NAVAL AEROSPACE MEDICAL RESEARCH LABORATORY
280 FRED BAUER STREET, BUILDING 1811 PENSACOLA, FLORIDA 32508

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THE EFFICACY OF ARMODAFINIL FOR MAINTAINING VIGILANCE AMONG NAVY AIR TRAFFIC CONTROLLERS EIGHT TO TWELVE HOURS POST-DOSE

Jeffrey B. Phillips
Rita G. Simmons
Melissa Strompolis
Richard D. Arnold

Executive Summary

Introduction: The Navy does not currently impose FAA shift limitations on military Air Traffic Control (ATC) crews during high-tempo combat-related operations. Military ATC crews must accommodate extended and rotating shift schedules and manpower and workloads unique to the demands of a specific mission or duty station. In an ATC context, a maximum level of vigilance is required to ensure that controllers can safely monitor numerous aircraft on radar over prolonged periods of time. Despite the overwhelming evidence linking long shift durations and fatigue with lapses in vigilance, no fatigue countermeasures are approved for use in the ATC community. Armodafinil, a single isomer formulation of modafinil, has been shown to promote alertness, without the detrimental side effects associated with traditional stimulants. The purpose of this study was to test the ability of armodafinil to maintain vigilance among ATC operators 8 to 12 hours post-dose. It was hypothesized that participants receiving armodafinil would experience significantly fewer lapses in vigilance compared to participants receiving placebo, while sustaining higher levels of performance on a simulated ATC task. **Method:** Using a double blind procedure, forty-eight Navy ATC students, 41 males and 7 females, were assigned to one of two groups, 150 mg dose of armodafinil or placebo. At 0800 participants were administered three pills, either active or placebo, and then they completed a standard work day. Participants returned at 1545 to complete the 4 hour performance portion of the study, consisting of the psychomotor vigilance task (PVT) and the precision approach radar (PAR). Participants completed three 10 minute blocks of the (PVT), followed by a 30 minute PAR task. The PVT/PAR task combination was completed four times with a 15 minute break at 2 hours, resulting in a 4 hour sustained performance period. Levels of fatigue, alertness, and mental workload were derived from the BFI, KSS, and GRQ administered immediately following each 30 minute PVT and PAR session. **Results:** The analysis showed a significant difference in vigilance between the armodafinil group and placebo ($p < .05$). PVT data revealed that participants receiving a single dose of 150 mg of armodafinil experienced significantly fewer lapses of attention compared to the control group. Results from the BFI, KSS, and GRQ failed to show significant effects for group, block, or the group by block interaction. This suggests that participants were unaware of the accumulation of fatigue across the performance period. **Conclusions:** Armodafinil should be considered for limited use in military ATC operations when high-operational tempo requires shifts to be significantly longer than FAA regulations dictate. Despite its apparent efficacy, armodafinil should never replace a standard 8-hour regimen of sleep.

Introduction

Background

The Federal Aviation Administration (FAA) cited air traffic controller fatigue as a contributing factor in five runway incursions since 2001. One of these incursions resulted in the death of 49 crew members and passengers onboard Comair flight 5191 in Lexington, Kentucky, on August 27, 2006, (NTSB SR A-07-30 TO 32). These fatigue-related accidents motivated the FAA to place strict restrictions on shift durations. The current FAA regulation, Title 14, Part 65, Subpart B, § 65.47, states that "except in an emergency, a certified air traffic control operator must be relieved of all duties for at least 24 consecutive hours at least once during each 7 consecutive day period. Such an operator may not serve or be required to serve for: (a) more than 10 consecutive hours; (b) more than 10 hours during a period of 24 consecutive hours, unless they have had a rest period of at least 8 hours at, or before, the end of the 10 hours of duty." However, these FAA shift limitations do not apply to military air traffic control (ATC) crews during high-tempo combat-related operations. Military ATC crews must accommodate shift schedules, manpower, and workloads unique to the demands of a specific mission or duty station, and, as a result, shift durations may be significantly extended to meet operational demands.

In an ATC context, a maximum level of vigilance is required to ensure that controllers can safely monitor numerous aircraft on radar over prolonged periods of time. In most 24-hour facilities, military ATC crews work counterclockwise rotating shift schedules, which have been shown to be highly associated with an accumulation of sleep debt (Barton & Folkard, 1993). Reports suggest that controllers working counterclockwise rotating shifts get an average of 2.2 hours of sleep between their day and midnight shifts (Signal & Gander, 2007). Fatigue-inducing shift schedules utilized at many Naval ATC facilities increase the probability that breakdowns in vigilance will occur, as fatigue has a well-established negative effect on vigilance (e.g., Dinges et al., 1997; Jewett, Dijk, Kronauer, & Dinges, 1999). Additionally, combining long shift durations with a lack of adequate crew rest is historically problematic and is thought to contribute to breakdowns in vigilance on ATC tasks (Schroder, Touchstone, Stern, Stoliarov, & Thackray, 1994). These conditions, in conjunction with low workload and the circadian trough between 3:00 a.m. and 6:00 a.m., raise significant operational safety concerns associated with fatigue-induced deterioration of vigilance (Luna, 2007). The Navy has approved pharmaceutical countermeasures to bolster wakefulness and performance for other occupations requiring high levels of vigilance during extended shifts and op-tempo circumstances; however, there are no pharmaceutical fatigue countermeasures approved for use by military controllers.

Armodafinil: a longer lasting isomer of Modafinil

Modafinil, a non-amphetamine psychostimulant, has been shown to provide significant improvements in wakefulness and alertness with minimal side effects (Walsh, Randazzo, Stone, & Schweitzer, 2004). Specifically, unlike traditional stimulants already used by military communities, modafinil does not appear to severely affect normal sleep patterns or appetite and has a lower potential for abuse (Lyons & French, 1991; Myrick, Malcom, Taylor, & LaRow,

2004). While these qualities appear to make modafinil well-suited as a military fatigue countermeasure, the relatively short therapeutic effect (≤ 6 hrs) of a single dose of modafinil potentially means inadequate coverage for an entire operational mission (Wesensten et al., 2002). The wake-promoting benefits of modafinil are typically extended by re-dosing every 4-6 hours. Recent pharmacokinetic studies have shown that Armodafinil, the longer half-life enantiomer of modafinil, maintains blood plasma levels of modafinil for up to 15 hours (Darwish, Kirby, Hellriegel, Yang, & Robertson, 2009) at lower dosages compared to racemic modafinil. In a parallel group study comparing armodafinil to modafinil and placebo, Dinges, Arora, Darwish, and Niebler (2006) found that armodafinil had a comparable peak plasma concentration to modafinil, but with higher concentrations and improved wakefulness and sustained attention for 6-14 hours post-dose. Other studies examining armodafinil's effectiveness during sleep deprivation or in clinical populations with excessive daytime sleepiness have shown that armodafinil significantly improved alertness, increased vigilance, and reduced the subjective feeling of fatigue (Hirshkowitz et al, 2007; Harsh et al., 2006; Dinges et al., 2006). Maintaining blood plasma levels of armodafinil longer should provide significantly greater protection against fatigue and lapses in vigilance and would eliminate the need to re-dose.

Objective

The current study is designed to test the efficacy of a single dose of 150 mg armodafinil as a countermeasure against fatigue-induced lapses in vigilance among air traffic control (ATC) students 8 to 12 hours post-dose.

Method

Subjects

Forty-eight U.S. Navy and Marine Corps ATC students, 41 males and 7 females, with an age range of 18-35 years (mean = 20.98 yrs, SD = 3.29) voluntarily participated in the study. Descriptive statistics for the groups are summarized in Table 1. The research protocol was approved by the Naval Aerospace Medical Research Laboratory Institutional Review Board. All volunteers were informed of their rights as research participants and of possible side effects associated with armodafinil. After participants were given the opportunity to ask questions, written informed consent was obtained. All participants were healthy ATC students with current physical exams on record. Prospective participants were asked to complete a confidential medical questionnaire (Appendix A) and were excluded if they met any of the following conditions: drug allergies to modafinil or armodafinil, asthma, severe allergies, sleep apnea, seizure disorder, liver/kidney problems, urinary retention, heart/circulatory disease, high blood pressure, glaucoma, emphysema, enlarged prostate, gastrointestinal disorders, epilepsy, pneumonia, or a history of drug or alcohol dependency. They were also excluded if they were taking prescribed or over-the-counter-medications; were pregnant, lactating or had premenstrual syndrome; or were currently or had been sick in the last seven days. Participants were instructed to refrain from consumption of alcohol and herbal or sports supplements for 72 hours prior to

testing. Participants were also instructed to refrain from excess caffeine intake (three cups or one more than usual amount) for 24 hours prior to testing.

Study Design

A power analysis assuming a medium effect size ($f^2 = .15$) revealed that a sample size of 40 participants would provide 90% power (Erdfelder, Faul, & Buchner, 1996). This mixed factorial design compared treatment and placebo groups across a 4 hour sustained performance period, following an extended workday, on the psychomotor vigilance task (PVT), precision approach radar (PAR) task, and results from alertness and workload self-report questionnaires. Both groups were tested under the same fatigue-inducing schedule, requiring participants to work a normal 8 hour day and then report for study testing for the successive 4 hours. Participants were assigned randomly to either the treatment or placebo group, and double blinding was used to prevent demand characteristics. Task presentation of PVT and PAR was counterbalanced to control for possible order effects.

Drug preparation

Both active and placebo oral medication preparations were manufactured by Cephalon Pharmaceuticals (Cephalon, Inc., Frazer, PA). Study medications were delivered in individual vials and pre-marked with participant numbers to maintain double-blind integrity. Armodafinil capsules are a standardized compound manufactured by Cephalon, and the oral placebo provided was a capsule containing a lactose-based powder. A 150 mg dose of armodafinil was selected based on the pharmacokinetic profile. Because the time of therapeutic action and half-life of armodafinil are considerably longer than modafinil, a 150 mg dose was estimated to be sufficient to achieve the anticipated preservation, or increase, in alertness. Both the armodafinil and the placebo were dosed in three 50 mg capsules. Human pharmocokinetics for a single dose of armodafinil can be found in the manufacturer's product monograph for Nuvigil®.

Procedure

On test day participants completed a medical form (Appendix B) to ensure compliance with inclusion criteria. Participants were then given a symptom profile (Appendix C) to establish their potential medication side effect symptom baseline prior to drug administration. Participants received three pills to ingest at 8:00 a.m. Double-blind treatment administration was used to randomly assign participants to either a treatment or control condition, with participants in the treatment condition receiving a 150 mg oral dose of armodafinil and participants in the control condition receiving an identical oral placebo. Participants completed a standard work day during which potential medication side effects were documented via symptom profile sheets at 10:00 a.m., 12:00 p.m., and 2:00 p.m. At 3:45 p.m. the performance portion of the study was conducted. Participants performed three 10 minute blocks of the psychomotor vigilance task (PVT) and a 30 minute simulated precision approach radar (PAR) task (both described in the apparatus section). Participants alternated between the PVT and PAR four times, resulting in a sustained performance period of approximately 4 hours. Vigilance scores were recorded by a

PVT response box, and PAR performance was graded by the same certified ATC instructor for all participants. Self-report measures of fatigue, sleepiness, and mental workload were collected immediately following each 30 minute PVT and PAR trial (Appendices D-G). A 30 minute break was given after approximately 2 hours of testing during which the participants were provided a meal. The meal consisted of a sandwich and a drink (choice of Gatorade or water). Following the meal, participants completed the final 2 hours of PVT and PAR performance. After completion of the performance portion of the study, participants completed one additional symptom profile to ensure resolution of any side effects prior to being discharged. A study timeline is provided in Table 2.

Dependent measures included the following: performance on the PVT (lapses and mean reciprocal reaction time for responses in the 90th percentile), performance on a simulated PAR task, and scores on subjective measures [Symptom Profile, Brief Fatigue Inventory (BFI), Karolinska Sleepiness Scale (KSS), and Global Rating Questionnaire (GRQ)].

Apparatus

Psychomotor Vigilance Task-192. The PVT is a simple reaction time test administered on a hand-held device. The PVT requires participants to respond to the presentation of a visual stimulus as quickly as possible by pressing a button with the thumb or finger of their dominant hand (Dinges & Powell, 1985). The PVT was included in this study because of its sensitivity to the effects of fatigue. The PVT is also very reliable with little evidence of practice effects (Balkin et al., 2004). These characteristics made the PVT a useful instrument to test the efficacy of armodafinil in a young, healthy population with relatively low levels of fatigue.

Precision Approach Radar Simulator. The simulated precision approach radar (PAR) task requires operators to monitor aircraft approaching for landing and to verbally direct pilots to follow an appropriate glide slope. This task is tedious and requires a high degree of sustained attention. All participants were adequately trained to perform this task as part of their ATC curriculum. Performance was evaluated by a trained ATC instructor, using the on-the-job training ATC performance criterion established by NAVAIR 00-80T-114. The same instructor evaluated all PARs across and within subjects. Performance was graded on the following aspects of ATC operation: aircraft separation, control judgment, traffic management, operating methods and procedures, coordination and communication, phraseology, and equipment. Aircraft separation refers to the ability to plan and provide adequate instruction so that FAA separation standards are maintained at all times. Control judgment is the ability to maintain continuous situational awareness of all aspects of ATC operations. Traffic management is the ability to maintain an adequate flow of air traffic during periods of high workload and stress. Operating methods and procedures refer to the maintenance of all standard ATC procedural rules, including local airspace restrictions. Coordination and communication refers to the ability to coordinate and communicate with other ATC operators and pilots to ensure that the correct decisions are made and that all pertinent information is conveyed. Phraseology refers to the use of standard ATC phraseology to convey information with the operator's voice and rate of speech

facilitating accurate receipt of information. Operators were also rated on their awareness of the status of navigation equipment utilized by aircraft in their airspace and their ability to use ATC equipment. Finally, they were rated on their ability to initiate the use of backup equipment in the event of primary equipment failure. Performance ratings were assigned in accordance with NAVAIR 00-80T-114. All participants began with 100 points, and points were subtracted as procedural errors were committed.

Questionnaires

Brief Fatigue Inventory-The BFI is a self-report measure of fatigue that asks participants to rate their levels of fatigue "right now", "averaged across the past 24 hours", and "the highest level within the last 24 hours". Participants were asked to provide a rating between zero and 10 with zero indicating "no fatigue" and 10 indicating "as bad as you can imagine." Participants were then asked to describe how fatigue had impacted different aspects of their lives within the past 24 hours. Again participants were asked to provide a rating between zero and 10 with zero indicating that fatigue "does not interfere" and 10 indicating that fatigue "completely interferes" with that aspect of their lives. An example of the BFI can be found in Appendix D.

Global Rating Questionnaire-The GRQ is a self-report measure of mental workload. The GRQ asks questions about four separate aspects of mental workload including overall demand, time demand, mental demand, and stress demand. Participants were required to rate each aspect of mental demand by giving it a score between one and five with one insinuating no demand and five, extreme demand. Two examples of the GRQ can be found in Appendices E and F.

Karolinska Sleepiness Scale- The KSS measures sleepiness, using a nine point scale, based on five states, ranging from "extremely alert" to "extremely sleepy, fighting sleep." There are four intermediary states that are not designated with words. Previous research has found that the KSS is closely linked to the objective measures of encephalographic and oculographic signs of sleep onset (Akerstedt & Gillberg, 1990; Kaida et al., 2006). Scores on the KSS were used to determine the potential effect of the extended work day and/or armodafinil on alertness. A sample of the KSS can be found in Appendix G.

Symptom Profile- The Symptom Profile Sheet is a self-report measure that asks participants to indicate whether symptoms are present at specific times of the day (0800, 1000, 1200, 1400, 1500, 1700, and 1930). If symptoms were present, participants were asked to indicate whether they were mild, moderate, or major and whether they were continuous or intermittent. The Symptom Profile Sheet was composed of the most common side effects associated with armodafinil including nausea, headache, dizziness, decreased appetite, upset stomach, stuffy nose, anxiety, and dry mouth. There was also a space for participants to list any other side effects that they may have experienced. An example of the Symptom Profile Sheet can be found in Appendix C.

Analysis

Statistical analyses were performed, using SPSS version 12.0 for Windows® (SPSS Inc., Chicago, IL). A value of $p \leq 0.05$ was considered statistically significant. All outlying data points were identified within each block by treatment cell using boxplots and omitted from the subsequent PVT analyses. Of the 48 participants 47 were included in the analyses. One participant was given a 200 mg dosage of armodafinil and was omitted from the analyses. A series of mixed MANOVAs was conducted to examine the effect of armodafinil on PAR performance, PVT reciprocal mean reaction time for responses in the 90th percentile, number of lapses per block, BFI ratings, and KSS ratings. To analyze group differences across blocks for PVT reciprocal mean reaction time for responses in the 90th percentile and number of lapses, two mixed MANOVAs were conducted. Both included one between-subject factor (treatment) with two levels and one within-subject factor (block) with 12 levels. To analyze group differences across blocks for PAR performance, a mixed MANOVA was conducted with one between-subject factor (treatment) and one within-subject factor (block) with 20 levels. Also two mixed MANOVAs were conducted to examine group differences over time for self-reported sleepiness and fatigue. Both of these analyses included one between-group factor (treatment) with two levels and one within-subject factor (block) with eight levels. Finally, self-reported workload was analyzed, using a mixed MANOVA with one between-subject factor (treatment) with two levels and one between-subject factor (workload) with 8 levels.

Results

Efficacy

Analyses of PVT lapses showed a significant effect for block, F (11, 26) = 5.34, $p < .01$, $\eta_p^2 = .69$. This result suggests that significant fatigue effects were elicited by the time of day and the 4 hours of sustained performance. Analyses of PVT lapses also revealed a significant treatment by block interaction, F (11, 26) = 2.64, $p < .05$, $\eta_p^2 = .53$. A least significant differences analysis, conducted post-hoc, showed that significant group differences were present for the number of lapses experienced in block 11 of the PVT (Figure 1). These results suggest that participants assigned to the treatment condition experienced significantly fewer lapses of attention than participants assigned to the placebo condition. Table 3 depicts mean number of lapses for each group across the performance period. The analysis of reciprocal mean reaction time of responses in the 90th percentile also resulted in a significant effect for block, F (11, 29) = 15.59, $p < .01$, $\eta_p^2 = .86$. This result provides further evidence that significant fatigue effects were present. Although trends were apparent, no significant group by block interaction was detected for reciprocal mean reaction time of responses in the 90th percentile, F (11, 29) = 1.85, $p = .09$, $\eta_p^2 = .41$. Table 4 depicts the average reciprocal mean reaction time of responses in the 90th percentile for each group across blocks. PAR performance also failed to reveal a significant group by block interaction. PAR performance continued to show significant practice effects across blocks, F (3, 39) = 14.11, $p < .01$, $\eta_p^2 = .52$, thereby, negatively affecting the power and interpretability of the analysis (Figure 2). Mean PAR scores for both groups across blocks are presented in Table 5. No significant effects were detected for self-reported fatigue, sleepiness, or

workload. Average ratings for the BFI, KSS, and GRQ for both groups across blocks are reported in Tables 6, 7, and 8 respectively. Table 9 contains a summary of reported side effects among participants in the treatment and placebo conditions.

Discussion

Efficacy

The present study was designed to evaluate the effectiveness of a single dose of armodafinil (150 mg) for maintaining vigilance during an extended work day. The analysis of PVT data indicates that a single dose of armodafinil significantly reduced the number of attention lapses more than 11 hours post-dose. Although no significant treatment by block interaction was detected for PVT reciprocal mean reaction time for responses in the 90th percentile, strong trends were apparent($p = .09$, $\eta_p^2 = .41$). The reciprocal mean reaction time of responses in the 90th percentile among participants in the treatment condition were faster than reaction times (RTs) falling within the 90th percentile among the placebo group (Figure 3). Research has clearly shown that of all PVT measures, the mean number of lapses, and the mean reciprocal reaction time of responses falling within the 90th percentile are the most sensitive to sleep pressure and circadian time (Dinges et al., 1997; Jewett et al., 1999). The increased sensitivity shown by these measures is thought to be associated with the state instability hypothesis (Doran, Van Dongen, & Dinges, 2001). The state instability hypothesis posits that when people are under significant sleep pressure, their arousal levels are highly variable across brief intervals of time. Periods of low arousal result in lapses and high RTs which evoke brief periods of compensatory effort, resulting in short spurts of relatively normal performance. Theoretically, by analyzing the number of lapses and the reciprocal mean reaction time of responses in the 90th percentile, one isolates periods of low arousal from periods where participants were actively compensating for their low arousal state. Taken together, the results of the two PVT analyses indicate that periods of low arousal experienced by the treatment group were less severe, at the end of a prolonged workday, than those experienced by the placebo group (Dinges et al., 1997; Jewett et al., 1999).

Analysis of PAR data failed to show a significant treatment effect. Although a significant main effect was found for block, further examination revealed that participants performed significantly better across blocks, suggesting that this effect was associated with practice effects as opposed to fatigue effects. The analysis of BFI and KSS ratings failed to show significant main effects for block on self-reported sleepiness and fatigue. The lack of self-reported sleepiness and fatigue observed in this study implies that participants were subjectively unaware of their fatigue state despite observed negative effects on vigilance. This may be due in part to the lack of sleep restriction used in this study. Significant increases in self-report of sleepiness and fatigue may have been found across performance blocks if a more aggressive fatigue-inducing experimental design had been used. Analysis of the GRQ data showed that subjective workload did not increase in later blocks for PAR or PVT performance. Taking into consideration the apparent practice effects associated with the PAR performance data, the lack of

significant increase in self-reported workload across blocks for the PAR should not be surprising. The PVT is a low-workload task that does not vary in difficulty, making it especially sensitive to fatigue effects (Wilson, Caldwell, & Russell, 2007). The lack of variance in workload from block to block imposed by the PVT is apparent in GRQ ratings across blocks. Self-reported increases in subjective workload may have been observed across blocks through the use of more complex tasks, resistant to practice effects.

The observed effect size associated with the PVT analysis is especially large, indicating that the treatment resulted in an operationally significant abatement of fatigue on performance. This finding is particularly noteworthy considering that participants were healthy, young adults who were not subjected to extensive sleep deprivation, but tested during an extended work day, lasting into the evening hours. Also, performance assessments were not conducted during a circadian nadir, but during a period of low sleep pressure between the hours of 1600 to 2030 (Bes, Jobert, & Schultz, 2009). Despite the lack of sleep deprivation and testing during a period of low sleep pressure, armodafinil appears to have dramatically improved sustained vigilance in the treatment group 11 hours after drug administration. These results are consistent with findings from Dinges et al. (2006) who conducted studies on clinical populations and reported that armodafinil's therapeutic effects lasted almost twice the duration as the cited effects of modafinil, eliminating the need for re-dosing every 4 to 6 hours.

The most commonly reported side effect among participants in the treatment condition was mild headache. Six out of 23 participants receiving armodafinil reported this symptom at some point between dosing and being released from the study compared to three out of 24 in the control condition. Among the participants assigned to the treatment condition who reported a mild headache, one participant attributed the headache to caffeine withdrawal, one reported a mild headache at baseline, and the third reported always having a mild headache. The incidence rate of headaches appeared to peak in the treatment condition at 1600 (8 hours post-dose) and level off until time of discharge. Among participants assigned to the treatment condition, four reported dry mouth, two reported experiencing slight dizziness, one reported slight nausea, one reported a mild upset stomach, and one reported experiencing a decrease in appetite. Similar incident rates for mild headache were reported by Hirshkowitz et al. (2007) and Dinges et al. (2006). A complete summary of reported side effects is provided in Table 9.

One adjunctive aim of the current study was to determine if the lower of the two approved doses of armodafinil would be as effective in this young, healthy population as previous studies have reported for clinical populations. Studies evaluating the effectiveness of armodafinil have used doses ranging from 100-300 mg with reported effectiveness at all dose levels (Dinges et al., 2006; Harsh et al., 2006; Hirshkowitz et al., 2007). Harsh and colleagues tested 150 and 250 mg doses over a 12 week period to determine armodafinil's ability to treat excessive sleepiness in narcolepsy patients and found both doses effective for improving memory, attention, and fatigue. Similarly, Hirshkowitz et al., investigating a 150 mg dose as adjunctive treatment for excessive sleepiness, reported a significant improvement in episodic secondary memory and wakefulness and in reduced fatigue. The study by Dinges et al. (2006) compared 100, 150, 200 and 300 mg doses of armodafinil to 200 mg modafinil and placebo and

concluded that all four doses of armodafinil and the 200 mg dose of modafinil significantly improved wakefulness and reduced the number of PVT lapses of attention. A common finding among the studies was a dose dependent increase in adverse events, with the majority of complaints listed as headache, dizziness, and nausea, but at higher doses cardiovascular impacts were observed. The present study chose a low dose of armodafinil to ensure the safety of students in training, but the results of the present study, using a healthy population, agree with the current literature that a single dose of 150 mg of armodafinil is effective for promoting alertness and maintaining vigilance in a young, fatigued population. However, more work should be conducted on armodafinil in operational settings to comprehensively establish the drug's side effect profile at various dosage levels and to consider the risk-benefit ratio of lower versus higher dosing.

Study Limitations

The current study had several methodological limitations resulting from restrictions on experimental manipulation of the study population. Participant availability was limited to 12 hours; therefore, the testing time line was limited to a moderately extended work day. This restricted access to participants did not allow for a more aggressive fatigue-inducing experimental design. Ideally, greater levels of fatigue through sleep reduction would have better simulated extreme operational conditions; however, disruption of participants' normal ATC training schedule was not permitted. Additionally, testing during the circadian nadir was desired rather than the evening circadian peak, but the timing of testing was unavoidable due to the scheduling restrictions associated with this population. Lastly, the PAR task was chosen to allow simulation of ATC operations under a fatigued state. Because the study population was composed of recent ATC school graduates, the level of proficiency was overestimated, and practice effects were found across blocks. These practice effects eliminated the ability of the statistical tests to detect a treatment effect on PAR performance. A better approach would have been to use a different task or to use a population more proficient at a simulated ATC task. Despite these limitations, the efficacy demonstrated in the present study suggests the potential of larger effects, for longer periods of time.

Conclusions

The best solution for fatigue mitigation is to provide for adequate sleep and optimum scheduling of personnel. As previously described, demands during high tempo operations and a frequent shortage of qualified personnel often preclude sailors and marines from getting adequate sleep. In these situations, an effective pharmaceutical countermeasure would improve the safety of operations. The findings from the present study indicate that armodafinil may be beneficial to military ATC operators when FAA shift length regulations cannot be observed. As with any new medication, treatment regimens should be designed and monitored by a physician, and personnel should be given an opportunity to experience the effects of armodafinil before being required to use it in an operational setting.

Suggestions for Future Studies

The present study was conducted on Navy ATC students nearing the end of primary ATC training. Student schedules are extremely regimented and could not be disrupted by study procedures. Future studies should be conducted on military personnel with more flexible schedules (i.e., Navy personnel awaiting training) so that sleep restriction can be used to induce higher levels of fatigue and so that fatigue assessments can be taken at times known to be associated with lower levels of physiological arousal. Future studies must also take methodological steps to identify the optimal dosage of armodafinil specific to particular military operational environments.

Disclaimer

The study protocol was approved by the Naval Aerospace Medical Research Laboratory Review Board in compliance with all applicable Federal regulations governing the protection of human subjects.

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Copyright Statement

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Table 1. Subject Demographics

Characteristic	Placebo *n* = 24		Armodafinil 150 mg *n* = 24	
Mean Age (SE), years	21.4	(.87)	20.5	(.39)
Range	18-35		18- 25	
Sex, n (%)				
Men	18	(75)	23	(96)
Race, n (%)				
White	21	(88)	21	(88)
Black	0	(0)	1	(4)
Hispanic/Latino(a)	1	(4)	1	(4)
Asian American/Pacific Islander	0	(0)	1	(4)
Other	2	(8)	0	(0)
Mean (SE) BMI	23.7	(.66)	24.4*	.53

* BMI for the Armodafinil group (n = 23).

Table 2. Test Day Timeline

	Study Event	Assessments	
0730	Check-in	Medical Form	
0800	Dosing	SP	
1000		SP (self administered)	
1200		SP (self-administered)	
1300		SP (self administered)	
1500		SP (self administered)	
1545	P.M. Check-in		
		Order 1	Order 2
1600		PVT followed by BFI, GRQ, KSS	PAR followed by BFI, GRQ, KSS
1630		PAR followed by BFI, GRQ, KSS	PVT followed by BFI, GRQ, KSS
1700		PVT followed by BFI, GRQ, KSS, SP	PAR followed by BFI, GRQ, KSS, SP
1730		PAR followed by BFI, GRQ, KSS	PVT followed by BFI, GRQ, KSS
1800	Meal Break		
		Order 1	Order 2
1830		PVT followed by BFI, GRQ, KSS	PAR followed by BFI, GRQ, KSS
1900		PAR followed by BFI, GRQ, KSS	PVT followed by BFI, GRQ, KSS
1930		PVT followed by BFI, GRQ, KSS, SP	PAR followed by BFI, GRQ, KSS, SP
2000		PAR followed by BFI, GRQ, KSS	PVT followed by BFI, GRQ, KSS
2030	Discharge		

Note: PVT = Psychomotor Vigilance Task, BFI = Brief Fatigue Inventory, GRQ = Global Rating Questionnaire, KSS = Karolinska Sleepiness Scale, SP = Symptom Profile, and PAR = Precision Approach Radar.

Table 3. Mean PVT Lapses

	Session 1			Session 2			Session 3			Session 4		
	Block			Block			Block			Block		
	1	2	3	1	2	3	1	2	3	1	2	3
Placebo	1.00	1.00	1.10	2.20	3.00	3.95	2.45	2.55	3.95	4.95	6.30	6.55
Armodafinil, 150 mg	0.50	0.83	1.06	1.83	2.22	2.44	2.17	3.28	2.89	3.22	2.94	4.50

PVT = Psychomotor Vigilance Task

Table 4. PVT Reciprocal Mean Reaction Time for Responses in the 90th Percentile

	Session 1			Session 2			Session 3			Session 4		
	Block			Block			Block			Block		
	1	2	3	1	2	3	1	2	3	1	2	3
Placebo	2.68	2.55	2.48	2.24	2.07	2.06	2.27	2.14	2.06	1.91	1.81	1.81
Armodafinil, 150 mg	2.67	2.60	2.50	2.42	2.28	2.18	2.38	2.09	2.18	2.15	2.18	2.01

PVT = Psychomotor Vigilance Task

Table 5. Mean PAR Scores

Session		Placebo	Armodafinil, 150 mg
1	Block		
	1	71.96	75.67
	2	69.04	73.50
	3	71.74	72.29
	4	74.52	77.96
	5	79.70	80.96
2	Block		
	1	83.30	73.96
	2	87.61	85.13
	3	87.17	83.54
	4	91.35	89.33
	5	89.87	86.58
3	Block		
	1	87.17	84.13
	2	88.35	89.67
	3	91.43	87.75
	4	85.09	87.21
	5	94.57	86.17
4	Block		
	1	88.70	93.62
	2	91.39	87.71
	3	92.91	89.58
	4	93.30	91.21
	5	91.87	89.13

PAR = Precision Approach Radar

Table 6. Mean BFI Scores after the PVT and PAR

Session	Block		Question								
			1	2	3	4a	4b	4c	4d	4e	4f
1	1	Placebo	4.00	3.17	4.79	2.33	2.83	0.79	1.50	1.58	1.67
		Armodafinil, 150 mg	4.21	3.54	5.71	2.38	2.71	1.21	2.33	2.54	1.79
	2	Placebo	4.50	2.92	4.96	1.92	2.17	0.58	1.29	1.58	1.38
		Armodafinil, 150 mg	4.08	3.83	5.63	2.63	2.63	1.04	2.29	2.46	1.71
2	1	Placebo	4.04	3.29	5.38	1.67	2.13	0.50	1.67	1.46	1.54
		Armodafinil, 150 mg	4.63	3.63	5.50	2.50	2.42	1.00	2.17	2.38	1.71
	2	Placebo	4.29	3.13	4.88	1.71	2.08	0.58	1.21	1.50	1.58
		Armodafinil, 150 mg	4.21	3.54	5.38	2.46	2.38	1.08	2.33	2.54	1.50
3	1	Placebo	3.83	3.21	4.96	1.79	2.00	0.63	1.33	1.46	1.67
		Armodafinil, 150 mg	4.46	3.63	5.42	2.04	2.38	1.13	2.29	2.25	1.62
	2	Placebo	4.25	3.17	5.17	1.63	2.04	0.58	1.25	1.50	1.62
		Armodafinil, 150 mg	4.21	3.71	5.46	2.13	2.38	0.92	2.33	2.33	1.29
4	1	Placebo	4.08	3.25	5.08	1.63	1.92	0.58	1.25	1.42	1.54
		Armodafinil, 150 mg	4.29	3.83	5.46	2.21	2.33	0.96	2.13	2.33	1.42
	2	Placebo	4.29	3.21	5.17	1.63	1.88	0.54	1.33	1.50	1.50
		Armodafinil, 150 mg	4.13	3.58	5.46	2.13	2.38	1.04	2.38	2.33	1.42

Note: PVT = Psychomotor Vigilance Task, BFI = Brief Fatigue Inventory, and PAR = Precision Approach Radar.

Table 7. Mean KSS Scores after the PVT and PAR

PVT

	Session			
	1	2	3	4
Placebo	5.29	5.58	5.21	5.50
Armodafinil, 150 mg	5.13	5.21	5.29	5.13

PAR

	Session			
	1	2	3	4
Placebo	4.42	4.63	4.71	5.00
Armodafinil, 150 mg	4.13	4.13	4.58	4.63

KSS = Karolinska Sleepiness Scale, PVT = Psychomotor Vigilance Task, PAR = Precision Approach Task.

Table 8. Mean GRQ Scores after the PVT and PAR

		PVT		PAR	
Session	*Question*	Placebo	Armodafinil, 150 mg	Placebo	Armodafinil, 150 mg
1	Overall Demand	2.38	2.63	2.83	3.38
	Time Demand	2.92	3.13	2.88	3.21
	Mental Demand	2.67	2.83	3.13	3.46
	Stress Demand	1.96	1.88	2.75	3.04
2	Overall Demand	2.58	2.67	2.75	3.00
	Time Demand	2.83	2.75	2.79	2.83
	Mental Demand	2.63	2.67	2.67	3.13
	Stress Demand	2.13	1.96	2.38	2.54
3	Overall Demand	2.46	2.50	2.58	2.63
	Time Demand	2.42	2.75	2.58	2.54
	Mental Demand	2.50	2.42	2.67	2.75
	Stress Demand	1.96	1.79	2.21	2.33
4	Overall Demand	2.33	2.58	2.46	2.54
	Time Demand	2.50	2.83	2.54	2.54
	Mental Demand	2.58	2.33	2.63	2.71
	Stress Demand	2.13	1.96	2.33	2.13

GRQ = Global Rating Questionnaire, PVT = Psychomotor Vigilance Task, PAR = Precision Approach Task.

Table 9. Adverse Events after Armodafinil or Placebo.

Adverse Events	Number (%) of Participants	
	Placebo *n* = 24	Armodafinil, 150 mg *n* = 24
Nausea	1 (4)	1 (4)
Headache	3 (13)	6 (25)
Dizziness	0 (0)	2 (8)
Decreased Appetite	0 (0)	1 (4)
Upset Stomach	0 (0)	1 (4)
Stuffy Nose	2 (8)	1 (4)
Anxiety	0 (0)	0 (0)
Dry Mouth	0 (0)	4 (17)
Other	1 (4)	2 (8)

Figure 1: Number of PVT Lapses Per Block

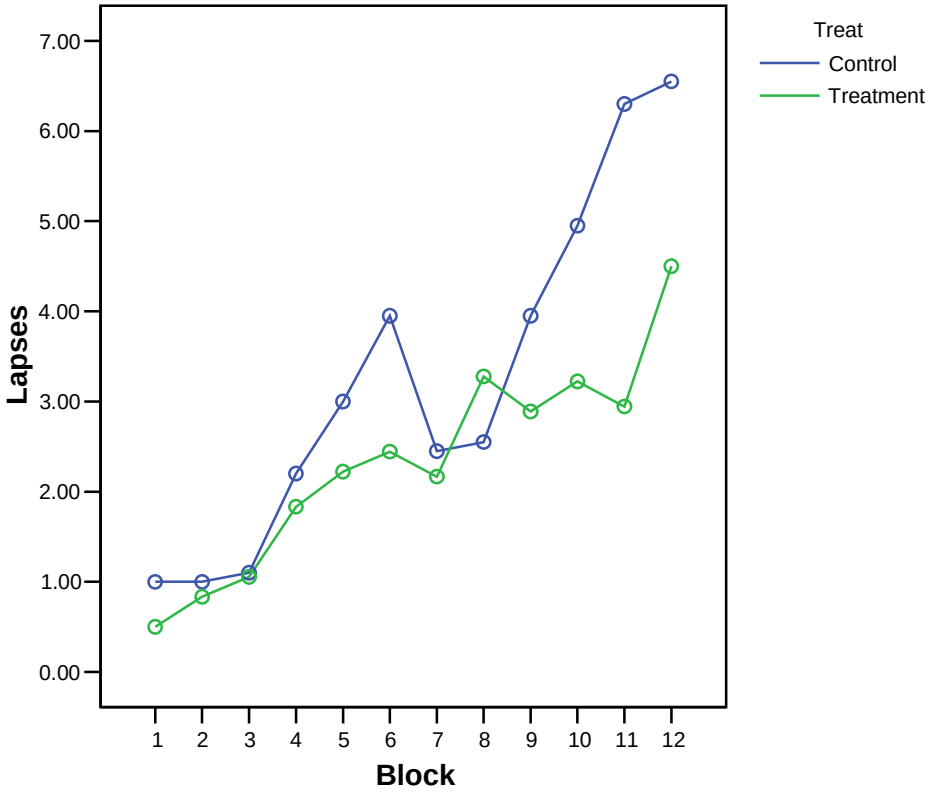


Figure 2: Average PAR Score Per Block

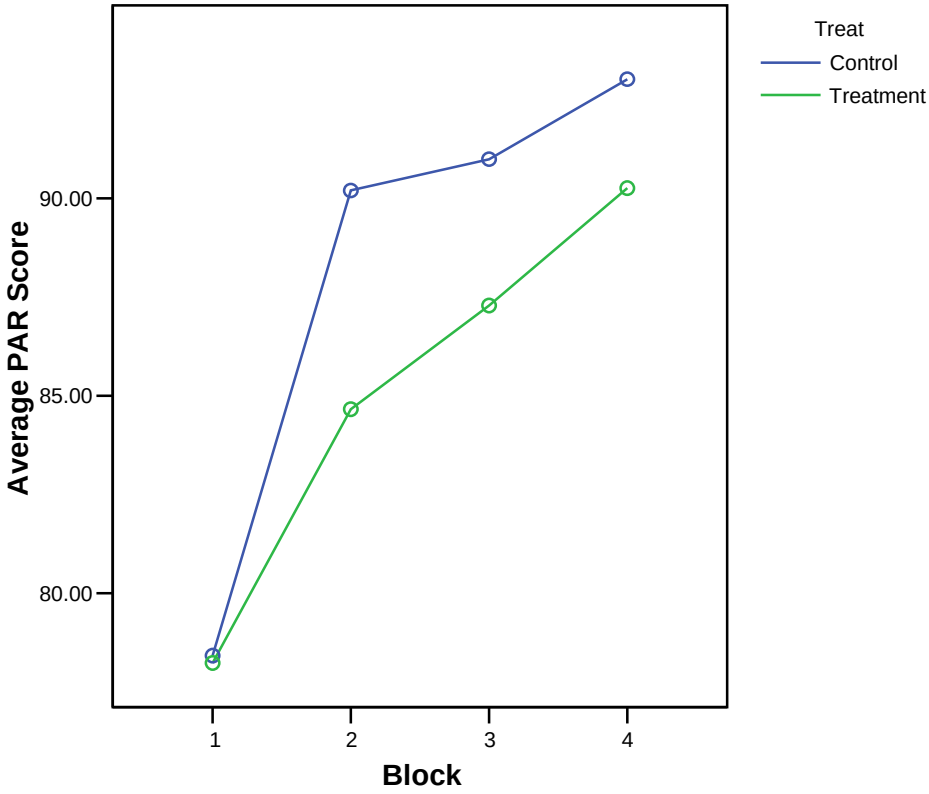
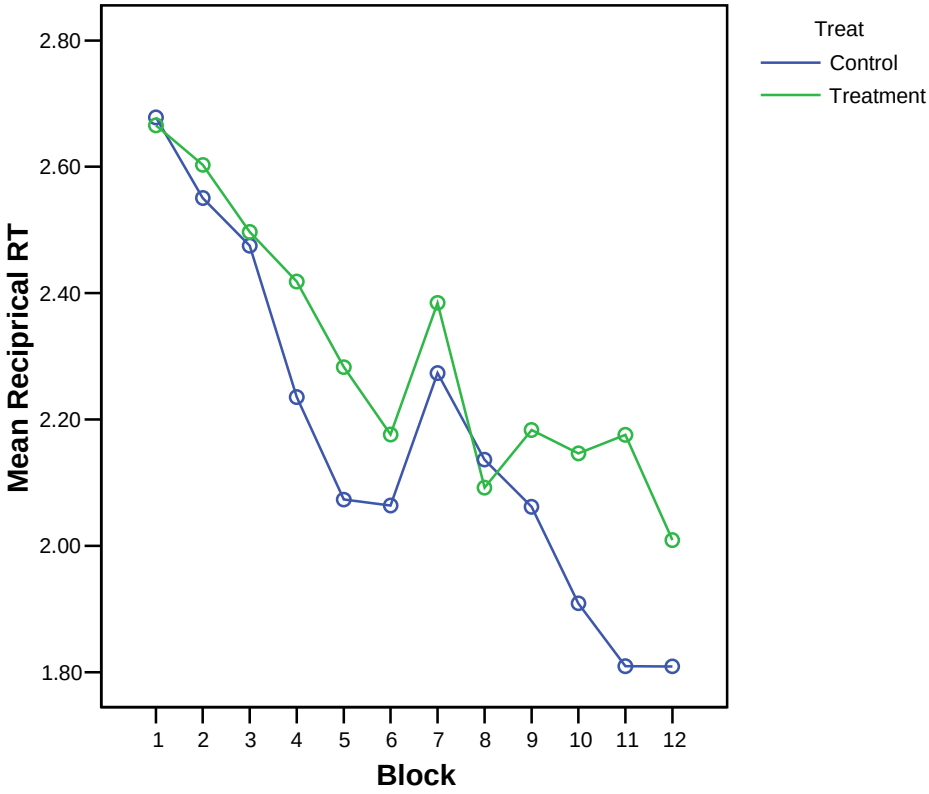


Figure 3: PVT Reciprocal Mean Reaction Time for Responses above the 90th Percentile Per Block



Appendix A. Confidential Medical Questionnaire

Screening Number:_____ Subject Number: _____ Date: _____

Sex (check one): Male ☐ Female ☐

Age: _____ Height: _____ Weight: _____

Part 1- Directions: **Circle "Yes"** if you currently suffer from or have ever been diagnosed with the condition **AND** explain below the question.

Circle "No" if they don't apply.

These questions are being asked to ensure your safety in this study.

ALL ANSWERS WILL BE KEPT CONFIDENTIAL

1.	Do you currently or have you ever been diagnosed with asthma?	Yes	No
2.	Do you have a history of or currently suffer from severe allergies?	Yes	No
3.	Have you ever been diagnosed with sleep apnea?	Yes	No
4.	Have you ever been diagnosed with a seizure disorder?	Yes	No
5.	Do you currently or have you ever suffered from liver/kidney problems?	Yes	No
6.	Do you have a history of urinary retention?	Yes	No
7.	Have you ever been diagnosed with heart/circulatory disease?	Yes	No
8.	Do you currently suffer from high blood pressure?	Yes	No
9.	Have you ever been diagnosed with glaucoma?	Yes	No

10.	Have you ever been diagnosed with emphysema?	Yes	No
11.	Have you ever been diagnosed with an enlarged prostate?	Yes	No
12.	Do you have a history of gastrointestinal disorders? (e.g. bowel distention, irritable bowel syndrome)	Yes	No
13.	Have you have been diagnosed with epilepsy?	Yes	No
14.	Have you ever suffered from pneumonia?	Yes	No
15.	Do you have a history of alcohol and drug dependency?	Yes	No
16.	Have you used any tobacco products in the last 30 days?	Yes	No
17.	Do you take any prescribed medication on a regular basis?	Yes	No
18.	Have you taken a prescribed medication within the past 7 days?	Yes	No

Females:

19.	Are you currently pregnant or lactating?	Yes	No
20.	Do you currently suffer from premenstrual syndrome (PMS)?	Yes	No

Part II- Directions: Note any medication to which you currently or have ever had an allergic reaction or sensitivity.

21. Modafinil (Provigil) Yes No
22. Armodafinil (Nuvigil) Yes No
23. Other(s) (Please list each medication.)

_____

_____

Part III- Directions: Answer the following questions to the best of your ability.

1. Are you in your usual state of fitness? (*circle one*) Yes No

a. If not, please indicate the reason _____

2. Have you been ill in the past week? (circle one) Yes No

a. If yes, please indicate the nature of the illness (e.g., flu, cold, etc.). _____

b. Rate the severity of the illness (*circle one*).

Very mild----------1----------2----------3----------4----------5----------**Very Severe**

c. Length of the illness Hours:_____ Days:_____

d. Major Symptoms: _____

e. Are you fully recovered? Yes No

3. Indicate all medication you have used in the past 72 hours.
(circle all that apply)

a. None
b. Sedatives/Tranquilizers
c. Aspirin/Tylenol/any analgesic

d. Antihistamines

e. Decongestants

f. Other (please specify)

_____

4. Do you take any over the counter medications (e.g., antacids, Benadryl, Tylenol, etc.) two (2) or more times a month? Yes No

5. Do you use tobacco products? Yes No

a. If yes, please indicate how often._____

Appendix B. **Nuvigil Confidential Exclusionary Behavior Questionnaire**

Subject Number: _____ Date: _____

Gender: *(please check one)* **Male** ☐ **Female** ☐ **Age: _____**

Ethnicity *(please check one) **Used only to determine the diversity of the subject pool***

Caucasian	African-American	Hispanic	Asian/ Pacific Islander	Other
☐	☐	☐	☐	☐

Directions: Answer the following questions to the best of your ability. Some questions relate to past experiences.

1a. How many hours did you sleep last night? _____

1b. Is this your usual sleep pattern? Yes No

1c. "The quality of my sleep last night was very good."

Strongly Disagree 1 2 3 4 5 Strongly Agree

Please circle the number that best reflects this statement.

2. Have you eaten regular meals today? Yes No

3a. Did you consume alcohol in the last 72 hours? Yes No

3b. If yes, how many alcoholic drinks did you consume? _____ (Please give number)

3c. Total number of alcoholic drinks in the past week? _____ (Please give number)

4. In the past 7 days, have you taken any prescription or over-the-counter medications? Yes No

5a. In the past 30 days, have you used any tobacco products? Yes No

5b. If yes, how much of each tobacco product have you used?

(State the number of cigarettes, cigars, “dips,” “chew,” times a pipe was smoked, or other methods of tobacco intake.)

_____
_____
(Please give number and type of product.)

_____
_____
(Please give number and type of product.)

6. In the past 7 days, have you consumed any herbal products, vitamins, or performance enhancing drinks? Yes No

_____
_____
(Please list products and amounts.)

_____
_____
(Please list products and amounts.)

7a. In the past 7 days, have you had any grapefruit juice? Yes No

7b. If yes, how much?

_____
(Number of 8 oz. cups)

8. How much caffeine have you had today?

_____
(Number of 8 oz. cups)

8a. Is this a normal amount for you? Yes No

Females

9a. Are you currently experiencing symptoms related to your monthly cycle? Yes No

9b. If yes, please list symptoms: _____
_____
(Please list symptoms)

10. Date of your last menstrual cycle: _____

Thank you for your participation!

Appendix C. Symptom Profile Sheet

Symptom Profile Sheet

Subject Number: **Date:**

Med Dose Time:

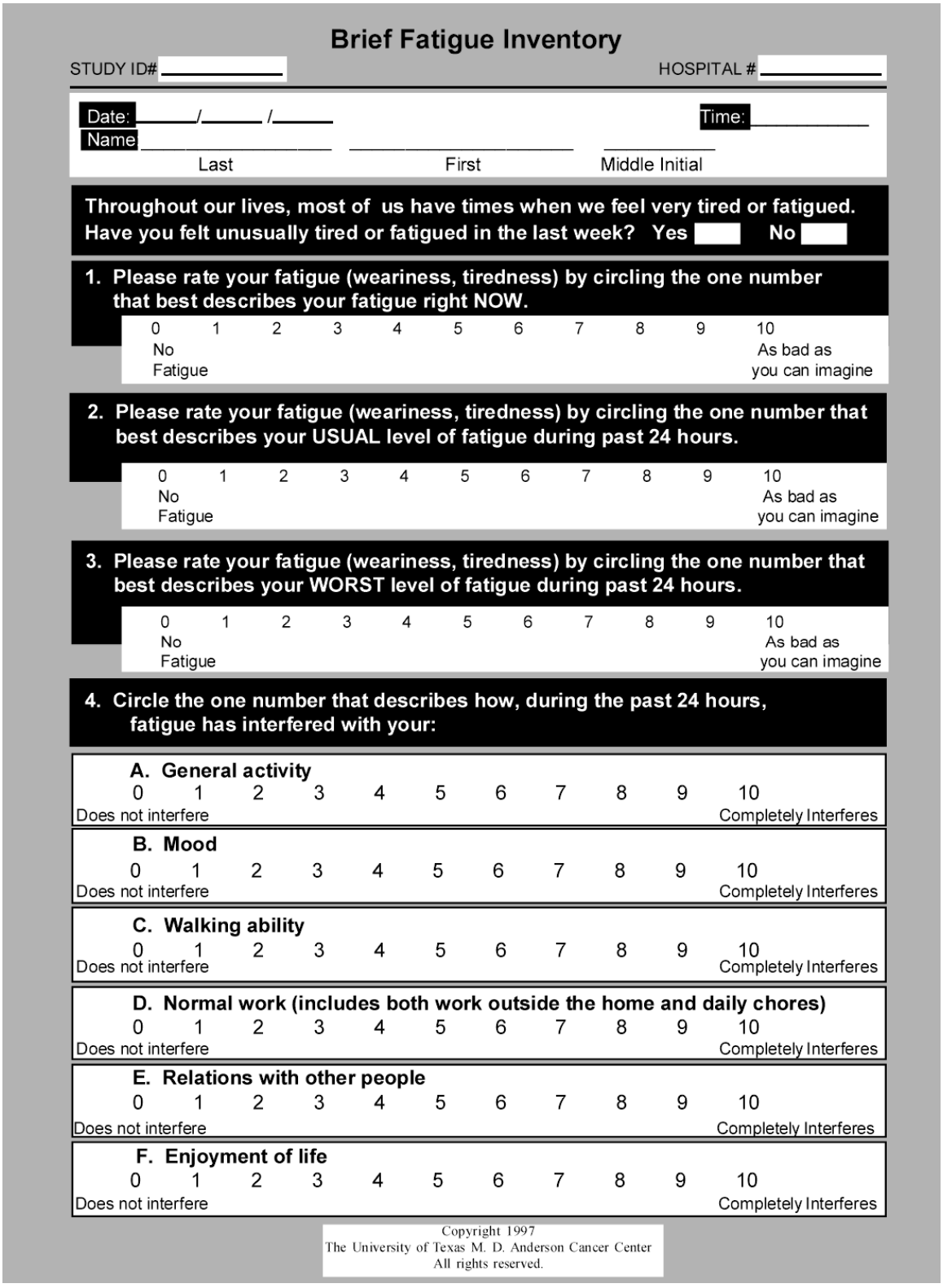
	Time	Nausea	Headache	Dizziness	Decreased Appetite	Upset Stomach	Stuffy Nose	Anxiety	Dry Mouth	Other
Baseline 0800										
1000										
1200										
1400										
1500										
1700										
1930										

Severity: 1=Mild 2=Moderate 3=Major 4=NA

C = Continuous I = Intermittent

Comments: _____

Appendix D. Brief Fatigue Inventory



Brief Fatigue Inventory

STUDY ID# _____ HOSPITAL # _____

Date: _____/_____/_____ Time: _____

Name _____ _____ _____

Last First Middle Initial

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes ☐ No ☐

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0 1 2 3 4 5 6 7 8 9 10

No Fatigue — As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Fatigue — As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Fatigue — As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General activity

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

C. Walking ability

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

D. Normal work (includes both work outside the home and daily chores)

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

F. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

Appendix E. Global Rating Questionnaire (GRQ) Psychomotor Vigilance Task (PVT)

Date: ☐☐-☐☐-☐☐

Subject Number: ☐☐☐☐

Assessment Number: ☐

We would like to characterize the task in terms of "global" demand on the person performing it. Below are the names and descriptions of several global dimensions. Please read each carefully so that you understand the nature of the dimension. Then rate the task on the extent to which it uses each dimension, using the following scale.

1	2	3	4	5
No Demand	Light Demand	Moderate Demand	Heavy Demand	Extreme Demand

1. **Overall Demand** – Required overall demand on the performer.

   Rating_____

2. **Time Demand** – Required time pressure on the performer, including pressure to perform continuously without lapse of attention.

   Rating_____

3. **Mental Demand** – Required mental and perceptual demand on the performer.

   Rating_____

4. **Stress Demand** – The anxiety, confusion, and frustration experienced by the performer.

   Rating_____

Appendix F. GLOBAL RATING QUESTIONNAIRE (GRQ) Precision Approach Radar (PAR)

Date: ☐☐-☐☐-☐☐

Subject Number: ☐☐☐☐

Assessment Number: ☐

We would like to characterize the task in terms of "global" demand on the person performing it. Below are the names and descriptions of several global dimensions. Please read each carefully so that you understand the nature of the dimension. Then rate the task on the extent to which it uses each dimension, using the following scale.

1	2	3	4	5
No Demand	Light Demand	Moderate Demand	Heavy Demand	Extreme Demand

1. **Overall Demand** – Required overall demand on the performer.

   Rating_____

2. **Time Demand** – Required time pressure on the performer, including pressure to perform continuously without lapse of attention.

   Rating_____

3. **Mental Demand** – Required mental and perceptual demand on the performer.

   Rating_____

4. **Stress Demand** – The anxiety, confusion, and frustration experienced by the performer.

   Rating_____

Appendix G. Karolinska Sleepiness Scale

Date: ☐☐-☐☐-☐☐

Subject Number: ☐☐☐☐

Assessment Number: ☐

Which statement best describes your SLEEPINESS
during the PREVIOUS FIVE (5) MINUTES?
Please check the appropriate box below.

☐ 1 Very alert

☐ 2

☐ 3 Alert, normal level

☐ 4

☐ 5 Neither alert nor sleepy

☐ 6

☐ 7 Sleepy, but no effort to keep awake

☐ 8

☐ 9 Very sleepy, great effort to keep awake

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6. AUTHORS **Jeffrey B. Phillips, Rita G. Simmons, Melissa Strompolis, and Richard D. Arnold**

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14. ABSTRACT

This study is designed to measure the efficacy of armodafinil as a fatigue countermeasure during military air traffic control (ATC) operations. ATC operations require extended periods of sustained attention without room for error. Military ATC crews accommodate shift schedules unique to demands of military operations which often exceed FAA regulations. Armodafinil, a slow-release form of modafinil, improves wakefulness and alertness without affecting normal sleep patterns making it an ideal fatigue counteragent for military ATC operations. **Methods:** Forty-eight US Navy and Marine Corps ATC students participated. Subjects were assigned to a treatment (150 mg armodafinil) or placebo condition (identical non-active pills). Double-blinding was used to prevent demand characteristics. Subjects reported at 0800 for dosing, followed by their normal work day (0800-1530). Subjects reported at 1600 for the performance portion of the study. Subjects performed 3 successive 10-minute blocks of the Psychomotor Vigilance Task (PVT) once an hour for 4 hours. Subjects completed questionnaires every thirty minutes including: a symptom profile to document adverse events, the Brief Fatigue Inventory (BFI) to measure fatigue, the Karolinska Sleepiness Scale (KSS) to assess subjective sleepiness, and the Global Rating Questionnaire (GRQ) to measure subjective cognitive workload. **Results:** Analysis of PVT data showed that participants assigned to the treatment condition experienced significantly fewer lapses of attention than participants assigned to the placebo condition $f\,(11,26) = 2.64$, $p < .05$, $\eta^2 = .53$. No significant effects were detected for the subjective measures of fatigue, sleepiness, or workload. **Conclusion:** A single dose of armodafinil (150mg) appears to significantly reduce the number of attention lapses experienced by participants eleven hours post-dose. Armodafinil should be considered for use by military ATCs when FAA shift length regulations cannot be observed due to operational demands or emergencies.

15. SUBJECT TERMS: Workload, Physiological Measurement, Self-Report Measurement

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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