

Tobacco Withdrawal and Nicotine Replacement Influence Objective Measures of Sleep

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Research has not adequately characterized the impact of tobacco withdrawal on objectively assessed sleep parameters despite the recent inclusion of insomnia as a nicotine withdrawal sign in the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; American Psychiatric Association, 1994). Moreover, whether 24-hr nicotine replacement aids or interferes with sleep during withdrawal is unknown. In a double-masked, randomized clinical trial, 34 cigarette smokers who were motivated to quit received either active nicotine patches or placebo patches while quitting. Sleep was polysomnographically monitored for 2 precessation nights and 3 postcessation nights. The study demonstrates that among dependent smokers (a) tobacco withdrawal increases objectively assessed sleep disturbance (sleep fragmentation) and (b) nicotine replacement results in postcessation improvements in important polysomnographic measures of sleep quality (sleep fragmentation, Stage 3 and Stage 4 sleep).

The study of nicotine withdrawal is important for several reasons. First, nicotine withdrawal causes clinically significant distress similar in severity to that experienced by psychiatric outpatients (Hughes & Hatsukami, 1986), as well as cognitive and psychomotor performance decrements (see Hughes, Higgins, & Hatsukami, 1990). Second, the belief that nicotine deprivation will precipitate withdrawal discourages quit attempts (Gritz, 1980; Hall, 1984). Finally, nicotine withdrawal may cause relapse or an inability to quit smoking. Important facets of withdrawal have not been studied in depth, however. In particular, research has not adequately characterized the impact of to-

bacco withdrawal on objective measures of sleep, despite the recent inclusion of insomnia as a nicotine withdrawal sign in the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; American Psychiatric Association, 1994).

Nicotine Withdrawal and Sleep

The inclusion of insomnia in *DSM-IV* was primarily based on a consistent and reliable increase in self-reported nocturnal awakenings during withdrawal (Hatsukami, Hughes, Pickens, & Svikis, 1984; Hughes & Hatsukami, 1986; Hughes, Hatsukami, Pickens, & Svikis, 1984). Unfortunately, there is limited agreement between self-report and polysomnographic measures of sleep (Carskadon et al., 1976), and some important sleep dimensions cannot be assessed at all using self-report.

There have been only two published full reports of polysomnographically assessed sleep during nicotine withdrawal (Prosise, Bonnet, Berry, & Dickel, 1994; Soldatos, Kales, Scharf, Bixler, & Kales, 1980). Soldatos et al. (1980) found that sleep latency and total time awake decreased during withdrawal among eight male smokers. On the basis of these findings, they concluded that sleep improves during withdrawal. However, recent evidence suggests that sleep latency and total time awake are less valid indices of sleep quality than are measures such as sleep fragmentation, percentage of deep sleep (Stage 3 plus Stage 4 sleep), time awake after sleep onset, and rapid eye movement (REM) latency (Carskadon & Dement, 1989; Hudson et al., 1992; Stepanski, Lamphere, Badia, Zorick, & Roth, 1984).

More recently, Prosise et al. (1994) polysomnographically assessed the pre- and postcessation sleep of 16 smokers. Three assessments occurred during the week before quitting, and three assessments occurred during the week after quitting. Nic-

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otine withdrawal was found to increase the number of arousals, awakenings, and sleep stage changes (Prosser et al., 1994). These findings are congruent with self-report data and suggest that withdrawal increases sleep fragmentation, which is characterized by frequent arousals and often accompanied by a lower percentage of Stage 3 and Stage 4 sleep and REM sleep (Carskadon & Dement, 1989; Espinoza, Thornton, Sharp, Antic, & McEvoy, 1991).

Withdrawal-induced sleep disturbance could be important clinically because disturbed sleep might contribute to other symptoms of withdrawal such as anxiety, irritability, or inability to concentrate (Berry & Webb, 1985; Berry, Webb, Block, Bauer, & Switzer, 1986; Sink, Bliwise, & Dement, 1986). In turn, these effects might increase relapse vulnerability. For instance, sleepiness and fatigue may leave an abstinent smoker less able to cope with negative affect and stress without smoking. Some self-report evidence indicates that eventual relapsers awaken more during withdrawal than do successful abstainers (Persico, 1992).

Transdermal Nicotine Replacement Therapy and Sleep

If sleep disruption is a valid sign of nicotine withdrawal, treating such disturbance and determining how current treatments affect sleep may be important. Currently, the most widely used treatment for smoking cessation is transdermal nicotine replacement therapy (Fiore, Smith, Jorenby, & Baker, 1994). If sleep disturbance during withdrawal is the result of nicotine deprivation, then nicotine replacement (NR) by means of a transdermal patch may attenuate or reverse this disruption.

Contrary to this hypothesis, it has been suggested that 24-hr NR may increase sleep difficulties (Fagerstrom, Lunell, Molander, Forshell, & Sawe, 1990; Glover, 1993). Unfortunately, no objective (polysomnographic) studies examining the effects of NR on sleep have been published, and the majority of studies of NR either have not examined sleep or have not reported significant differences on self-reported sleep between participants receiving active and placebo patches. However, several studies do suggest that NR may be associated with sleep disturbance (Fagerstrom et al., 1990; Hurt et al., 1994; Imperial Cancer Research Fund General Practice Research Group, 1993; Mulligan, Masterson, Devane, & Kelly, 1990; Transdermal Nicotine Study Group, 1991). A large study in a general medical practice setting found that smokers in the active NR group were almost three times as likely as placebo NR participants to report sleep-related adverse events (20.4% vs. 7.5%; Imperial Cancer Research Fund General Practice Research Group, 1993). The Transdermal Nicotine Study Group (1991) found a dose-related increase in patient reports of mild-to-moderate sleep disturbance (insomnia, abnormal dreams) with use of 7-, 14-, and 21-mg patches.

In a study comparing "continuous" with "intermittent" administration of nicotine, participants with continuous administration reported more insomnia than did those receiving intermittent administration (Fagerstrom et al., 1990). However, the sample size in this study was small, sleep was assessed only by means of self-report, and the dosing regimen was unrepresentative of standard clinical practice. Specifically, the continu-

ous 24-hr administration condition may have produced peak nicotine blood levels at night rather than during the day, and these levels may have been higher than those achieved with standard patch use.

In summary, several NR studies have suggested that the patch may increase self-reported sleep disturbance, although evidence for this association is relatively weak as other studies have not found a significant difference between withdrawn smokers who received NR and those who did not. Furthermore, no studies have used polysomnographic assessment.

Study Purpose and Design

The purpose of this investigation was to characterize the effects of tobacco withdrawal and NR on sleep parameters assessed by standardized polysomnographic recording among smokers motivated to quit. To accomplish these goals, smokers were randomly assigned to one of three groups: (a) smokers who quit smoking and received placebo NR (placebo patch group); (b) smokers who quit smoking and received active NR (active patch group); and (c) smokers who continued to smoke throughout the study (repeated assessment group). We examined the repeated assessment group to rule out the possibility that repeated polysomnographic assessments might affect sleep and account for obtained results.

Method

Participants

Participants were 43 cigarette smokers who were motivated to quit smoking. They were recruited through newspaper advertisements and other media announcements. After a description of the study, informed consent was obtained and participants were evaluated for inclusion and exclusion criteria. Inclusion criteria were as follows: an age from 20 to 65 years; a smoking history of at least 20 cigarettes a day for at least 1 year; an expired air carbon monoxide (CO) level >10 parts per million (ppm); an agreement to refrain from all alcohol use, illicit drug use, and sleep medication use during the first 2 weeks of the study; an agreement to limit caffeine intake to a maximum of six cups of coffee or the equivalent per day for the first 2 weeks of the study; and, agreement to refrain from off-study nicotine use during the first 5 days after quitting.¹ Self-reported abstinence after quitting was verified by a breath CO sample of <10 ppm.

Exclusion criteria were as follows: history of myocardial infarction, angina, cardiac arrhythmias, or Buerger's disease; active substance dependence or regular use of tobacco products other than cigarettes; current psychiatric disorder or use of psychiatric medications; use of sleep medications within 14 days of study initiation; pregnancy or lactation; skin allergies or chronic dermatosis; previous use of a transdermal nicotine patch; or use of an investigational drug within 30 days of study initiation.

Procedure

Eligible participants were assigned to one of three study groups in a double-masked, randomized clinical trial. The effects of nicotine with-

¹ Biochemical assays of caffeine indicated that there were no significant changes over time within groups and no significant differences among groups.

drawal and NR on sleep were examined in two experimental groups of smokers—those who quit smoking and received placebo NR (placebo patch group, $n = 17$) and those who quit smoking and received active NR (active patch group, $n = 17$). In addition, a smaller group of smokers ($n = 9$) was included as a repeated assessment group. These participants were randomly assigned and received the same assessments as other participants but smoked ad lib throughout the study. The purpose of the repeated assessment group was to reveal whether repeated polysomnographic assessments would affect sleep measures. Because participants in the experimental groups quit smoking during the study, whereas repeated assessment participants continued to smoke throughout, masking of participants and experimenters was not possible for this group.

For the two experimental groups, a quit day was chosen and participants were scheduled for five overnight polysomnographic sleep sessions conducted at the sleep laboratory of the University of Wisconsin Specialized Center of Research in cardiopulmonary disorders of sleep. Experimental participants underwent two baseline polysomnography sessions during the week before quitting (7 and 5 days before quitting) and three sessions during the week after quitting (Days 1, 3, and 5 after quitting). Repeated assessment participants underwent five polysomnography sessions with the same temporal spacing of the sleep sessions as the experimental participants.

Polysomnographic Sleep Data

The nocturnal polysomnogram consisted of continuous polygraphic (Polygraph model 78; Grass Instruments, Quincy, MA) recording of the following: electrooculography (EOG); electroencephalography (EEG); electromyography of the submental musculature (EMG); electrocardiography (single lead; ECG); tracheal sounds (microphone); nasal airflow (thermocouples); oral airflow (end-tidal carbon dioxide gauge); thoracic and abdominal respiratory effort (inductance plethysmography; Respitrace, Ambulatory Monitoring, Ardsley, NY); and oxygen hemoglobin saturation (finger-pulse oximeter; Ohmeda 3740, Englewood, CO). All monitoring equipment allowed normal changes in position during sleep.

Three sleep domains were examined: (a) sleep fragmentation, (b) sleep staging, and (c) other general sleep measures. Sleep data were scored in 30-s epochs. Sleep fragmentation was assessed by the mean time between arousals; arousals were defined as a shift in sleep state to either Stage 1 sleep or being awake. Thus, a shift in sleep state to awake from Stage 1, 2, 3, 4, or REM sleep as well as a shift in sleep state to Stage 1 sleep from Stage 2, 3, 4, or REM sleep constituted an arousal. An increase in mean time between arousals indicates a decrease in sleep fragmentation. Sleep stages (1, 2, 3, 4, and REM) were scored using the system of Rechtschaffen and Kales (1968). Stage 3 and Stage 4 sleep were combined to yield a measure of "deep" or "slow-wave" sleep. Other general sleep measures consisted of REM latency, sleep latency, sleep duration, and time awake after sleep onset.

Only the second of the first two polysomnographic sessions was used as baseline data because previous sleep laboratory research has documented a "first night effect," with sleep tending to be more disrupted on the first night than on subsequent nights (Schmidt & Kaelbling, 1971). Similar results were obtained in this study. Thus, there were four data points for polysomnographic parameters: baseline (pre-quit), Day 1 (quit day), Day 3, and Day 5.

Self-Report Diary Data

Beginning on the morning of the first polysomnographic session (1 week before quitting for experimental participants), all participants were instructed to complete a diary twice daily at approximately 10:00 a.m. and 9:00 p.m. Both the morning and evening diaries contained

questions assessing mood, sleepiness, and urges to smoke. The morning diary also included items assessing sleep.

Diary data on self-reported sleep were assessed by seven items: (a) sleep latency, (b) number of awakenings, (c) time awake after sleep onset, (d) sleep duration, (e) sleep quality relative to sleep during the previous month (1 = *much worse than my average*, 5 = *much better than my average*), (f) sleep quality on an absolute scale (1 = *extremely poor sleep, about the worst I can imagine*, 5 = *excellent sleep, solid and completely restful*), and (g) restorative value (1 = *not at all restorative, derive no benefit from my time in bed*, 5 = *very satisfactory, feel completely refreshed and ready for the day*). In addition, sleepiness was assessed by a single item with possible responses ranging from 1 (*most alert*) to 7 (*most sleepy*). Data from our laboratory shows high levels of internal consistency for such items (coefficient alphas $> .75$).

Diary data on mood were assessed by the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1992). Urges to smoke were assessed by 11 items from the two scales of the Questionnaire of Smoking Urges (QSU; Tiffany & Drobes, 1991). The first QSU scale is characterized by anticipation of pleasure from smoking, and the second scale is characterized by anticipation of relief from negative affect and nicotine withdrawal. We labeled these scales as Positive Reinforcement Urges and Negative Reinforcement Urges, respectively. Both the POMS and the QSU scales have been shown to have good internal consistency (McNair et al., 1992; Tiffany & Drobes, 1991).

All diary data were collapsed across completion times and days to yield four data points: baseline (the fifth, fourth, and third days before quitting), Days 1 and 2 (the quit date and following day), Days 3 and 4 (the third and fourth days after quitting, and Days 5 and 6 (the fifth and sixth days after quitting). Therefore, the baseline data point comprised three consecutive days, whereas the postcessation data points included the day of a polysomnographic session and the following day.

Other Data

Before quitting smoking, participants completed several assessment instruments, including the Fagerstrom Tolerance Questionnaire (FTQ; Fagerstrom, 1978), Beck Depression Inventory (BDI; Beck, 1967), Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983), and *Symptom Checklist—90—Revised (SCL-90-R; Derogatis, 1983)*. Participants also provided a urine sample for testing cotinine levels. All participants completed additional testing and questionnaires not presented here.

Nicotine Patch and Counseling Treatment

Transdermal nicotine patch therapy consisted of 6 weeks of either active nicotine patches (22 mg absorbed dose; PROSTEP, Lederle Laboratories) or identical-appearing placebo patches containing no nicotine. Experimental participants were instructed to wear each patch for 24 hr and to apply a new patch within 1 hr after awakening each day. Participants applied their first patch on the morning of their quit day (Day 1).

Smoking cessation and relapse prevention counseling was delivered in both a group and an individual format to participants in the experimental groups to reduce smoking during the data collection period. Experimental group participants received a total of four individual counseling sessions (two pre-quit and two post-quit) and eight group counseling sessions (one pre-quit and seven post-quit). Participants in the repeated assessment group received free patches and counseling treatment after completion of all polysomnography sessions.

Data Analyses

Because of large individual differences found in response to nicotine withdrawal, researchers have recommended the use of within-

Table 1
Participant Characteristics by Group

Group	n	% male	M (and SD)		
			Age (years)	No. of cigarettes per day	Fagerstrom Tolerance Questionnaire score
Placebo patch	17	53	44.5 (9.1)	29.4 (8.6)	6.9 (1.3)
Active patch	17	47	39.1 (9.4)	31.6 (9.0)	7.3 (1.7)
Repeated assessment	9	44	41.2 (8.6)	28.3 (6.3)	7.1 (1.4)

Note. There were no significant differences among groups.

subjects statistical analyses that reflect pre- to postcessation change (Hughes et al., 1984). Thus, in the present research, we tested pre- to postcessation trends using within-subjects tests in mixed-model analyses of variance (ANOVAs). Additional within-subjects pre- to postcessation tests (paired *t* tests) were conducted when the ANOVA results were significant.

The repeated measures factor in the ANOVA consisted of four data points—baseline, Day 1, Day 3, and Day 5 for polysomnographic parameters; and baseline, Days 1 and 2, Days 3 and 4, and Days 5 and 6 for self-report measures. Linear and quadratic trends were tested and interpreted. We theorized that the only interpretable trends would be linear disturbances or improvements across sessions (e.g., a steady exacerbation or improvement of sleep because of withdrawal or increasing blood nicotine levels from the active patch; Palmer, Buckley, & Faulds, 1992) or a peaking and diminution of effect consistent with the nicotine withdrawal syndrome (i.e., a quadratic trend; Hatsukami, Dahlgren, Zimmerman, & Hughes, 1988; Hatsukami et al., 1984).

If the sphericity assumption was violated as assessed by the Mauchly test of sphericity, the Huynh-Feldt correction to the degrees of freedom was applied and test results were analyzed with the corrected degrees of freedom (Tabachnick & Fidell, 1989). Outliers were eliminated from analyses and were defined as scores that were plus or minus three standard deviations from the mean.

Results

Participants

Participant characteristics are shown in Table 1. There were no significant differences among groups on precessation measures. Two placebo patch participants reported substantial smoking during the first 6 days after quitting (i.e. during the postcessation data collection period). One of these participants smoked 10 cigarettes on the first day and none thereafter, whereas the other participant smoked 3 cigarettes on the fourth day, 7 cigarettes on the fifth day, and 26 cigarettes on the sixth day after quitting. These participants were eliminated from all further analyses. Including these participants does not appreciably change the pattern of results obtained. Both an active patch participant and a placebo patch participant smoked one cigarette on the fifth day after quitting. These participants were retained for all analyses as the amount of smoking was judged to have little impact on sleep parameters. Two active patch participants had missing data on a single postcessation polysomnographic session, one because of equipment failure and one because of illness. These participants were excluded from the re-

peated measures polysomnography analyses but were included in the self-report analyses. Thus, for the experimental groups, two participants were excluded from all analyses ($n = 32$) and four were excluded from the repeated measures polysomnography analyses ($n = 30$).

Effects of Repeated Assessment

The repeated assessment group showed no effect of repeated measurements (i.e. polysomnographic sleep data were consistent [unchanged] across the four polysomnography sessions used for data analyses—baseline, Day 1, Day 3, and Day 5). This lack of effect was not due to lack of power, as effect sizes for the repeated assessment group were minimal and substantially smaller than those found for the two experimental groups. Thus, significant effects found for the experimental groups are unlikely to be the consequence of repeated assessments per se. All further analyses focus on the two experimental groups.

Polysomnographic Sleep Analyses

Sleep fragmentation. The Group \times Linear trend interaction was significant for mean time between arousals, $t(71) = -3.08, p < .01$. There was a significant linear increase in mean time between arousals for active patch participants, $t(42) = 2.17, p < .05$, and a significant linear decrease for placebo patch participants, $t(25) = -2.24, p < .05$ (Figure 1). Within-groups analyses (paired *t* tests) revealed that by Day 5, active patch participants had less sleep fragmentation than they did at baseline, $t(15) = 2.16, p < .05$, whereas placebo patch participants had more sleep fragmentation on Day 3 than they did at baseline, $t(14) = -2.16, p < .05$.²

Sleep staging. The Group \times Linear Trend interaction was significant for Stage 2 Percent, $t(84) = 2.02, p = .05$. There was a significant linear decrease in Stage 2 Percent for active patch participants, $t(42) = -2.66, p < .05$, and no linear trend for

² Objective data on the number of awakenings indicated that mean values ranged from 21.0 to 26.0 across repeated assessments, whereas self-report data indicated that the mean number of awakenings ranged from 1.4 to 2.5. As with our data, there is a wealth of data in the sleep literature showing that self-reported awakenings dramatically underestimate objective awakenings.

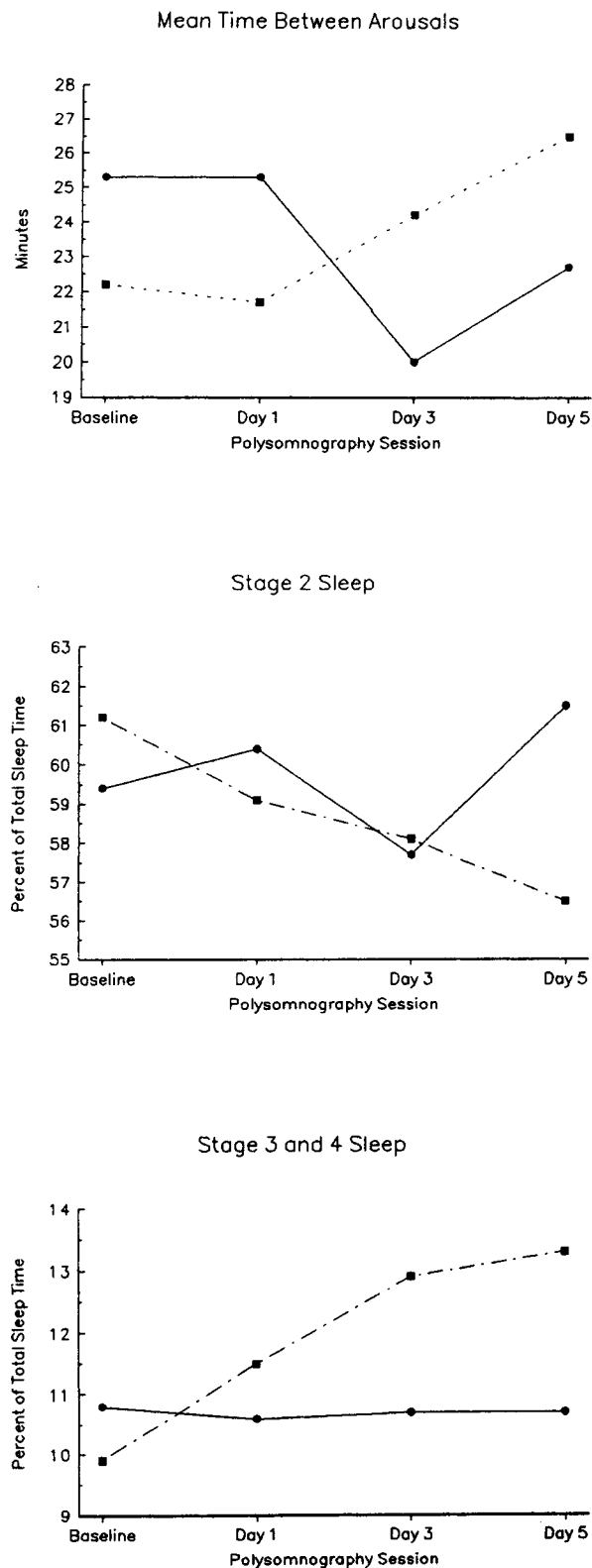


Figure 1. Polysomnographic sleep parameters for active nicotine patch participants (represented by squares) and placebo nicotine patch participants (represented by circles).

placebo patch participants, $t(42) = 0.45$, $p = .66$ (Figure 1). Within-groups analyses showed that active patch participants had less Stage 2 Percent on Day 5 than they did at baseline, $t(15) = -2.14$, $p < .05$.

The Group \times Linear Trend interaction approached significance for Stage 3 and 4 Percent, $t(70) = -1.77$, $p = .08$. The linear increase for active patch participants approached significance, $t(42) = 1.96$, $p = .06$, whereas the linear trend for placebo patch participants was nonsignificant, $t(30) = -0.38$, $p = .71$ (Figure 1). Within-groups analyses indicated that active patch participants had significantly more Stage 3 and 4 Percent on Day 3, $t(16) = 2.30$, $p < .05$, and Day 5, $t(15) = 2.15$, $p < .05$, than they did at baseline.

Other sleep analyses. There were no significant findings for sleep latency, sleep duration, time awake after sleep onset, or REM latency.

Self-Report Sleep Analyses

The distribution of three self-reported sleep variables were skewed and required data transformation to normalize the distributions. Self-reported sleep latency required a log transform, whereas self-reported awakenings and self-reported time awake after sleep onset required a square root transform. There were no significant effects for self-reported sleep duration and self-reported restorative value of sleep.

Sleep latency. There was a significant Group \times Quadratic Trend interaction for self-reported sleep latency (log), $t(90) = 2.28$, $p < .05$. Placebo patch participants displayed a significant quadratic trend, $t(35) = 2.17$, $p < .05$, whereas active patch participants did not, $t(48) = -1.48$, $p = .16$ (Figure 2). Within-groups analyses revealed no significant differences between baseline scores and any of the postcessation data points for either active or placebo patch participants.

Awakenings. As displayed in Figure 2, there was a significant linear trend, $t(90) = 4.03$, $p < .001$, and a significant quadratic trend, $t(90) = -3.42$, $p < .01$, but no interactions for self-reported awakenings (square root). For placebo patch participants, there was a significant linear increase, $t(42) = 2.74$, $p < .05$, and a significant quadratic trend, $t(42) = -2.77$, $p < .05$. There was also a significant linear increase for active patch participants, $t(40) = 3.18$, $p < .01$. Placebo patch participants reported significantly more awakenings on Day 1, $t(14) = 2.93$, $p < .05$; Day 3, $t(14) = 3.04$, $p < .01$; and Day 5, $t(14) = 3.04$, $p < .01$, than they did at baseline. Active patch participants also reported significantly more awakenings on Day 1, $t(16) = 2.85$, $p < .05$; Day 3, $t(16) = 4.13$, $p < .01$; and Day 5, $t(16) = 3.03$, $p < .01$, than they did at baseline.

Time awake after sleep onset. There was a significant linear trend, $t(87) = 2.65$, $p < .05$, and a significant quadratic trend, $t(87) = -2.62$, $p < .05$, but there were no interactions for self-reported time awake after sleep onset (square root; Figure 2). The linear, $t(48) = 2.95$, $p < .01$, and quadratic trends, $t(48) = -2.74$, $p < .05$, were significant only for active patch participants, however. Active patch participants reported spending significantly more time awake after sleep onset on Day 1, $t(16) = 3.01$, $p < .01$; Day 3, $t(16) = 3.97$, $p < .01$; and Day 5, $t(16) = 2.91$, $p < .05$, than they did at baseline.

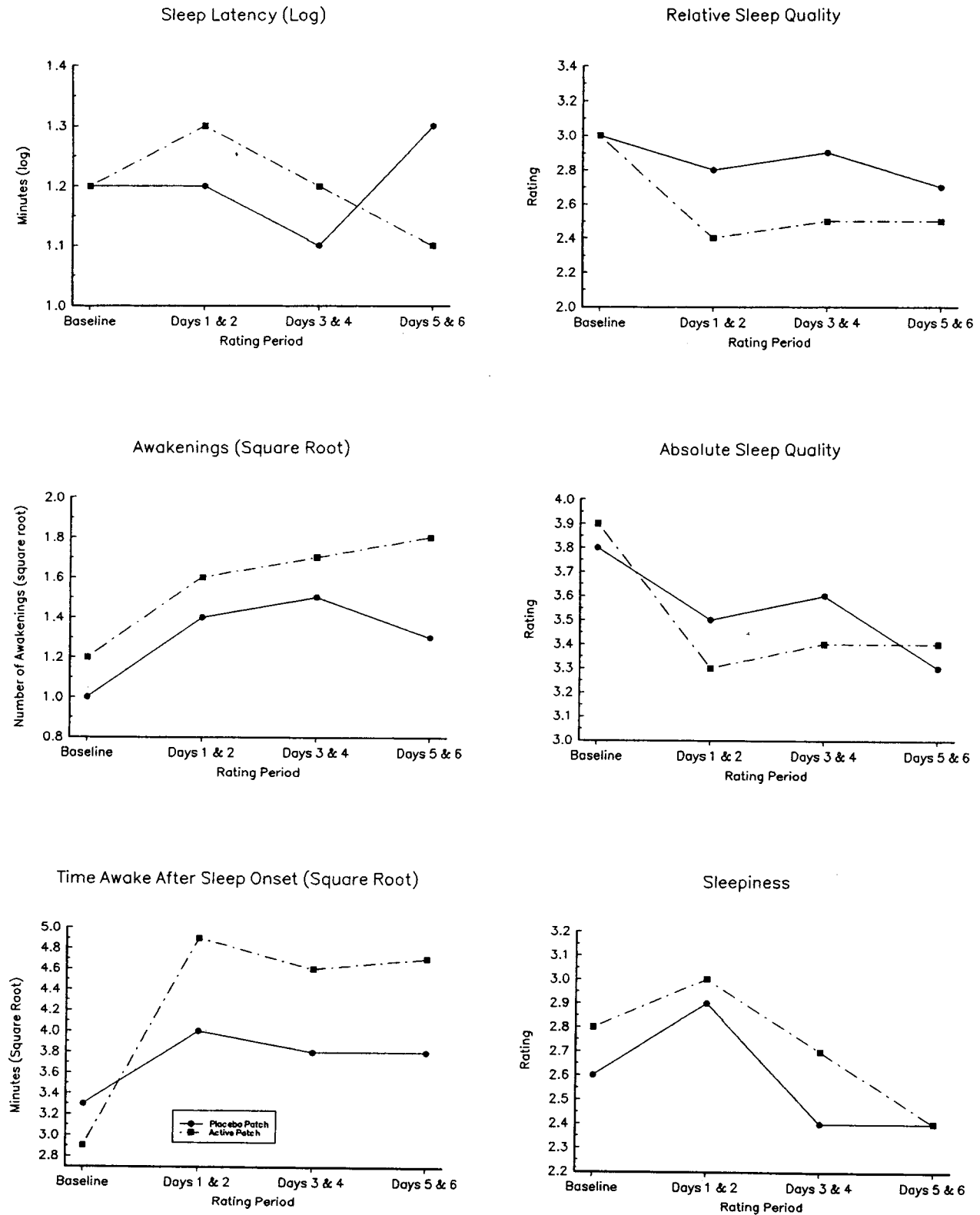


Figure 2. Self-report sleep parameters for active nicotine patch participants (represented by squares) and placebo nicotine patch participants (represented by circles).

Relative sleep quality. Although a significant linear trend was found for self-reported relative sleep quality, $t(90) = -2.23$, $p < .05$; the linear decrease was not significant for either the placebo patch group, $t(42) = -1.58$, $p = .14$, or the active patch group, $t(48) = -1.65$, $p = .12$, when examined separately.

Absolute sleep quality. The linear trend was significant for self-reported absolute sleep quality, $t(87) = -4.05$, $p < .001$ (Figure 2). Both placebo patch, $t(42) = -3.34$, $p < .01$, and active patch groups, $t(45) = -2.67$, $p < .05$, displayed significant linear decreases. Placebo patch participants reported a significant decrease in absolute sleep quality on Day 5, $t(14) = -4.25$, $p < .001$, whereas active patch participants reported significant decreases on Day 1, $t(16) = -3.48$, $p < .01$; Day 3, $t(16) = -2.51$, $p < .05$; and Day 5, $t(16) = -2.27$, $p < .05$.

Sleepiness. Finally, there was a significant linear trend for self-reported sleepiness, $t(90) = -2.77$, $p < .01$, although the linear trends were only marginally significant for both the placebo patch, $t(42) = -1.97$, $p = .07$, and active patch groups, $t(48) = -2.06$, $p = .06$, when examined separately.

Relations Among Postcessation Measures

For experimental participants, we examined the relations between the polysomnographic sleep variables that exhibited a significant effect and other postcessation variables. Significant effects were found on measures of mean time between arousals, Stage 2 percent, and Stage 3 and 4 percent. The three postcessation time points were collapsed to form a single postcessation mean score, and correlations were computed separately for active and placebo patch participants.

There was no evidence for a consistent pattern of relations between the polysomnographic sleep parameters and the self-reported sleep items, mood (Total Mood Disturbance Scale of the POMS), or urges to smoke (Positive Reinforcement Urges and Negative Reinforcement Urges). The number of significant correlations was about what would be expected by chance, and relations were weak and inconsistent across groups.

Predicting Postcessation Polysomnographic Sleep Parameters

Numerous baseline measures were used to predict postcessation polysomnographic sleep parameters among active and placebo patch participants separately. These precessation variables were age, sex, number of cigarettes per day, FTQ, urine cotinine, BDI, PSS, and the *SCL-90-R* Global Severity Index. Only 2 of the 48 possible correlations were significant. Thus, there was no evidence that postcessation sleep was related to precessation demographic, dependence, affect, stress, or psychological symptom indices.

Discussion

This study provides objective evidence that sleep disturbance is a valid component of the tobacco withdrawal syndrome. In particular, polysomnographically assessed sleep fragmentation increased among participants quitting without NR. This finding is consistent with other recent polysomnographic data indi-

cating that nicotine withdrawal increases arousals, awakenings, and sleep stage changes (Prosise et al., 1994). The results are also congruent with self-report research indicating that withdrawal increases self-reported nocturnal awakenings, that self-reported awakenings appear to peak 2 to 3 days after quitting and that frequent awakenings are more common among smokers in withdrawal in contrast to continuing smokers or to smokers undergoing a partial reduction in nicotine intake (Hatsukami et al., 1988; Hatsukami et al., 1984; Hughes & Hatsukami, 1986). The self-report data in the present study also suggest that tobacco withdrawal results in negative subjective appraisals of sleep. Withdrawing participants given no NR showed pre- to postcessation deterioration on self-report measures of sleep latency, awakenings, and absolute sleep quality. Thus, the data support the inclusion of insomnia as a nicotine withdrawal sign in *DSM-IV*. However, it is important to note that significant pre- to postcessation deterioration in objective sleep appears to be confined to measures of sleep fragmentation both in our study and in other polysomnographic research (Prosise et al., 1994).

Contrary to suggestions that nicotine withdrawal increases REM sleep (Kales, Allen, Preston, Tan, & Kales, 1970; Soldatos et al., 1980), there was no evidence that withdrawal affected REM sleep or sleep staging. Furthermore, although smoking cessation has been linked to the development of depressive symptoms (Glassman et al., 1990) and depression is often characterized by a decrease in REM latency (Reynolds, 1987), there was no evidence for a decrease in REM latency during withdrawal. These results are actually consistent with previous research; no study to date has reported a statistically significant effect of withdrawal on REM sleep or sleep staging. Although withdrawing smokers may report an increase in dreams relative to precessation levels (Hajek & Belcher, 1991), one reason for this may be an increase in sleep fragmentation rather than an increase in REM sleep, as more frequent awakenings tend to facilitate greater dream recall (Hartmann, 1989). In addition, there was no evidence that sleep latency or total time awake decreased during withdrawal as reported by Soldatos et al. (1980).

Continuous 24-hr NR appears to reduce sleep fragmentation and boost Stage 3 and Stage 4 sleep relative to both unmedicated withdrawal and precessation levels. Neither ad lib smokers nor smokers experiencing withdrawal without NR showed these improvements. The improved sleep of participants receiving NR might be attributed to alleviation of the nicotine withdrawal syndrome, a beneficial effect of continuous nicotine administration independent of withdrawal relief, or a combination of these effects. Regardless of the specific mechanisms involved, the temporal course of sleep improvement suggests that the beneficial effects are related to the rise in nicotine blood levels that occur with continuous patch usage. Pharmacokinetic studies of the nicotine patch show that steady-state blood nicotine levels are reached only after 2 to 4 days of continued patch application (Palmer et al., 1992), which parallels the temporal pattern of postcessation sleep improvement found in the present study. NR may be beneficial to sleep relative to ad lib smoking because NR produces low, constant nocturnal blood nicotine levels (approximately 7–10 ng/mL) whereas smoking typi-

cally results in a precipitous nocturnal drop (from about 30–40 ng/mL to 5 ng/mL; Benowitz, 1993; Benowitz, Kuyt, & Jacob, 1982). Moreover, features of cigarette smoking other than the pattern of nicotine delivery might disturb sleep and mask a beneficial effect of nicotine on sleep in dependent smokers. For example, the pulmonary and respiratory effects attributable to smoking (e.g., airway inflammation, wheeze, cough, phlegm production, chronic bronchitis, emphysema, asthma, chronic obstructive pulmonary disease) may lead to an increase in sleep-disordered breathing (Wetter, Young, Bidwell, Badr, & Palta, 1994) despite a potentially beneficial effect of nicotine on sleep apnea (Gothe, Strohl, Levin, & Cherniack, 1985).

This study demonstrates that objective sleep measures provide unique information on the tobacco withdrawal syndrome (i.e., information not available through self-report). For example, polysomnographic data suggested that NR benefitted sleep (reduced sleep fragmentation, increased deep sleep), whereas self-report measures indicated that active patch participants reported more awakenings, more time awake after sleep onset, and poorer absolute sleep quality after quitting than they did precessation. In other words, NR seemed to improve the objective signs of sleep disturbance but not the subjective symptoms. Moreover, there was a general pattern of weak and anomalous relations between objective and subjective measures of sleep, suggesting that these measures may tap different constructs. These findings are consistent with other sleep research (Bixler, Kales, Leo, & Slye, 1973; Carskadon et al., 1976) and underscore the fact that sleep, like other complex biobehavioral phenomena, cannot be thoroughly assessed using a single response domain (Lang, Levin, Miller, & Kozak, 1983); physiological and attitudinal-verbal assessments of sleep appear to exhibit only limited coherence. In fact, sleep fragmentation may be particularly vulnerable to inconsistencies between objective and subjective measures because periodic arousals are often imperceptible to the sleeping person although daytime functioning is impaired (Guilleminault et al., 1988; Roehrs, Zorick, Wittig, Conway, & Roth, 1989; Stepanski et al., 1984). In addition, subjective appraisals of sleep did not demonstrate reliable or straightforward relations with other theoretically relevant variables such as negative affect and urges to smoke (analyses not shown), despite shared method variance. Previous research has also found little relationship between self-reported sleep and other symptoms of withdrawal (Hughes, 1992). In summary, the results emphasize the multicomponential nature of the tobacco withdrawal syndrome and demonstrate that sole reliance on subjective measures may present a distorted picture of the nature, duration, severity, and clinical significance of the syndrome.

Several findings deserve further comment. First, epidemiologic data indicate that current smokers have more sleep problems than do former smokers (Wetter & Young, 1994; Wetter et al., 1994). Thus, although an acute effect of nicotine withdrawal is sleep disturbance, the chronic effect of quitting smoking may be an improvement in sleep quality.

Second, the clinical implications of the objective and subjective effects of NR on sleep are unclear (i.e., do NR effects on sleep mediate other clinically significant outcomes: severity of other withdrawal signs or symptoms, relapse likelihood, or

patch use compliance?). Our results suggest that sleep, whether assessed objectively or subjectively, has little impact on withdrawal severity. Furthermore, a large study ($N = 1,686$) by the Imperial Cancer Research Fund General Practice Research Group (1993) suggests that self-reports of sleep disturbance do not lead to a differential discontinuation of patch usage despite the fact that almost three times as many active as placebo patch participants reported such disturbance. Further research addressing these issues is clearly needed.

Third, previous research suggested that measures of nicotine dependence, negative affect, stress, and demographics might predict sleep disturbance during withdrawal (Ford & Kamerow, 1989; Hatsukami, Hughes, & Pickens, 1985; Healey et al., 1981; Mellinger, Balter, & Uhlenhuth, 1985; Rodin, McAvay, & Timko, 1988; Wetter, Young, Bidwell, Badr, & Palta, 1994). In addition, there was reason to believe that sleep disturbance might be related to other symptoms of withdrawal (Berry & Webb, 1985; Berry et al., 1986; Sink et al., 1986). However, these constructs were unrelated to polysomnographic sleep parameters. Thus, in the present study, there was little association between objective sleep measures and numerous theoretically relevant pre- and postcessation variables.

Study Strengths and Limitations

To the best of our knowledge, this study has the largest sample size of any study using polysomnographic ascertainment of sleep parameters during nicotine withdrawal. Similarly, this is the only study to assess objectively the effects of nicotine replacement on sleep during withdrawal. The latter is particularly important given the widespread use of NR and current concerns about the impact of 24-hr NR on sleep (Fagerstrom et al., 1990; Glover, 1993). Another strength of the study was the minimization of smoking during the first week after quitting. Postcessation smoking is a widespread problem in studies of nicotine withdrawal and subjects who smoke are typically removed from the analyses, although those very participants may suffer the most severe withdrawal. Thus, accurate assessment of withdrawal and its consequences may be prevented. In the present study, only 2 of 34 participants (6%) were lost to analyses because of postcessation smoking.

However, the study is not without limitations. First, generalizability may be compromised by the large amount of experimental contact received by the participants and the precise magnitude of withdrawal-induced sleep disturbance under more "normal" cessation conditions is unknown. Second, participants in the present study were relatively heavy smokers and the impact of quitting smoking on sleep in lighter smokers is unclear. Third, the long-term effects of sleep disturbance after smoking cessation were not addressed and the overall time course of withdrawal and NR effects on sleep is unknown. Finally, although this is the largest study of its kind, the sample size is relatively small. Thus, power was limited for some analyses and the results require independent replication.

Issues for Future Research

The present study raises several issues regarding the nature, significance, and treatment of sleep during withdrawal. For in-

stance, an issue of practical importance pertains to the motivational significance of withdrawal-induced sleep disturbance; in other words, does sleep disturbance contribute to the magnitude of withdrawal severity or relapse (or both)? The present study suggests that sleep disturbance does not influence withdrawal severity. Similarly, what are the long-term effects of nicotine withdrawal and NR on sleep? This issue was not addressed, but it may yield important insights into the relevance of withdrawal-induced sleep disturbance and NR-induced sleep improvement with respect to important clinical outcomes. Moreover, can withdrawal-induced sleep disturbance be predicted? If sleep disturbance during withdrawal has implications for smoking cessation and relapse, it will be important to identify at-risk individuals so that appropriate treatments can be initiated. Finally, are there important determinants of sleep quality that are not adequately captured by polysomnographic assessment? This a question of fundamental importance for sleep research.

In summary, the present study demonstrates that, among heavy smokers, (a) nicotine withdrawal appears to increase objectively assessed sleep disturbance (sleep fragmentation), (b) NR by means of a transdermal patch may lead to postcessation improvements in important measures of objective sleep quality (sleep fragmentation, Stage 3 and Stage 4 sleep), and (c) NR may have different effects on objective versus subjective measures of sleep. Given the refractory nature of nicotine addiction and the impact of smoking on public health, our results provide impetus for further research on both the effects of nicotine on sleep as well as on the nature, significance, and treatment of sleep disturbance during nicotine withdrawal.

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