenine dinucleotide, reduced form Coenzyme 1). We investigated the effects of stabilized, sublingual NADH on the cognitive functioning of healthy individuals on the day following an overnight flight across North America.

The sublingual form of NADH (ENADAlert™, Menuco Corporation) was chosen to maximize the absorption and optimize bioavailability of the coenzyme. Previously, NADH has been shown to facilitate production of dopamine and norepinephrine (13). NADH has also been demonstrated to increase cellular energy production of ATP (1), to aid in the repair of damaged DNA (25), and to function as a potent antioxidant (21). Furthermore, NADH has been shown to be effective at improving symptoms of fatigue in Chronic Fatigue Syndrome (7) and improving cognitive functioning in patients with Alzheimer's Disease and Parkinson's Disease (2,3). Given these findings, and the availability of a new rapidly absorbed sublingual formulation of NADH, the first author, friends and colleagues began taking ENADAlert in conjunction with their own travels and found the agent to have beneficial effects. We therefore decided to test whether NADH may be an effective and safe countermeasure for jet lag. It was decided to conduct a double-blind, placebo controlled trial of NADH under highly realistic travel conditions.

We hypothesized that administration of sublingual NADH to travelers would specifically result in a reduction of the impact jet lag has on cognitive functioning and sleepiness, enabling travelers to return to their normal levels of physical and mental activity upon arriving in a new time zone.

METHODS

Subjects

Subjects (n=36) were volunteers between 35 and 55 years of age, in good general physical health. Subjects were recruited from the community by advertising. All subjects were verbally informed of the intent and procedures of the study during a pre-screening telephone interview. Written informed consent was obtained prior to the

history and physical. At the screening visit, subjects were urine tested to screen for the use of illicit drugs and pregnancy. Cognitive screening with the Trail Making Test and Symbol Digit Modalities Test (11) was used to exclude subjects with cognitive function test scores > 1 SD below the mean for their age. Subjects were required to be gainfully employed, to have completed 14 years of formal education, and to have none of the following conditions; history of substance abuse, obesity (body mass index > 30 kg/m^2), air sickness, pregnancy, nicotine use (within 6-months), mental health disorder (within 1 year), or sleep disorder. In addition, subjects were required to have a normal day/night sleep schedule in their home time zone, and to have an Epworth Sleepiness Scale rating < 8 at baseline (8). Subjects were not permitted to be taking antidepressant medications, CNS stimulants, neuroleptics, Ginseng, Gingko Biloba, melatonin, phosphatidylserine, n-acetyl carnitine, or other medications/nutritional supplements reported to enhance cognitive functioning within 90 days of the study. Subjects were not permitted to have participated in other clinical trials within 90 days prior to screening. During the study, subjects were not permitted to use caffeine, alcohol or to take any prescription or over-the-counter medications known to enhance or depress CNS functioning. The study protocol and consent form were reviewed and approved for human subjects by the Biomedical Research Institute of America (San Diego, California).

Procedure

Subjects arrived at the San Diego, California test site at 1200 hours on the day of the flight. The study protocol was reviewed with the subjects and they were then each issued a laptop computer (IBM Thinkpad Model 760) and familiarized with the tests and measures to be used in the study. At approximately 1500 hours subjects were administered the entire battery of tests to establish their baseline performance (Baseline). Subjects also received training in the method for taking the sublingual tablets. Subjects were transported to the San Diego Airport and flown by commercial jet aircraft (coach

class) to Phoenix, Arizona where they were shuttled to a conference room at a nearby hotel, provided dinner, and re-administered the battery of tests at approximately 2030 hours. Subjects were shuttled back to the airport and boarded a flight to Baltimore, Maryland at 2230 hours. Thirty minutes into the flight the subjects were instructed to complete a subset of the battery of tests. Subjects were permitted to sleep after completing the tests. The duration of the flight from Phoenix to Baltimore is approximately 4 hours. Furthermore, there is a 3-hour time difference between San Diego and Baltimore. The local time in Baltimore upon arrival was approximately 0600 hours. After breakfast, subjects were shuttled to the Washington, DC test site where they arrived at approximately 0800 hours.

Sublingual NADH 20 mg (4 tablets of sublingual ENADAlert® 5 mg) or an equal number of placebo tablets of identical size, shape, color and taste were administered by study site personnel to the subjects upon their arrival at the Washington test site. At the test site, subjects' activities were carefully monitored to avoid dehydration, exposure to daylight (subjects were kept indoors) and hunger (they were provided breakfast and lunch, which all subjects ate.) Caffeine intake was strictly prohibited. Study drug was provided in moisture-proof, airtight, labeled medication bottles labeled with the subject's identification number.

Subjects completed the battery of tests 90 minutes after dosing, at approximately 0930 hours (AM test). Testing was repeated at 1230 hours (PM test). Subjects were dismissed from the study at 1400 hours.

The study was carried out during a 1-month period over the course of three weekends with groups of approximately equal size (i.e., 13, 12, and 10 subjects).

Measurements

Cognitive Tests

Kay Continuous Performance Test (KCPT) (9)

Measure of sustained attention and vigilance: On this 13-minute computer-administered cognitive test, subjects watch a computer monitor and respond only when seeing a target symbol that occurs at low frequency (i.e., 5%). There are a total of 220 trials. The number of errors of omission (i.e., lapses of attention) and errors of commission were used to calculate total errors.

CogScreen® (9)

The following four CogScreen subtests were administered:

Shifting Attention Test: Instruction Condition: Measure of working memory: Subject reads a two-word instruction and then applies the instruction to the screen that follows. There are 32 trials requiring approximately three minutes to be completed. The accuracy, throughput (number of correct responses per minute), and median response time for correct responses were recorded.

Matching to Sample Test: Measure of visual perceptual processing speed and working memory: Subject views a 4x4 checkerboard pattern and then on the screen that follows, the subject selects the matching checkerboard pattern. There are 20 trials requiring three minutes to be completed. The accuracy of responses, the throughput (number of correct responses per minute) and the median response time for correct responses were recorded.

Visual Sequence Comparison: Measure of visual processing of number/letter sequences: There are 20 trials requiring approximately three minutes to be completed. The accuracy of responses, the throughput (number of correct responses per minute) and the median response time for correct responses (VSCRTC) were recorded.

Dual Task Test: Tracking Alone: Measure of psychomotor functioning: Subject's task is to maintain the central position of an unstable cursor that moves along a horizontal line using the left and right cursor keys for a period of 90 seconds. The average absolute tracking error and the number of tracking failures were recorded.

Mark Numbers Test: Complex Cognitive Assessment Battery (CCAB) (18):

Measure of working memory and divided attention: The subject identifies and "marks" numbers in a spreadsheet according to an instruction (e.g. Mark all even numbers between 20 and 46). While performing this one-minute task, the subject is twice interrupted and instructed to locate and mark the smaller or larger of two flashing numbers. After performing the secondary task the subject resumes the primary task. There are four 1-minute trials. The total score (a derived measure of the total number of correct marks, the speed of completing the task, and performance on the secondary task) and the mean reaction time to responding to the secondary task were recorded.

Automated Neuropsychological Assessment Metrics (ANAM) (9)

Two sub-tests were selected from the ANAM battery of tests:

Running Memory Test: Measure of vigilance and working memory: A total of 160 letters are presented during the five-minute duration of the test. Subject is instructed to indicate whether or not the letter being shown on the screen is the same as the previous letter. The accuracy of responses, the throughput (number of correct responses per minute) and the mean response time for correct responses were recorded.

Math Test: Measure of working memory and math reasoning: The subject is presented with 3 numbers and two operation signs (e.g., 3 + 5 - 2) and is

instructed to decide whether the total is greater than 5 or less than 5. Forty problems are presented during this 7-minute test. The accuracy of responses, the throughput (number of correct responses per minute) and the mean response time for correct responses were recorded.

Self-Report Mood Measures

Walter Reed Mood Scale (9)

Subjects indicate their agreement or disagreement (i.e., Agree, Somewhat Agree, or Disagree) with 36 adjectives that are presented as a description of their current mood. Scales include measures of fatigue and activity.

Stanford Sleepiness Scale (8)

This is a 7-point self-report scale of current sleepiness, with 1 being least sleepy and 7 being most sleepy.

Statistical Analyses

The primary outcome measure was defined *a priori* as total errors on the KCPT; all other measures are considered secondary. Statistical significance was set at $P < .05$. The study was powered to find a 0.5 SD difference in the mean number of KCPT errors. For continuous measures, the effects of sublingual NADH were assessed by repeated measures analysis of variance and analysis of change from baseline scores by analysis of variance (SPSS-PC, Version 10.1). Tests with categorical results (Dual Task Test tracking errors, Stanford Sleepiness Scale) were analyzed by Chi-square test. These methods were used to provide a comparison of the NADH and placebo groups at Baseline in San Diego, CA, the morning in Washington, D.C. (AM), and the afternoon in Washington, D.C. (PM).

RESULTS

Subject Demographics: Thirty-six subjects enrolled in the study (19 males and 17 females) between 35 and 55years of age. One male subject who had completed screening failed to appear for the test session. Subjects were randomly assigned to the placebo and NADH groups. The groups did not differ in age (NADH age = 43.9 +/- 6.9; Placebo 42.8 +/- 6.1) or gender composition (NADH 9 males/9 females; Placebo 9 males/8 females).

Adverse Events: Fourteen subjects reported having headaches during the study. The onset of the headache occurred before the administration of NADH or placebo for ten of these subjects. Two subjects in each group had headaches that began after the administration of either NADH or placebo. Subjects were given acetaminophen or ibuprofen for the headaches. For eight subjects the headache resolved prior to the administration of NADH or placebo.

Vigilance: Errors on the KCPT was defined *a priori* as the primary outcome measure of the study. At baseline, 30 subjects (14 NADH, 16 Placebo) obtained a normal performance (i.e., > 1 s.d. below the mean). KCPT results for the remaining five subjects were not analyzed. On the AM test, 5 NADH subjects and 7 Placebo subjects made two or more vigilance errors. By the PM, subjects receiving NADH made significantly fewer total errors (compared to baseline) than subjects receiving placebo ($P<.05$) [Figure 1 Here]. Twelve of the 14 NADH subjects had resumed a normal level of performance (i.e., less than two vigilance errors) compared to 10 of the 16 placebo subjects ($P<.08$).

Useable data for the ANAM Running Memory Test was obtained for only 27 subjects. Five of the subjects were not using the correct key to respond and three subjects had response times (at all 3 sessions) that were extreme outliers. For the remaining 14

NADH and 13 placebo subjects, there was a baseline difference in reaction time (*P* =.005). There were no treatment related differences observed for this test.

Working Memory: There were no baseline group differences in throughput (i.e., correct responses per minute) on the Shifting Attention Test-Instruction Condition. The Group x Session effect was significant (*P*<.05). Analysis of contrasts shows that subjects in the NADH group correctly completed 13.2 more problems per minute at AM vs. baseline compared to 6.8 more problems correctly completed per minute for the placebo group [Figure 2 Here].

On the ANAM Math Test the Group x Session effect approached significance for the measure of throughput (*P* <.07). For subjects in the NADH group there was a 15% improvement relative to baseline at the AM test and an 11% improvement at the PM test. By comparison, subjects in the placebo group showed a 6% improvement at the AM test and a 4% improvement at the PM Test. The mean difference between groups was not significant (*P*<.08).

Divided Attention: The principal measure of divided attention was the secondary task reaction time for the CCAB Mark Numbers Test. The Group x Session effect was significant for the secondary task reaction time (*P* =.038). The secondary task reaction time decreased for NADH subjects by 0.15 seconds and increased by 0.44 seconds for the placebo subjects (*P* =.016). The PM Total score for NADH subjects increased by 77.5 points, compared to an increase of 19.2 points for placebo subjects (*P* = .011) [Figure 3 Here].

Visual Perceptual Speed and Accuracy: The CogScreen Matching to Sample and Visual Sequence Comparison tests provided measures of visual perceptual speed and accuracy. For the Visual Sequence Comparison Test there was a significant Group x

Session interaction for the throughput measure (correct responses per minute; $P < .05$). NADH subjects correctly completed 5.4 more items per minute at the PM test compared to baseline. By comparison, the placebo subjects correctly completed 1.4 more items per minute ($P = .026$). There was no significant Group x Session effect for the Matching to Sample Test. Nevertheless, the NADH group showed a tendency ($P = .078$) for more improvement in throughput from baseline to PM testing; 4.9 more correct responses per minute compared to 1.0 more correct response per minute for placebo subjects [Figure 4 Here].

Psychomotor Performance: The CogScreen Dual Task Test Tracking Alone measure provides a measure of skilled motor activity. A significant practice effect on this test is generally reflected by an improvement in tracking errors over trials. This pattern of performance is evident for the NADH group where 31% had tracking failures at baseline, 33% at the AM test and 11% at the PM test. In contrast, for the subjects in the placebo group, 29% had tracking failures at baseline, 41% at the AM test and 29% at the PM test. Group comparisons show a trend for better tracking performance for NADH subjects ($P < .09$).

Sleepiness and Mood: At baseline, 14 subjects (82%) in the NADH group rated their sleepiness a 1 or 2 on the 7-point Stanford Sleepiness Scale (SSS) and three subjects rated their sleepiness a 3. Sixteen placebo subjects (94%) rated their sleepiness a 1 or 2 at baseline. One placebo subject had a sleepiness rating of 3. One NADH subject was an extreme outlier on the SSS and was excluded from the SSS analyses. In the morning, both groups had identical sleepiness ratings; six in each group (35%) had a rating of 1 or 2 and 11 (65%) had ratings of 3 or more. However, in the afternoon there was a trend toward less sleepiness in the NADH group ($p=.07$); eight subjects had ratings of 1 or 2 and nine had ratings of 3 or more. For the placebo group, four subjects had ratings of 1

or 2 and 13 had ratings of 3 or more [Figure 5 Here]. There were no significant differences found between groups on measures of self-reported fatigue and activity level.

DISCUSSION

The present study was designed to assess the impact of jet lag as well as the effects of a potential jet lag countermeasure under realistic travel conditions. Results indicated that an overnight ("red-eye") flight crossing four time zones (i.e., a three-hour forward time shift) is effective in generating subjective symptoms of jet lag, including fatigue and sleepiness. The cognitive test employed in the study (CogScreen®) detected cognitive changes following the flight. Furthermore, stabilized NADH was found to have a beneficial effect on cognitive functioning when administered upon arrival. Subjects who received NADH performed significantly better than subjects who received placebo on the primary outcome measure (KCPT Total Errors, a measure of vigilance), and on 3 of the 7 secondary cognitive and psychomotor test measures. On the remaining four cognitive measures, NADH subjects showed a trend ($P \leq .10$) for better performance than subjects who received placebo. These findings suggest that NADH may mitigate the effects of jet lag on the cognitive and psychomotor functions considered particularly sensitive to sedation; vigilance, working memory, psychomotor tracking and divided attention.

The only adverse effects reported during the study were headaches (14 subjects), fatigue and sleepiness. Only two subjects reported headaches following the administration of NADH. The headaches were not deemed to be attributable to NADH. The absence of treatment related side effects following administration of NADH is consistent with earlier clinical studies (2,3,7).

The KCPT, the primary outcome measure of the study, demonstrated a notable increase in lapses of attention, as reflected by omission errors, on the morning following the flight. By the afternoon, only 14% of NADH subjects had omission errors on the

KCPT and mean accuracy on the Running Memory Test was 96%. In contrast, 37% of placebo subjects made omission errors on the KCPT and the mean accuracy on the Running Memory Test was 91%. NADH subjects made significantly fewer total vigilance errors on the PM test.

Subjects who received NADH were also better able to temporarily hold information in mind and perform mental operations (i.e., working memory). Subjects who received NADH correctly completed more problems per minute on the Shifting Attention Test-Instruction Condition. Test accuracy dropped for subjects in the placebo condition. On a second measure of working memory, ANAM Math Test, there was a trend for better performance.

The negative impact of jet lag on divided attention, the ability to perform simultaneous mental operations, was readily apparent. During the morning test session, subjects who received placebo were 0.15 seconds slower, compared to baseline, in their response to the secondary task on the CCAB Mark Numbers Test. By comparison, subjects who received NADH improved, compared to baseline, by 0.44 seconds on this task ($P<.05$). The total score on the Mark Numbers test also improved significantly more for subjects who received NADH.

On two measures of visual perceptual speed and accuracy (CogScreen Visual Sequence Comparison and Matching to Sample), NADH subjects demonstrated greater improvement in the number of correct responses per minute at the afternoon test session, compared to the placebo subjects.

This jet lag protocol was effective in inducing subjective symptoms of jet lag. During the morning test session 57.1% of the subjects in the NADH group and 62.5% of the subjects in the placebo group reported an increase in sleepiness compared to baseline. By the afternoon test session, 42.3% of the NADH subjects and 75% of the placebo subjects were continuing to report sleepiness (relative to their baseline rating). The effect of NADH on sleepiness ratings and other mood ratings was not significant.

The present study did not directly assess circadian effects or the hours of sleep obtained by subjects during the flight. It is not possible, from the current study, to determine the contribution that each of these factors plays in the development of the symptoms of jet lag. Our intent was to provide subjects a realistic overnight flight experience. The relatively low power of sleepiness ratings made it less likely that we would be able to detect a significant effect of NADH on sleepiness with the number of subjects enrolled in this trial. On several tests, we were also hampered by missing data resulting from limitations in our training of subjects on the cognitive test procedures. Furthermore, the computerized cognitive testing programs were not designed to notify subjects when they were pressing an invalid key.

The public health, occupational health, and economic impact of jet lag have likely been underestimated (12). There are an increasing number of business travelers making transcontinental and intercontinental flights. These travelers are subjected to the effects of jet lag demonstrated in the current study. The "jet lagged traveler" is more likely to experience lapses of attention (i.e., vigilance errors), to have difficulty concentrating (i.e., working memory difficulty), and to be less efficient at handling the demands of the work environment (i.e., decreased divided attention). In addition the jet lagged traveler feels less alert, less active and more fatigued. For the traveling athlete these effects of jet lag are likely to be evident in reduced performance. Travelers, and the aircrew who transport them, need to be made more aware of the effects and consequences of jet lag. They also need to learn about the benefits and risks of different jet lag countermeasures. Employers, business travelers, and athletes need to adjust their expectations and allow for an adequate opportunity to recover from the effects of jet lag.

The implications of this work are that activities that require attention to multiple tasks, continuous concentration and rapid interpretation of visual cues will be affected by travel across time zones. Stabilized NADH was effective in mitigating against these cognitive effects. Piloting an aircraft is critically dependent on vigilance, memory and

visual perception. Solutions for jet lag that involve attempts to realign circadian rhythms appear to be especially impractical for commercial pilots (17). In contrast, NADH may prove to be a suitable short-term countermeasure for aircrew.

Further studies are needed to replicate and extend the present findings. In particular, there is a need to investigate optimal dosing parameters for this use of NADH. What is the duration of the effect of NADH on cognition and self-reported sleepiness? Furthermore, there is a dearth of evidence on the duration and course of the cognitive performance decrements over time that result from jet lag. Would NADH be helpful for symptoms occurring 48 to 72 hours after travel? Other conditions where sleep schedules and circadian rhythms are disturbed such as night call and shift work should also be investigated.

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DISCLOSURE

None of the study authors have an interest, financial or otherwise, in Menuco Corporation, ENADA, or ENADAlert.

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Legends for Illustrations

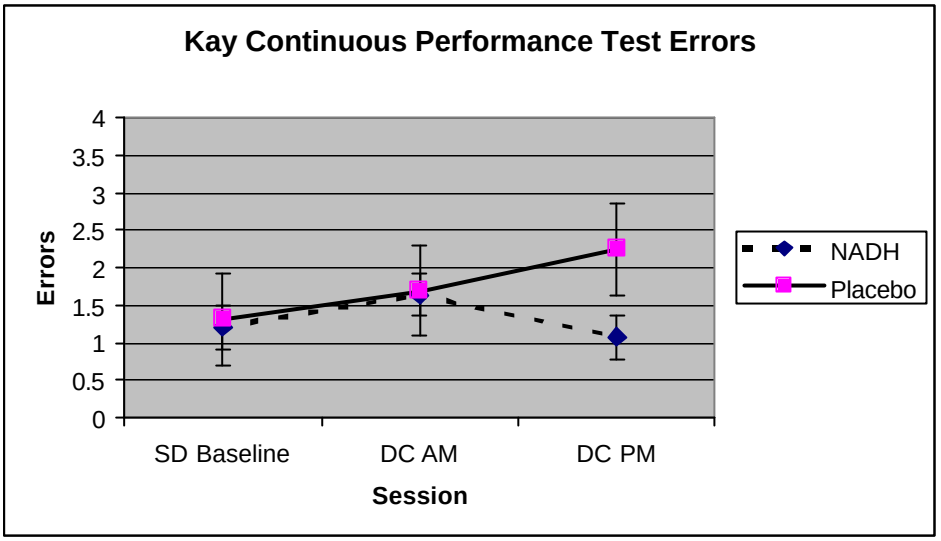
Figure 1: Mean errors and SEM by group on the Kay Continuous Performance Test, across the 3 test sessions. Results show a significant group difference in the PM session ($P<.05$). Note: SD Baseline refers to the testing in San Diego on the day of the flight; DC AM refers to morning testing in Washington, DC PM refers to afternoon testing in Washington.

Figure 2: Mean throughput (correct responses per minute) and SEM by group on the Shifting Attention Test Instruction Condition, across the 3 test sessions. Results show a significant group by session effect ($P<.05$).

Figure 3: Mean reaction time and SEM on the secondary task of the Complex Cognitive Assessment Battery Mark Numbers Test, across the 3 test sessions. Results show a significant group by session effect ($P <.05$).

Figure 4: Mean throughput (correct responses per minute) and SEM by group on the Visual Sequence Comparison test, across the 3 test sessions. Results show a significant group by session interaction ($P <.05$).

Figure 5: Percentage of subjects reporting sleepiness on the Stanford Sleepiness Scale (rating > 2). Results show a trend for less sleepiness in the NADH group in the PM ($P=.07$).


Kay Continuous Performance Test Errors
Errors
4
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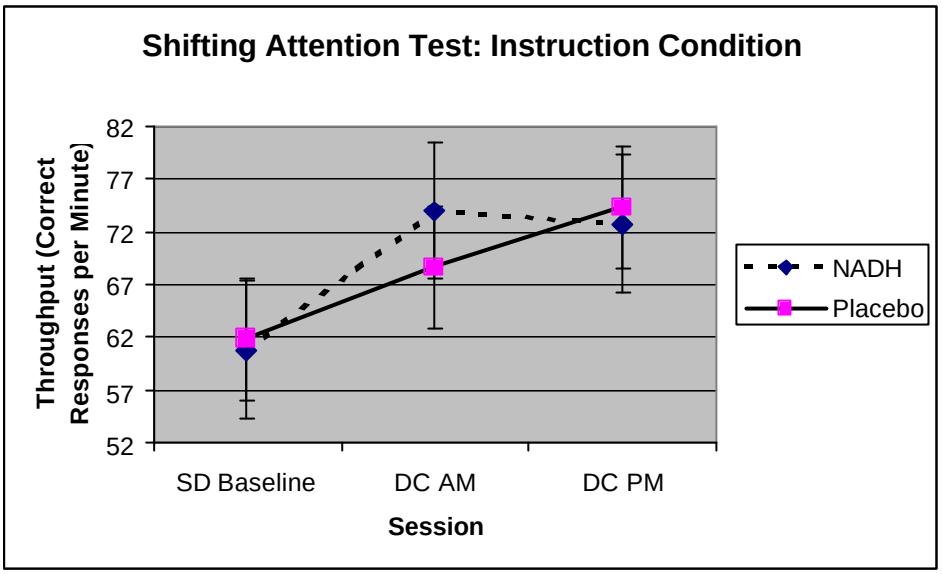
SD Baseline
DC AM
DC PM
Session
NADH
Placebo

Figure 1


Shifting Attention Test: Instruction Condition
Throughput (Correct Responses per Minute)
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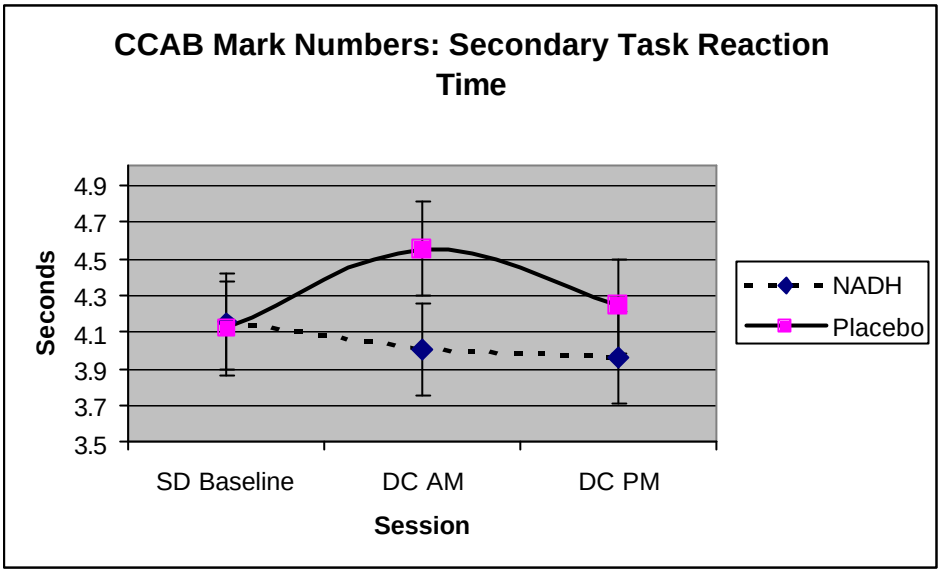
SD Baseline
DC AM
DC PM
Session
NADH
Placebo

Figure 2


CCAB Mark Numbers: Secondary Task Reaction Time
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4.9
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DC PM
Session
NADH
Placebo

Figure 3

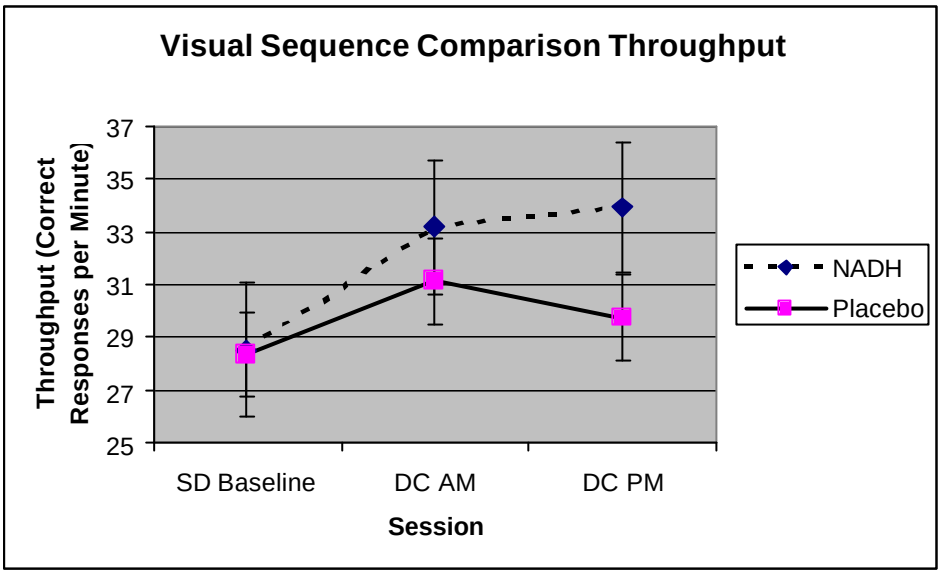
Visual Sequence Comparison Throughput
Throughput (Correct Responses per Minute)
37
35
33
31
29
27
25
SD Baseline
DC AM
DC PM
Session
NADH
Placebo

Figure 4

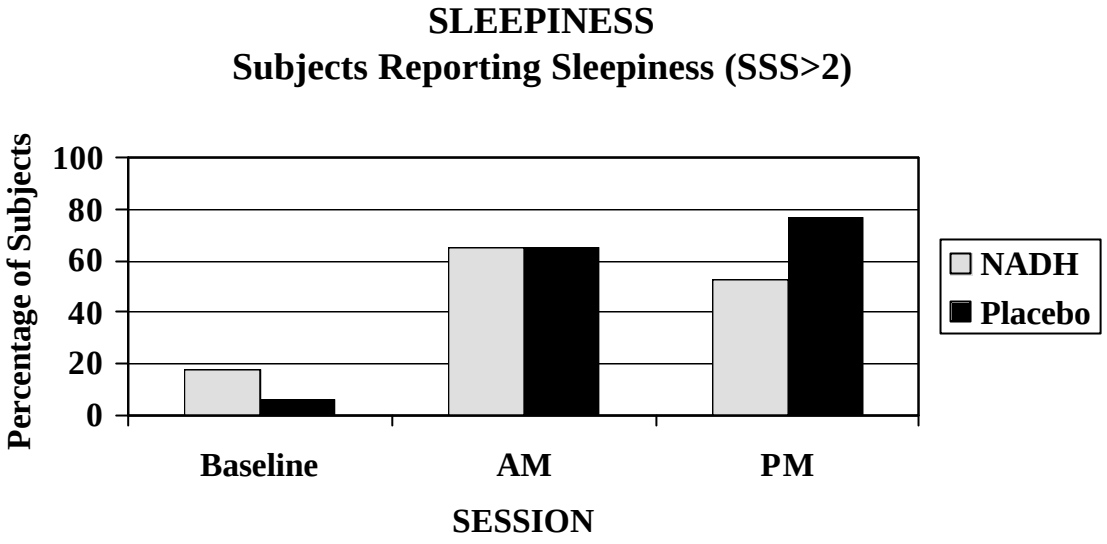
SLEEPINESS
Subjects Reporting Sleepiness (SSS>2)
Percentage of Subjects
100
80
60
40
20
0
Baseline
AM
PM
SESSION
NADH
Placebo

Figure 5