Published in final edited form as:

J Clin Psychopharmacol. 2014 April ; 34(2): 278–281. doi:10.1097/JCP.0000000000000080.

Behavioral Effects of Modafinil and Nicotine, Alone and in Combination, in Tobacco-Deprived Young Adult Smokers

Catherine Anne Martin, MD,

Departments of Psychiatry, and Behavioral Science, University of Kentucky Medical Center, Lexington, KY, cmartin@uky.edu

Joshua Lile, PhD,

Department of Behavioral Science, University of Kentucky Medical Center, Lexington, KY

Greg Guenthner, MLIS,

Department of Psychiatry, University of Kentucky Medical Center, Lexington, KY

Joye C. Anestis, MS,

Department of Psychiatry, University of Kentucky Medical Center, Lexington, KY

Seth R. Batten, BA, and

Department of Psychiatry, University of Kentucky Medical Center, Lexington, KY

Thomas H. Kelly, PhD

Departments of Psychiatry, and Behavioral Science, University of Kentucky Medical Center, Lexington, KY

To the Editors

Withdrawal symptoms such as weight gain, loss of energy, and inattention are thought to contribute to tobacco relapse, but therapies have generally not been tailored to address these symptoms. Modafinil promotes weight loss and improves attention, and therefore might be a useful adjunct to smoking cessation treatment. Two published studies have examined modafinil as a smoking cessation aid. In a human laboratory study, Sofuoglu et al¹ coadministered 200 and 400 mg of modafinil with 2 mg nicotine lozenges to abstinent smokers (mean [SD] age, 35 [8.7] years) and observed that the combination of modafinil and nicotine increased reports of feeling energetic, whereas modafinil alone improved attention. In a clinical trial in a population of older (mean [SD], 46.5 [9.7] years) daily users (17.2 [7.2] cigarettes per day), 200 mg of modafinil was less effective than placebo in reducing self-reported smoking rates.² No previous studies have evaluated the impact of modafinil on appetite and sleepiness of smokers during nicotine abstinence or assessed the safety and tolerability of modafinil combined with transdermal nicotine, the most popular form of nicotine pharmacotherapy used in smoking cessation attempts.³ Of particular importance is the examination of modafinil effects in young adults, the age group most

likely to report smoking to lose weight.⁴ Therefore, the current study examined the tolerability and behavioral effects of modafinil in combination with transdermal nicotine after tobacco deprivation under controlled laboratory conditions among young adult smokers.

Smokers between the ages of 18 and 24 years who reported smoking 10 or more cigarettes per day were recruited and evaluated for general health. Recruitment proceeded until 9 subjects completed the protocol (7 women and 2 men). The 9 completers aged 18 to 22 years (mean [SD], 19.6 [1.07] years) reported initiating smoking at the age of 12 to 18 years (14.7 [2.0] years) and started smoking daily at the age of 16 to 18 years (17.3 [0.9] years). The study was approved by the University of Kentucky Institutional Review Board, and subjects gave written consent. A double-blind, double-dummy, placebo-controlled, partially randomized, dose escalation design was used to examine the effects of modafinil (0, 100, and 200 mg orally) and nicotine (0, 7, and 14 mg transdermal patch), alone and in combination, resulting in 8 active dose conditions (nicotine low and high, modafinil low and high, and 4 combinations). Doses below the maximum used for treatment were chosen because of safety and tolerability concerns about the use of nicotine and modafinil in combination. A training session familiarized subjects with the protocol and tasks before participation in 11 experimental sessions (3 placebo sessions randomly intermixed with the 8 active dose conditions). Placebo session data were pooled and analyzed as a single-dose condition. Subjects abstained from psychoactive drug use for the duration of the study and from alcohol and nicotine for 8 hours before sessions. Subjects were asked to apply a transdermal patch at 8:00 A.M., 8 hours before each session, and then go about their daily routine. At the start of the session, expired breath samples were tested for alcohol and carbon monoxide (CO), and urine samples were tested for evidence of recent drug use and pregnancy among women participants. Subjects were asked to refrain from eating for 4 hours before the onset of the experimental session and consumed a light, low-fat, caffeine-free meal 1 hour before modafinil administration. Verification of smoking abstinence was obtained using CO levels. Levels were required to be 50% lower than the CO levels obtained during the screening and practice visits, which was 17.6 (6.3) ppm on average.⁵ The mean (SD) CO for experimental sessions was 3.69 (1.55), consistent with the cutoff value used in other research to establish recent abstinence. The nicotine patch was removed at the end of the session.

Assessments were conducted before and 1, 2, and 3 hours after the 5:00 P.M. modafinil administration and 8 hours after transdermal patch application and included the following: the Shiffman-Jarvik Withdrawal Questionnaire,⁶ the Modified Questionnaire of Smoking Urges-Brief,⁷ a locally developed visual analog scale (VAS; energetic, sleepy, high, anxious, down, hungry, stressed, and able to concentrate), a continuous performance task,⁸ and heart rate and systolic and diastolic blood pressure. A repeated-measures analysis of covariance was conducted for each measure with modafinil (0, 100, and 200 mg), nicotine patch (0, 7, and 14 mg), and time postdose (1, 2, and 3 hours) as the factors. Baseline measures (predose values) served as covariates. Interactions were examined using simple effect models. An α level of 0.05 was used as the cutoff for statistical significance. Sphericity was controlled by using the Huynh-Feldt adjustment.

An interaction of modafinil $\times$ nicotine was observed for heart rate ($F [4, 32] = 3.19; P < 0.05$; Fig. 1). The maximum observed heart rate was 101 beats per minute, which occurred in 1 subject (1 hour after receiving the combination of 100 mg of modafinil and 14 mg of nicotine). A main effect of modafinil ($F [2, 16] = 3.73; P < 0.05$) was associated with dose-related increases in systolic blood pressure. The highest measured systolic blood pressure was 157 mm Hg (2 hours after modafinil administration on the 14 mg nicotine patch session). No effects of either drug alone or in combination were observed on diastolic blood pressure. These results are consistent with the Sofuoglu et al¹ study that found elevations in systolic blood pressure and heart rate after modafinil administration alone. A main effect of modafinil ($F [2, 16] = 8.45; P < 0.01$) on the Physical Symptoms Scale of the Shiffman-Jarvik Withdrawal Questionnaire⁶ was associated with dose-related increases in self-reported ratings of heart beating faster, fluttery feelings in the chest, and hands being shaky. These results could be related to the cardiac effects of modafinil and/or a common adverse effect, nervousness. These effects suggest that cardiovascular signs should be monitored during combined modafinil and nicotine treatment if used in smokers who are at increased cardiovascular risk (eg, older long-term tobacco users).

Consistent with previous observations that modafinil suppresses appetite and food intake (eg, Makris et al⁹), a main effect of modafinil was observed on VAS ratings of “hunger” ($F [2, 16] = 14.16; P < 0.001$; Fig. 1). Increased hunger and weight gain contribute significantly to relapse in young adult smokers,^{10–12} so the ability of modafinil to possibly address this concern may support its use as an adjunct tobacco cessation pharmacotherapy. Similarly, modafinil $\times$ time interactions were associated with decreased VAS ratings of “sleepiness” ($F [4, 32] = 2.75; P < 0.05$; Fig. 1) and increased ratings of “energy” ($F [4, 32] = 2.72; P < 0.05$). Increases in ratings of “energy” were also associated with modafinil administration in an earlier study in abstaining smokers.¹ Because sleepiness and lack of energy are common symptoms of nicotine withdrawal,^{13,14} the ability of modafinil to increase energy and reduce sleepiness suggests that it might aid in ameliorating these aspects of tobacco withdrawal. No modafinil or nicotine replacement effects were found on the continuous performance task. A main effect of nicotine ($F [2, 14] = 4.42; P < 0.05$) on the Questionnaire of Smoking Urges (factors I and II) was associated with dose-related decreases in ratings, consistent with the ability of nicotine replacement therapy to reduce tobacco craving.

Several study limitations warrant discussion. The population of young adult, nontreatment seeking, smokers was relatively early in their smoking careers and may have been less nicotine dependent than the older, established smokers. This could translate into fewer withdrawal signs and symptoms, challenging the detection of modafinil and nicotine effects. Other limitations include the use of a single behavioral measure of attention and lower doses of both modafinil and nicotine, although these lower doses did engender significant behavioral and physiologic effects. Another limitation was the small sample size of 9 subjects, although this number is consistent with initial within-subject laboratory-based safety and tolerability studies. Lastly, whether these modafinil effects translate to a reduction in tobacco use remain to be determined.

The present results suggest that combining modafinil with nicotine replacement as a smoking cessation aid could provide complimentary effects on withdrawal symptoms, although further research is needed. A potential benefit of the combined use of these drugs is that lower doses of 2 complimentary medications might result in a therapeutic effect with fewer adverse effects associated with higher doses of the constituents alone (theorized in Goeders and Guerin¹⁵). These lower doses may be particularly important in early career smokers or long-term smokers with significant health concerns. Future research could evaluate the response to repeated administration of nicotine and modafinil combinations because that would better represent their therapeutic use and would permit the assessment of possible tolerance to the therapeutic or adverse effects of these drugs that might develop during long-term use. In addition, the ability of modafinil and nicotine combinations to reduce tobacco use under controlled laboratory conditions and/or in the natural environment would provide more direct evidence of its potential pharmacotherapeutic value.

Acknowledgments

This study and preparation of the article were supported by DA05312, RR15592, and DA031766.

REFERENCES

1. Sofuoglu M, Waters AJ, Mooney M. Modafinil and nicotine interactions in abstinent smokers. *Hum Psychopharmacol*. 2008; 23:21–30. [PubMed: 17868195]
2. Schnoll RA, Wileyto EP, Pinto A, et al. A placebo-controlled trial of modafinil for nicotine dependence. *Drug Alcohol Depend*. 2008; 98:86–93. [PubMed: 18541389]
3. Burton SL, Gitchell JG, Shiffman S. Use of FDA-approved pharmacologic treatments for tobacco dependence: United States, 1984-1998. *MMWR Morb Mortal Wkly Rep*. 2000; 49:665–668. [PubMed: 10943254]
4. Wee CC, Rigotti NA, Davis RB, et al. Relationship between smoking and weight control efforts among adults in the United States. *Arch Intern Med*. 2001; 161:546–550. [PubMed: 11252113]
5. Henningfield JE, Stitzer ML, Griffiths RR. Expired air carbon monoxide accumulation and elimination as a function of number of cigarettes smoked. *Addict Behav*. 1980; 5:265–272. [PubMed: 7435315]
6. Shiffman SM, Jarvik ME. Smoking withdrawal symptoms in two weeks of abstinence. *Psychopharmacology (Berl)*. 1976; 50:35–39. [PubMed: 827760]
7. Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine Tob Res*. 2001; 3:7–16. [PubMed: 11260806]
8. Conners, CK. The Conners' Continuous Performance Test. Toronto, Canada: Multi-Health Systems, Inc; 1994.
9. Makris AP, Rush CR, Frederick RC, et al. Wake-promoting agents with different mechanisms of action: comparison of effects of modafinil and amphetamine on food intake and cardiovascular activity. *Appetite*. 2004; 42:185–195. [PubMed: 15010183]
10. Perkins KA, Sexton JE, DiMarco A, et al. Acute effects of tobacco smoking on hunger and eating in male and female smokers. *Appetite*. 1994; 22:149–158. [PubMed: 8037439]
11. Pomerleau CS, Kurth CL. Willingness of female smokers to tolerate postcessation weight gain. *J Subst Abuse*. 1996; 8:371–378. [PubMed: 8934441]
12. Westmaas JL, Langsam K. Unaided smoking cessation and predictors of failure to quit in a community sample: effects of gender. *Addict Behav*. 2005; 30:1405–1424. [PubMed: 15896921]
13. Adan A, Prat G, Sánchez-Turet M. Effects of nicotine dependence on diurnal variations of subjective activation and mood. *Addiction*. 2004; 99:1599–1607. [PubMed: 15585051]
14. Wetter DW, Fiore MC, Baker TB, et al. Tobacco withdrawal and nicotine replacement influence objective measures of sleep. *J Consult Clin Psychol*. 1995; 63:658–667. [PubMed: 7673544]

15. Goeders NE, Guerin GF. Effects of the combination of metyrapone and oxazepam on cocaine and food self-administration in rats. *Pharmacol Biochem Behav.* 2008; 91(1):181–189. [PubMed: 18692521]

Figure 1.

Modafinil and nicotine alone and in combination increased heart rate (top panels); modafinil alone decreased VAS ratings of hunger (middle panels) and sleepiness (bottom panels). Data points represent the means of 9 subjects. Error bars represent 1 SEM. The x-axis shows session time after modafinil administration in hours.