
Cognitive Performance Following Modafinil versus Placebo in Sleep-deprived Emergency Physicians: A Double-blind Randomized Crossover Study

Michelle Gill, MD, Paul Haerich, PhD, Kelli Westcott, MD, Kristen L. Godenick, BA, Jennifer A. Tucker, BA

Abstract

Objectives: Modafinil has recently been approved for the treatment of shift work sleep disorder, making it potentially available for shift-working emergency physicians. The authors' objectives were to determine whether modafinil improved cognitive performance of emergency physicians following overnight shifts and to record symptoms and subjective evaluations of the effect of modafinil on the participants.

Methods: This was a randomized, double-blind, placebo-controlled crossover study that followed CONSORT guidelines. Participants were assigned to one of two study groups, with study sessions occurring at least seven weeks apart, and received either modafinil or placebo depending on their random allocation. Testing after night shifts included a coding task and an AX version of the Continuous Performance Task, both of which test cognitive function. Participants also completed visual analog scales for three subjective outcomes, and symptoms were elicited.

Results: Modafinil facilitated performance on long interstimulus-interval AX trials ($F [1, 23] = 6.65, p = 0.1$) and marginally reduced errors on AY trials in the Continuous Performance Task ($F [1, 23] = 3.59, p = 0.07$), suggesting facilitation of sustained attention, cognitive control, and working memory. Additionally, modafinil, compared with placebo, facilitated performance on the coding task at the first session. Subjective data from visual analog scales confirmed that modafinil increased perceived alertness during the simulated patient care sessions but worsened sleep onset when opportunities for sleep arose.

Conclusions: Modafinil increased certain aspects of cognitive function and subjectively improved participants' ability to attend post-night-shift didactic sessions but made it more difficult for participants to fall asleep when opportunities for sleep arose.

ACADEMIC EMERGENCY MEDICINE 2006; 13:158-165 © 2006 by the Society for Academic Emergency Medicine

Keywords: modafinil, shift work sleep disorder, fatigue, sleep deprivation

Despite improved understanding of the need for creative scheduling for emergency physicians,¹⁻³ methods to combat fatigue during night shifts are still desired. Techniques such as napping during night

shifts have been promising but are not practical,⁴⁻⁷ and results of testing of agents such as D-amphetamine, methylphenidate, pemoline, and caffeine in sleep-deprived individuals have been mixed.^{8,9} Therapies such as melatonin have been disappointing in regard to improving cognitive function during and after night shifts,¹⁰⁻¹² and studies on the effect of the addition of bright lights to the workplace have been variable.¹³

Recent media attention surrounding the Food and Drug Administration's approval of modafinil for excessive sleepiness in persons with shift work sleep disorder¹⁴ has created an awareness of its availability and potential use by afflicted medical professionals.¹⁵ This "awakening" agent is already approved by the Food and Drug Administration for the treatment of excessive sleepiness in patients with narcolepsy and obstructive sleep apnea/hypopnea syndrome¹⁶ but has not yet been systematically tested in a population at risk for shift work sleep disorder.

From the Department of Emergency Medicine, Loma Linda University School of Medicine (MG, KW), and the Department of Psychology (PH, KLG, JAT), Loma Linda University School of Science & Technology, Loma Linda, CA.

Received June 27, 2005; revision received August 12, 2005; accepted August 14, 2005.

Supported by the Loma Linda School of Medicine Seed Grant Committee and the Loma Linda University Department of Emergency Medicine Restricted Chair Fund.

Address for correspondence and reprints: Michelle Gill, MD, Loma Linda University Medical Center, 11234 Anderson Street, PO Box 2000, Room A-108, Loma Linda, CA 92354. Fax: 909-558-0121; e-mail: mgill@ahs.llumc.edu.

Emergency physicians should be aware of all potential remedies for fatigue during and following night shifts. We are inherently at risk for developing shift work sleep disorder^{17,18} and therefore may qualify for therapy with modafinil. Systematic testing of modafinil on emergency physicians should be aimed at demonstrating the efficacy and safety of this medication when used during patient care.

The primary goal of this study was to determine whether modafinil improved cognitive performances of emergency physicians following overnight shifts. Our secondary goal was to assess participants' symptoms and subjective evaluations of the effect of modafinil on them when sleep deprived.

METHODS

Study Design

This was a randomized, double-blind, placebo-controlled crossover study. We followed CONSORT guidelines¹⁹ throughout the conduct of the study. The study was approved by our hospital's institutional review board.

Study Setting and Population

The study was conducted in an academic institution that hosts an emergency medicine residency training program. The invited study participants were emergency department (ED) resident and attending physicians. Study participants were recruited by a non-ED investigator, who gave a PowerPoint presentation describing the study. This presentation introduced the prospective participants to modafinil, detailed our study hypothesis and methods, and invited attendees to consider enrolling in the study.

We opened the study to include any resident or attending emergency physician at our institution. We openly excluded those who may be at risk for adverse events when taking modafinil, including participants who were 1) pregnant or breastfeeding, 2) unable to limit caffeine intake to a daily maximum of the equivalent of three cups of coffee for 24 hours before and during session 1 and session 2 simulated night shifts, 3) known to have hypertension or kidney disorders, and/or 4) unable to complete both sessions due to scheduling or other conflicts. Due to concern for maintaining our colleagues' confidentiality, we did not inquire whether any of them were already using this medication or whether any met the above exclusion criteria if they did not request participation or respond to a second invitation to participate. All participants were required to review and sign a written consent form that included the listed exclusion criteria.

Study Protocol

Due to the need for a washout period for the outcome analysis (two cognitive tests), the study consisted of two sessions that took place at least seven weeks apart. During the study sessions, the participants were required to work a previously scheduled overnight ED shift. Participants were asked to refrain from the caffeine equivalent of more than three cups of coffee within the 24 hours preceding the night shift. Following the night shift, participants were asked to refrain from napping before attending a scheduled didactic session. Partici-

pants were asked to take the pill in the bottles marked "session #1" and "session #2" consecutively for each session, to take the pill between 6:30 AM and 7:30 AM, and to only take it after patient care activities had been completed. They then proceeded to attend didactic sessions that began at 8:00 or 8:30 AM and lasted until 10:00 AM, 11:30 AM, or 1 PM, depending on the day of the session. The participants then underwent cognitive testing immediately following didactic sessions.

Didactic Sessions. These sessions consisted of interactive didactics and workshops that are considered part of the regularly required work duty of ED residents and attending physicians at our institution. We did not control for the actual content of the sessions for the purpose of this study, and we did not directly assess the participants for their active participation in the sessions.

Randomization to Modafinil or Placebo. We followed CONSORT guidelines in regard to randomization technique.¹⁹ Each study participant was assessed for eligibility for entry into the study during the consent process. We recorded the number of participants who were interested but who could not participate, but because of the inability to be blinded to exact reasons and concerns about coercion, we were not able to list the exclusion characteristics for each potentially eligible participant who did not enroll.

Randomization was performed by a licensed pharmacist, who provided the principal investigator with sealed envelopes that could be unsealed for unblinding of the randomization in case of an adverse event. A numbered medication bottle was then delivered to each participant before each session. Neither the investigators nor the study participants were aware of which bottle contained the modafinil tablet or placebo.

Participants received the randomized bottles in chronological order. For example, the first participant in session #1 was allocated to be participant #1.

Study participants were given the bottle marked "session #1" containing either one capsule of 200 mg of modafinil (Cephalon, Inc., Frazer, PA) or one capsule of placebo at study session #1. For study session #2, they received the bottle marked "session #2," which contained the opposite pill. All pills were prepared by one of our institution's pharmacists, and the capsules in which they were contained were created such that the modafinil and placebo would look, taste, and smell identical.

We planned to record and investigate cases in which participants did not take their pills as requested. We also planned to record participants who were unable to complete both sessions (dropouts). Finally, we planned to record the number of participants who were eventually excluded from analysis.

Blinding Process. Emergency department investigators were blinded to whether participants received modafinil or placebo throughout the study and throughout the data analysis. Once the data were collected and all the participant study sessions were completed, the unblinding seal was broken by the non-ED investigator. The data were compiled and analyzed by this non-ED investigator and then forwarded to the ED investigators, who

remained blinded to the participants' randomization. The ED investigators were similarly blinded to the questionnaire results for each participant.

Outcome Measures

Primary Outcome Measures. Participants were given a visual analog scale questionnaire composed of three questions and were instructed to place a single vertical line through each 10-cm horizontal scale that we had divided and numerically scored in 1-cm intervals. The exact wording of the three items was: 1) "difficulty attending lecture after taking the pill," 2) "difficulty falling asleep after testing," and 3) "difficulty driving home." At the zero end of the scale was the phrase "not very difficult" and at the 10-cm end of the scale was the phrase "very difficult."

The questionnaire also contained a list of potential symptoms that the participants may have experienced and a line for them to list "other" symptoms. They were asked to circle any symptoms that they experienced or elaborate under "other." We requested them to complete this questionnaire within 24 hours of completing each study session. The questionnaires were then collected by a non-ED study investigator, with the ED investigators remaining blinded to each specific individual's questionnaire results.

Secondary Outcome Measures. The two cognitive tests chosen for this study were a coding task, and an AX version of the Continuous Performance Task (CPT).^{20,21} The coding task tests fluid cognitive processing and attention, simple learning, and response selection/execution. The AX-CPT tests attention, vigilance, impulsivity, and short-term memory.

The coding task is a computerized substitution task similar to the digit symbol substitution task of the Wechsler Adult Intelligence Scale. At the beginning of each 90-second trial, two rows of letters appear on the computer monitor and remain visible throughout. The first row includes the letters A–G, in order. The second row matches seven other letters, randomly, with the first row. Target stimuli from the second row appear, one at a time, in the middle of the monitor. Participants were instructed to enter the corresponding letter from the first row for each letter from the second row appearing as a target stimulus. A new target stimulus appeared as each response letter was entered. The dependent measure for this task is the number of correct coding substitutions in the 90-second trial. Each participant completed two letter–letter and one digit–letter substitution trials.

The AX-CPT requires participants to view a series of individual letters appearing in the center of the monitor display and respond as quickly as possible each time the target letter, X, appears immediate following the letter A. Each letter is presented for 250 milliseconds. Letters are presented with onset-to-onset interstimulus intervals (ISI) of one second or five seconds. Four letter–pair combinations are possible. In addition to the target AX sequence, the A may precede a non-X, the X may follow a non-A, and a non-A may precede a non-X, designated AY, BX, and BY, respectively. Failure to respond to the AX (an error of omission) is believed to reflect a lapse in

vigilance and therefore the failure to sustain attentional focus on the task. Errors of commission on BX and AY trials reflect impulsiveness. During the short-ISI blocks (one second), these errors reflect a failure to inhibit a prepotent response. During the long-ISI blocks (five seconds), these errors reflect a failure of working memory context. Each participant completed a block of 200 letters presented at a one-second ISI followed by a block of 200 letters presented at a five-second ISI. The dependent variables included the proportion of errors in each type of trial and the response latency for correct trials and errors of commission.

Data Analysis

Our sample size was based on results from prior similar studies of modafinil and other agents that have been tested for their ability to improve cognitive function in shift workers.^{22–25} One recent study that examined the cognitive performance of emergency physicians working serial night shifts contained 16 subjects.²⁶ Modafinil studies in sleep-deprived pilots^{22,24,25} have contained six to eight subjects. Because our cognitive tests did not contain traditional normative values or standard deviations, we estimated that we would require 15–20 study participants to adequately interpret the data and statistics derived from the study.

Data from the visual analog scales, the three substitution coding tasks, and the AX, AY, and BX trials of the AX-CPT task were analyzed using analyses of variance with a two (session drug) by two (session order) design to determine if modafinil was associated with improved cognitive function. Pairwise comparisons (Scheffé) were used to examine interaction effects. Systat version 11 (Systat Software, Inc., Point Richmond, CA) was used for all data analyses.

RESULTS

The trial flow diagram is seen in [Figure 1](#). Thirty-six physicians attended our recruitment conference, with 27 signing the consent form after the recruitment session. Two participants who signed the consent form did not participate in the study. The other 25 participants enrolled in and completed both study sessions. The age range of participants was 27–54 years (median, 30 years); 20 of the participants were men, and five were women. Blinding was successful and was maintained until final data analysis was initiated.

The ED shifts preceding didactic sessions ranged from six to nine hours in length. The time interval from pill consumption to testing for session #1 (range, four to six hours; median, four hours, 55 minutes) was approximately the same as that for session #2 (range, 3.5–5.5 hours; median, five hours).

Primary Outcomes

All 25 participants completed visual analog scales for each session. Although participants indicated that it was more difficult to attend the didactic sessions after taking placebo ($F [1, 22] = 13.5, p < 0.001$), they experienced more difficulty falling asleep after taking modafinil ($F [1, 22] > 4.7, p < 0.05$) ([Figure 2A](#) and [B](#)). No effect was indicated for difficulties driving home ([Figure 2C](#)). There was no significant effect of session order. These data

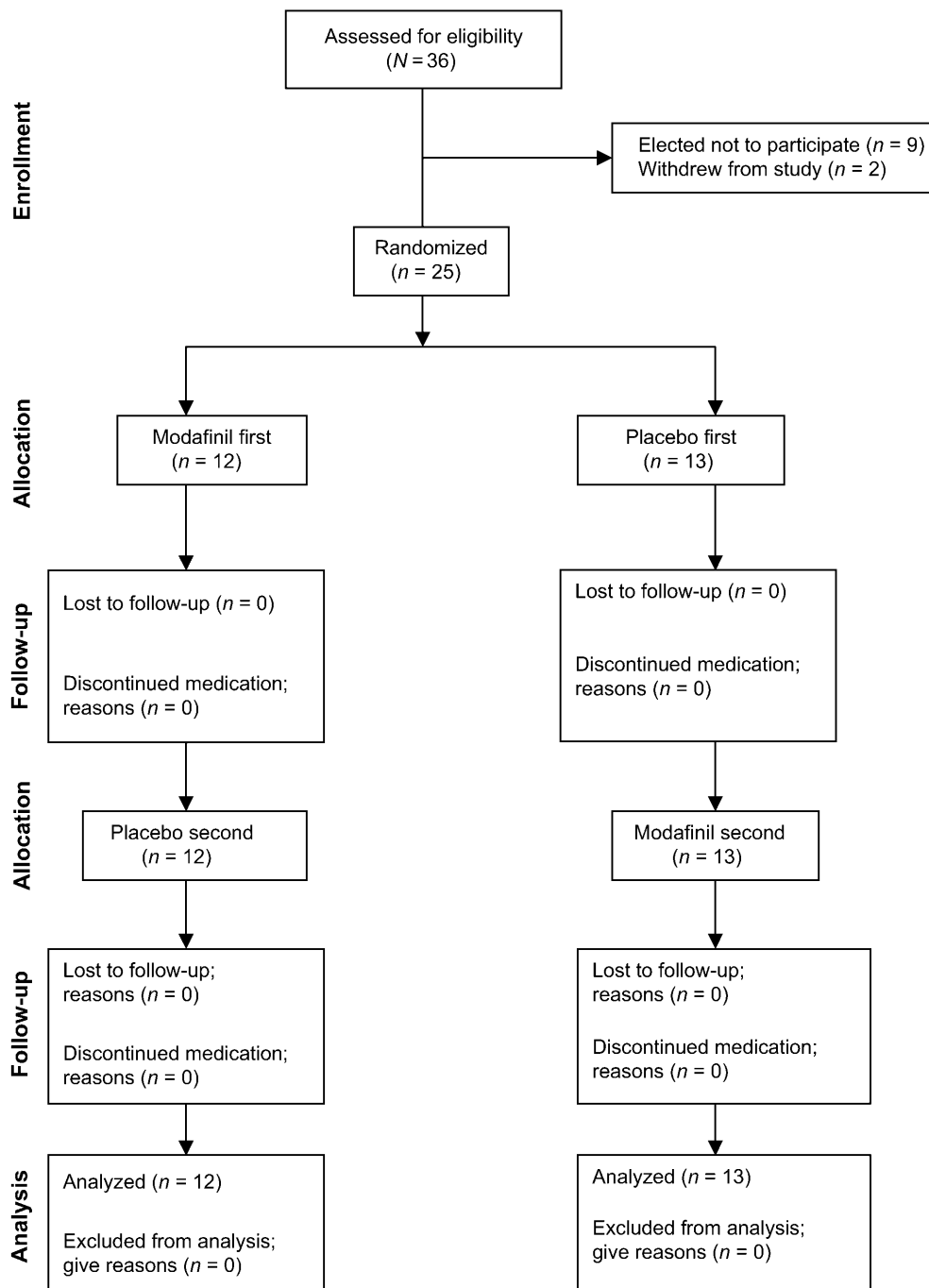


Figure 1. CONSORT flow diagram of study participants.

provide a manipulation check verifying the effect of modafinil with this sample.

Symptoms recorded by participants after taking modafinil included headache ($n = 2$), anxiety ($n = 2$), nervousness ($n = 2$), nausea ($n = 1$), euphoria ($n = 1$), abnormal vision ($n = 1$), light-headedness ($n = 1$), and diuresis ($n = 1$). The only symptom reported by participants taking placebo was diarrhea ($n = 1$).

Secondary Outcomes

Modafinil increased performance on the letter–letter substitution portion of the coding task during the first test session. However, a practice effect with performance

improving from the first to the second test session obscured any drug effect at the second test session (Figures 3 and 4). These effects were confirmed in the statistical analysis as a significant interaction between drug (modafinil, placebo) and the order of drug administration ($F [1, 22] > 29.78, p < 0.001$) and a significant difference between drug groups at the first session ($t [23] = 2.08, p < 0.05$) but not at the second session ($t [23] = 1.13, p = \text{NS}$). There was no significant effect of modafinil on the digit–letter substitution task.

Regarding the AX-CPT testing, on the standard AX trials, participants were better able to sustain attention and maintain attentional focus on the short-ISI trials as

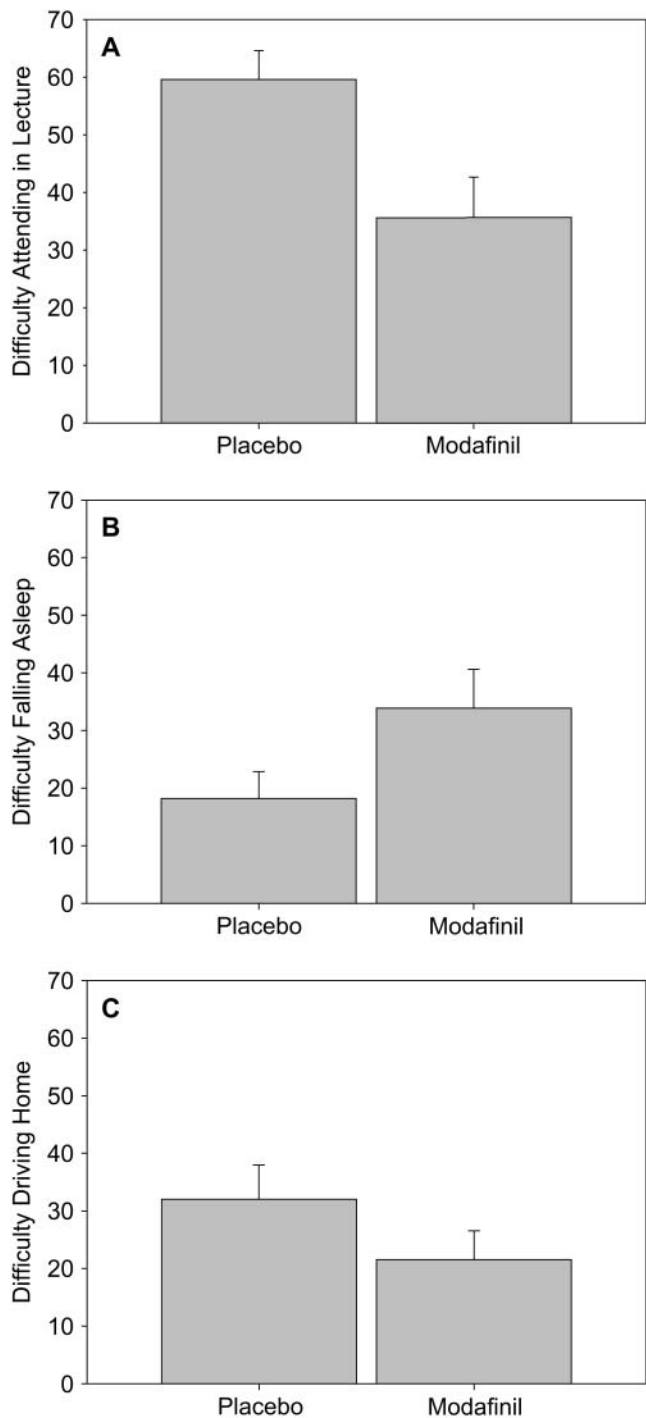


Figure 2. Responses to visual analog scales expressed as distance from lower anchor. (A) Reported difficulty paying attention during the morning lecture. (B) Reported difficulty falling asleep after study session testing. (C) Reported difficulty driving home. Error bars represent standard error.

compared with the long-ISI trials. This appeared as a significant reduction in errors of omission ($F [1, 23] = 8.79, p < 0.01$) (Figure 5A). Importantly, modafinil facilitated attention and memory for context. Errors of omission were reduced by modafinil on the long-ISI trials, independent of session order compared with placebo ($F [1, 23] = 6.65, p = 0.1$) (Figure 5A). Moreover, although all participants displayed a failure to inhibit prepotent responding

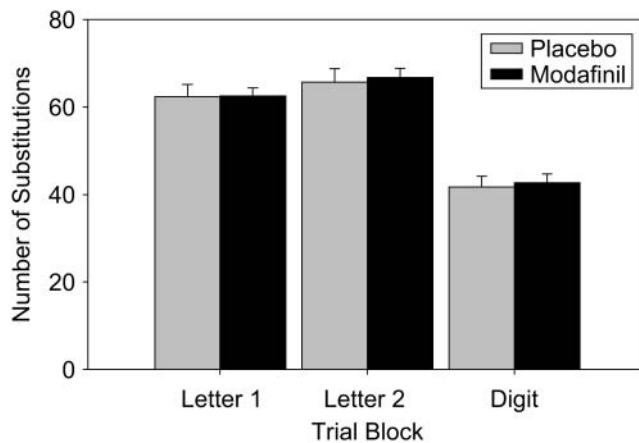


Figure 3. Number of correct substitutions in each trial block as a function of drug. Data are collapsed across session. The increase from the first letter block to the second is significant. Error bars represent standard error.

on short-ISI AY compared with AX trials ($F [1, 23] = 6.43, p < 0.02$), a trend for modafinil to facilitate response inhibition and reduce impulsiveness was observed, appearing as a marginally reliable reduction in errors of commission ($F [1, 23] = 3.59, p = 0.07$) (Figure 5B). No significant changes in errors of commission on BX trials were observed (Figure 5C).

DISCUSSION

Discomforts experienced by physicians on duty have historically been endured and accepted as part of the profession.^{27–30} However, research has recently suggested a link between physician fatigue and medical errors incurred during patient care.^{27–29,31–34} Although the exact contribution of physician fatigue and cognitive impairment to the larger issues of patient safety and medical error is not yet completely understood, what is known is that the effect of sleep deprivation on certain tasks may be equivalent to the effect of trying to perform those tasks while intoxicated with alcohol.³⁵

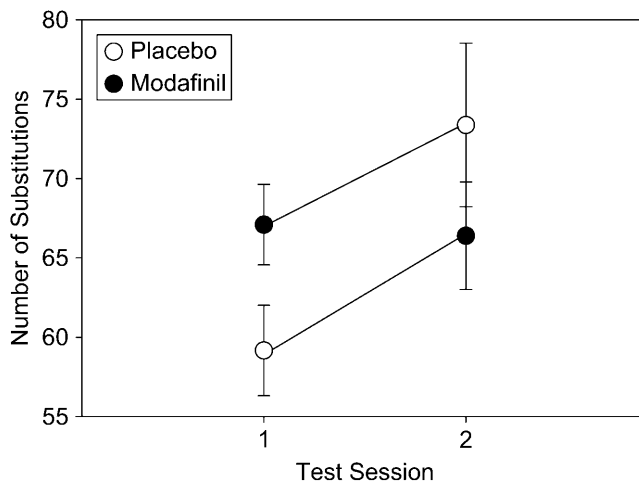


Figure 4. Number of correct substitutions as a function of drug and test session. Data are from the second block of letter–letter substitution trials only (the first block produced similar results). Error bars represent standard error.

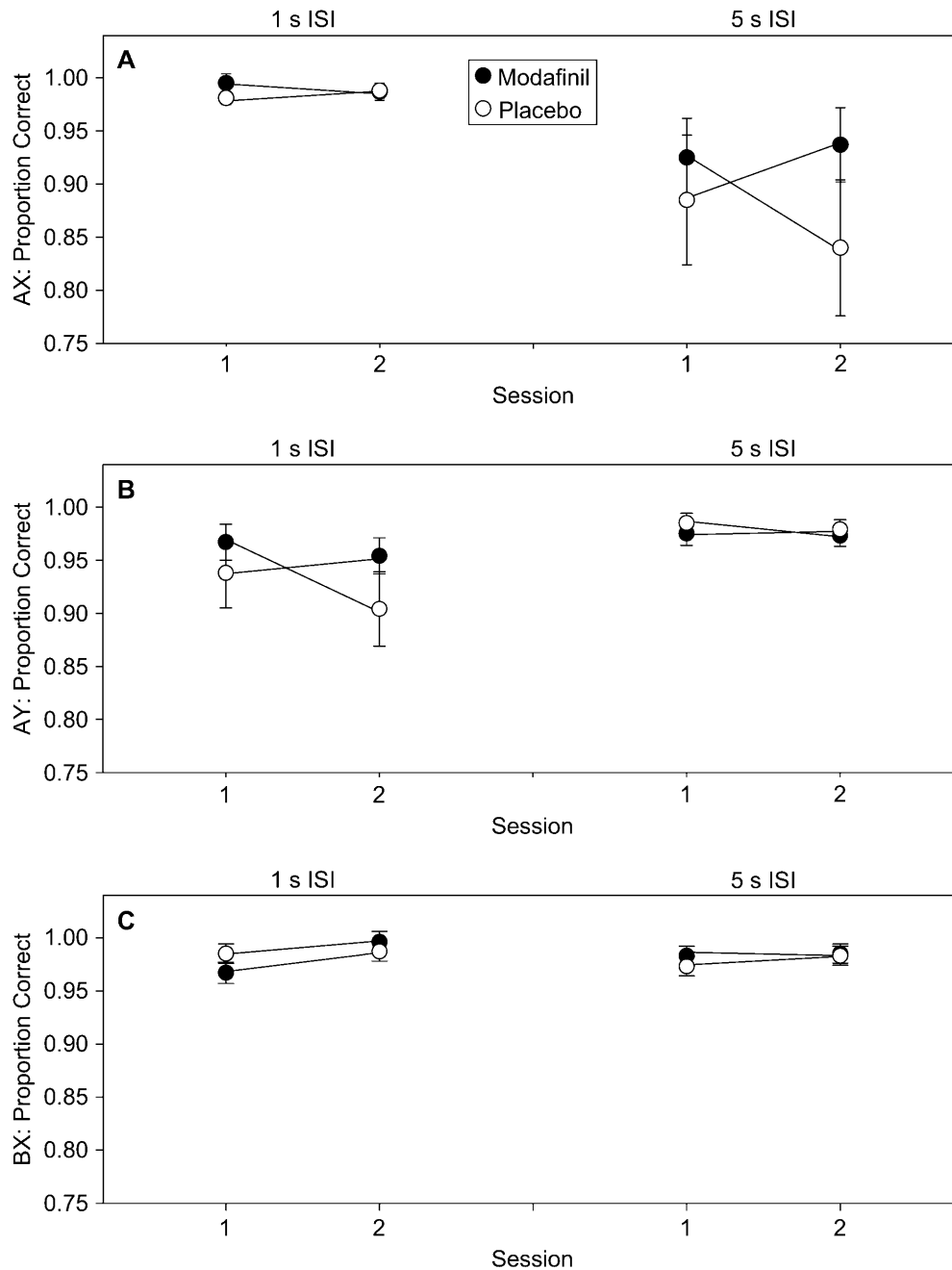


Figure 5. Proportion of correct responses in the AX Continuous Performance Task as a function of drug and session. The left column represents one-second interstimulus-interval (ISI) trials. The right column represents five-second interstimulus-interval trials. (A) Correct responses on AX trials. (B) Correct withholding of a response on AY trials. (C) Correct withholding of a response on BX trials. Error bars represent standard error.

Many attempts have been made to study methods and therapies for their ability to potentially combat fatigue⁴⁻¹³; however, none of these have met the criteria that would be required for use by health care providers tending to patients. The ideal treatment for physician fatigue and associated cognitive impairment would have to be effective, convenient, nonaddictive, and safe and would not be able to affect the ability of the physician to achieve rest when rest became available. In this study, we confirmed that modafinil may improve fluid cognitive processing, attentional focus, simple learning, and response selection/execution, reduce impulsivity, and in-

crease short-term memory, all components of cognitive function indexed by the coding and AX-CPT tasks. These findings are similar to the findings by Baranski and Pigeau, who found that modafinil improved judgment accuracy over placebo in volunteer Canadian forces,²³ and to those of Batejat and Lagarde, who showed that modafinil improved memory and tracking in French parachute detachment volunteers.²² They are in contrast to findings of Randall et al., who found no improvement in motor screening, memory, mental flexibility, and sustained attention in 30 healthy volunteers taking modafinil versus placebo.³⁶

The results of our coding tasks were less interpretable than the AX-CPT, because they were confounded by practice effects that are known to plague crossover studies of this nature.^{37,38} Because of the crossover effects, we must limit our interpretation of the results to the first test session. These data suggest that modafinil did facilitate fluid cognitive processing, attentional focus, simple learning, and response selection/execution, all of which are critical components of the cognitive skill set for physicians on duty. However, we note that presence of the crossover effects means we can draw only tentative conclusions from the results of the coding tasks in the current study.

The short-term safety and nonaddictiveness of modafinil were not studied here but have been reported previously.³⁹ To our knowledge, the long-term safety profile for modafinil has not yet been reported. In our study, we did observe a much higher number of adverse symptoms in those taking modafinil ($n = 11$) versus those taking placebo ($n = 1$). In a study by Wesensten et al. in which sleep-deprived participants were randomly assigned to receive one of five treatment regimens (modafinil 100, 200, or 400 mg; placebo; or caffeine 600 mg), participants in the caffeine group reported as many or more episodes of "heart pounding" (caffeine group, $n = 4$; modafinil 400 mg group, $n = 3$) and nausea (caffeine group, $n = 3$; modafinil 400 mg group, $n = 3$) as those in the modafinil 400 mg group. In addition, two instances of vomiting were witnessed in the caffeine group, and one instance of "extreme jitteriness and shaking" was seen in the modafinil 400 mg group.⁴⁰ Interestingly, Caldwell et al. found quite different results when they studied modafinil versus placebo in ten volunteer pilots, where there were a total of 20 side effects reported by those on placebo versus only 13 from those on modafinil.²⁵

Although participants did not report a significant difference in their ability to drive home while on modafinil versus placebo, they found that modafinil made it more difficult to fall asleep once they arrived home. In light of these findings, it appears as though the time available to physicians to sleep between work sessions may be negatively impacted by the use of modafinil during work sessions. Such a negative impact on sleep availability may render modafinil less feasible for use by resident emergency physicians who have fewer recovery hours between shifts. Contrary to this potentially negative effect of modafinil is the fact that participants were able to tolerate post-night shift didactics better on modafinil versus placebo. Whether the educational value of being able to stay awake during didactics when sleep deprived outweighs the problem of potentially worsening sleep deprivation by being unable to fall asleep afterward remains to be seen.

LIMITATIONS

Our theoretical model for this study differed from the actual study conducted in that we originally planned to have participants take modafinil or placebo during their actual overnight shift and then undergo testing following the shift. This would have more closely simulated our actual experience as emergency physicians working night shifts. However, because modafinil has not been studied

explicitly in physicians providing patient care, we chose to modify the study so that participants were only taking it during non-patient care activities. We did not follow this modification of the study plan with control for the content of the didactic sessions that were attended by our participants and did not evaluate their participation in these sessions. We also did not control for the exact time from modafinil/placebo intake to testing due to our participants' shifts ending at various hours. This limitation introduces the possibility that our participants were on various points in the peak and trough cycle of modafinil activity when tested, and this may have further introduced error into our results. Therefore, our results can only be interpreted in the context of attending didactic sessions after night shifts when attention and cognitive function may be naturally lower than when providing actual patient care.

CONCLUSIONS

Modafinil increased certain aspects of cognitive function and subjectively improved participants' ability to attend post-night shift didactic sessions but made it more difficult for participants to fall asleep when opportunities for sleep arose.

The authors thank Ralph Downey, PhD, Robin Clark, BS, William Wittlake, MD, and Desiree Wallace, PharmD, for their support and assistance with this study and thank Steven M. Green, MD, for his advice throughout the conduct of this study.

References

1. Smith-Coggins R, Rosekind MR, Buccino KR, Dinges DR, Moser RP. Rotating shiftwork schedules: can we enhance physician adaptation to night shifts? *Acad Emerg Med.* 1997; 4:951-61.
2. Zwemer FL, Schneider S. The demands of 24/7 coverage: using faculty perceptions to measure fairness of the schedule. *Acad Emerg Med.* 2004; 11:111-4.
3. Kuhn G. Circadian rhythm, shift work, and emergency medicine. *Ann Emerg Med.* 2001; 37:88-98.
4. Smith-Coggins R, Howard SK, Kwan S, et al. Do naps during the night shift improve performance in the emergency department? [abstract]. *Acad Emerg Med.* 2002; 9:466.
5. Bonnet MH. The effect of varying prophylactic naps on performance, alertness and mood throughout a 52-hour continuous operation. *Sleep.* 1991; 14:307-15.
6. Takahashi M, Arito H. Maintenance of alertness and performance by a brief nap after lunch under prior sleep deficit. *Sleep.* 2000; 23:813-9.
7. Muzet A, Nicolas A, Tassi P, Dewasmes G, Bonneau A. Implementation of napping in industry and the problem of sleep inertia. *J Sleep Res.* 1995; 4(S2):67-9.
8. Akerstedt T, Gillberg M. The circadian variation of experimentally displaced sleep. *Sleep.* 1981; 4:159-69.
9. Sicard BA, Perault MC, Enslin M, Chauffard F, Vandel B, Tachon P. The effects of 600 mg of slow release caffeine on mood and alertness. *Aviat Space Environ Med.* 1996; 67:859-62.
10. Jockovich M, Cosentino D, Cosentino L, Wears RL, Seaberg DC. Effect of exogenous melatonin on mood

- and sleep efficiency in emergency medicine residents working night shifts. *Acad Emerg Med*. 2000; 7:955–8.
11. Wright SW, Lawrence LM, Wrenn KD, Haynes ML, Welch LW, Schlack HM. Randomized clinical trial of melatonin after night-shift work: efficacy and neuropsychologic effects. *Ann Emerg Med*. 1998; 32: 334–40.
 12. Jorgensen KM, Witting MD. Does exogenous melatonin improve day sleep or night alertness in emergency physicians working night shifts? *Ann Emerg Med*. 1998; 31:699–704.
 13. Czeisler CA, Johnson MP, Duffy JF, Brown EN, Ronda JM, Kronauer RE. Exposure to bright light and darkness to treat physiologic maladaptation to night work. *N Engl J Med*. 1990; 322:1253–9.
 14. Provigil. Available at: <http://www.fda.gov/cder/consumerinfo/druginfo/provigil.htm>. Accessed Jun 24, 2005.
 15. Vastag B. Poised to challenge need for sleep, “wakefulness enhancer” rouses concerns. *JAMA*. 2004; 291: 167–70.
 16. Drug approvals for December 1998. Available at: <http://www.fda.gov/cder/da/da1298.htm>. Accessed Jun 24, 2005.
 17. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*. Washington, DC: American Psychiatric Association, 2000.
 18. Sleepiness versus sleeplessness: shift work and sleep disorders. *J Clin Psychiatry*. 2004; 65:1007–15.
 19. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet*. 2001; 357:1191–4.
 20. Cohen JD, Barch DM, Carter C, Servan-Schreiber D. Context-processing deficits in schizophrenia: converging evidence from three theoretically motivated cognitive tasks. *J Abnorm Psychol*. 1999; 108:120–33.
 21. Braver TS, Cohen JD, Barch DM. The role of prefrontal cortex in normal and disordered cognitive control: a cognitive neuroscience perspective. In: Stuss DT, Knight RT (eds). *Principles of Frontal Lobe Function*. New York, NY: Oxford University Press, 2002.
 22. Batejat DM, Lagarde DP. Naps and modafinil as countermeasures for the effects of sleep deprivation on cognitive performance. *Aviat Space Environ Med*. 1999; 70:493–8.
 23. Baranski JV, Pigeau RA. Self-monitoring cognitive performance during sleep deprivation: effects of modafinil, d-amphetamine and placebo. *J Sleep Res*. 1997; 6:84–91.
 24. Caldwell JA Jr, Caldwell JL, Smythe NK III, Hall KK. A double-blind, placebo-controlled investigation of the efficacy of modafinil for sustaining the alertness and performance of aviators: a helicopter simulator study. *Psychopharmacology (Berl)*. 2000; 150:272–82.
 25. Caldwell JA, Caldwell JL, Smith JK, Brown DL. Modafinil’s effects on simulator performance and mood in pilots during 37 h without sleep. *Aviat Space Environ Med*. 2004; 75:777–84.
 26. Dula DJ, Dula NL, Hamrick C, Wood GC. The effect of working serial night shifts on the cognitive functioning of emergency physicians. *Ann Emerg Med*. 2001; 38:152–5.
 27. Drazen JM. Awake and informed [editorial]. *N Engl J Med*. 2004; 351:1884.
 28. Gaba DM, Howard SK. Patient safety: fatigue among clinicians and the safety of patients. *N Engl J Med*. 2002; 347:1249–55.
 29. Steinbrook R. The debate over residents’ work hours. *N Engl J Med*. 2002; 347:1296–302.
 30. Barger LK, Cade BE, Ayas NT, et al. the Harvard Work Hours, Health, and Safety Group. Extended work shifts and the risk of motor vehicle crashes among interns. *N Engl J Med*. 2005; 352:125–34.
 31. Veasey S, Rosen R, Barzansky B, Rosen I, Owens J. Sleep loss and fatigue in residency training: a reappraisal. *JAMA*. 2002; 288:1116–24.
 32. Weinger MB, Ancoli-Israel S. Sleep deprivation and clinical performance. *JAMA*. 2002; 287:955–7.
 33. Lockley SW, Cronin JW, Evans EE, et al. Effect of reducing interns’ weekly work hours on sleep and attentional failures. *N Engl J Med*. 2004; 351:1829–37.
 34. Landrigan CP, Rothschild JM, Cronin JW, et al. Effect of reducing interns’ work hours on serious medical errors in intensive care units. *N Engl J Med*. 2004; 351:1838–48.
 35. Dawson D, Reid K. Fatigue, alcohol and performance impairment [letter]. *Nature*. 1997; 388:235.
 36. Randall DC, Shneerson JM, Plaha KK, File SE. Modafinil affects mood, but not cognitive function, in healthy young volunteers. *Hum Psychopharmacol*. 2003; 18: 163–73.
 37. Wears RL. The limits of techne and episteme. *Ann Emerg Med*. 2004; 43:15–6.
 38. Reed JF. Analysis of two-treatment, two-period crossover trials in emergency medicine. *Ann Emerg Med*. 2004; 43:54–8.
 39. Besset A, Chetrit M, Carlander B, Billiard M. Use of modafinil in the treatment of narcolepsy: a long term follow-up study. *Neurophysiol Clin*. 1996; 26:60–6.
 40. 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; 159:238–47.