

# Gender Differences in Response to Nicotine Replacement Therapy: Objective and Subjective Indexes of Tobacco Withdrawal

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K. A. Perkins (1996) recently proposed that nicotine reinforcement controls smoking to a greater degree among men than women and that consequently, nicotine replacement therapy (NRT) during smoking cessation should benefit men more than women. The authors tested this hypothesis. Polysomnographic measures of sleep and self-report indexes of tobacco withdrawal were collected pre- and postcessation from an active nicotine patch group and a placebo patch group in a randomized, double-blind clinical trial ( $N = 34$ ). Objective sleep parameters supported Perkins's hypothesis and indicated that among women, NRT may be less effective at suppressing certain withdrawal responses compared with men and may produce some iatrogenic effects. Valid and reliable self-report measures of withdrawal did not reveal gender differences in response to NRT.

Reviews of both self-quitter (Cohen et al., 1989) and treatment studies (Toneatto, Sobell, & Sobell, 1992) have reported no gender differences in smoking quit rates. However, data from several recent studies that used nicotine replacement therapy (NRT) suggest that women are less successful at quitting smoking than are men (Bjornson et al., 1995; Davis et al., 1994; Killen, Fortmann, Newman, & Varady, 1990; Sachs & Leischow, 1992). A recent study examined nicotine patch efficacy in smokers participating in

three multicenter clinical trials ( $N = 632$ ; Wetter et al., in press). In these trials, women were less likely than men to be abstinent at all follow-ups and across trials, sites, and treatments. However, there was little evidence that these effects were mediated or moderated by numerous variables that have been either empirically or theoretically linked to gender effects on abstinence (e.g., depression history, nicotine dependence, tobacco withdrawal, negative affect, stress, smoking outcome expectancies, coping style, health symptoms, and demographics). Unfortunately, Wetter et al.'s inability to identify the specific causes of gender differences in smoking cessation outcome is typical of research addressing this issue (see Wetter et al., in press).

Perkins (1996) recently proposed a hypothesis that could help explain why gender differences in abstinence are found in some studies and not in others. He posited that relative to men, women smoke less for nicotine reinforcement and more for nonnicotine reinforcement (e.g., sensory effects of smoking, secondary social reinforcement). That is, for women, reinforcement from smoking depends relatively less on nicotine delivery specifically and more on other contingent events and outcomes. Perkins based this hypothesis on evidence that women may be less sensitive to the interoceptive effects of nicotine, may be less affected by nicotine preloading, and may exhibit less robust self-administration of nicotine than men (see Perkins, 1996).

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## Gender and Response to NRT

An important implication of Perkins's (1996) hypothesis is that NRT may be more effective among men than among women (i.e., NRT should better substitute for smoking

among men). In theory, because smoking reinforcement is less related to nicotine for women than for men, NRT should not compensate as well for the loss of reinforcement due to smoking abstinence among women. Consistent with this, Perkins observed that differences in cessation rates between active and placebo NRT tend to be greater among men than women (see Davis et al., 1994; Killen et al., 1990; Sachs & Leischow, 1992). In our clinical trial data, active nicotine-patch therapy was somewhat more effective for men than women, but this difference was not significant (Wetter et al., in press). However, abstinence rates, particularly those obtained at temporally remote follow-up timepoints, constitute relatively gross measures of nicotine replacement effects. If there is a gender difference in NRT impact, it should be more sensitively indexed by variables that are sensitive to nicotine delivery and are measured during nicotine replacement.

Two general mechanisms are likely to account for gender differences in response to NRT, if they exist (Hughes, 1991). Withdrawal relief is one mechanism through which NRT is thought to influence abstinence (Hughes, 1993), and NRT does attenuate withdrawal severity (Jorenby et al., 1996; Leischow et al., 1997). Therefore, NRT might result in greater reduction of withdrawal severity among men than women. Alternatively, NRT might be more beneficial to men than women because the direct effects of nicotine, independent of withdrawal relief, are more positive for men.

Although most studies do not report gender differences in withdrawal suppression due to NRT, nicotine gum has been found to produce greater diminution of withdrawal and craving among men than women (Hatsukami, Skoog, Allen, & Bliss, 1995; Killen et al., 1990). In addition, Perkins and colleagues (Perkins et al., 1996) found an interaction between gender and postcessation use of nicotine nasal spray. Although men and women used equivalent amounts of placebo spray after quitting, men used significantly more active than placebo spray, whereas women did not. This finding is consistent with the notion that nicotine reinforcement may control smoking to a greater degree among men than women.

There are several reasons to conduct additional research on the relation between gender and response to NRT. First, this relation has implications for understanding basic gender-related differences in drug effects. For example, Perkins (1996) concluded that women do not display a generalized hypo- or hypersensitivity to nicotine but rather show a relatively specific reduction in the ability to discriminate the interoceptive effects of nicotine. Other psychophysiological research has indicated that women are less able than men to report physiological changes accurately (Roberts & Pennebaker, 1995). In contrast, Grunberg and colleagues (Grunberg, Winders, & Wewers, 1991) have argued that women are more biologically sensitive to the effects of nicotine than are men. Second, findings that women receive less benefit from NRT than do men could have important implications for treatment. In theory, men could receive treatments that

target nicotine-related aspects of tobacco addiction (e.g., NRT), whereas women could receive interventions that place greater emphasis on the nonnicotine-related aspects of smoking.

Finally, many studies examining gender effects have relied on a limited set of outcome measures. For instance, studies of gender differences in the clinical efficacy of NRT often rely on distal follow-up endpoints. Studies of the impact of NRT on withdrawal typically use only self-report measures. Thus, the ability to identify gender differences in response to NRT in previous studies may have been constrained by a heavy reliance on self-report assessments and measures of temporally remote events. The use of objective measures of tobacco withdrawal might more sensitively index gender differences in response to NRT.

### Sleep as an Objective Index of Tobacco Withdrawal and Response to Treatment

The National Advisory Mental Health Council (1995) recently concluded that sleep is "one of the most telling indicators of disturbed behavioral regulation" (p. 842). Furthermore, sleep disturbance is a withdrawal sign for virtually all drugs of dependence (for reviews, see Hughes, Higgins, & Bickel, 1994; West & Gossop, 1994), and insomnia is included as a nicotine withdrawal sign in the most recent edition of the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 1994). Nevertheless, the effects of drug withdrawal and treatment on objective measures of sleep have received little research attention.

Two recent studies that investigated the effects of tobacco withdrawal on objective measures of sleep found that withdrawal increased sleep fragmentation but did not affect sleep stage distribution or other general sleep measures (Prossie, Bonnet, Berry, & Dickel, 1994; Wetter, Fiore, Baker, & Young, 1995). In the only study to examine NRT effects on polysomnographic sleep parameters during withdrawal (Wetter et al., 1995), NRT appeared to improve postcessation measures of sleep fragmentation, relative to placebo. Thus, objective measures of sleep fragmentation appear to index both tobacco withdrawal and NRT effects.

Sleep fragmentation is a sensitive marker of overall sleep disruption and is characterized by frequent awakenings and arousals that are often imperceptible to the sleeping individual. The daytime consequences of sleep fragmentation include impaired cognitive function, mood disturbance, and sleepiness (Berry & Webb, 1985; Bonnet, 1985; Bonnet, 1989; Carskadon & Dement, 1994; Stepanski, Lamphere, Badia, Zorick, & Roth, 1984; Stoohs, 1996). Given that the sequelae of sleep fragmentation resemble those of nicotine withdrawal (e.g., negative affect, cognitive impairment), sleep fragmentation may function not only as an index of tobacco withdrawal and response to treatment but also as a mechanism that influences other withdrawal signs and symptoms.

## Study Purpose and Design

This study tested the hypothesis that women benefit less from NRT than do men (Perkins, 1996). More specifically, we sought to determine whether gender interacts with NRT condition (active vs. placebo) across measurement time-points in analyses of objective (sleep) and subjective (mood, urge, hunger, sleep) indexes of tobacco withdrawal. This article reports secondary analyses of relatively unique data that, to the best of our knowledge, are the only data to date that examine the effects of NRT on polysomnographic measures of sleep during withdrawal (Wetter et al., 1995). Polysomnographic and self-report measures were collected both pre- and postcessation from two groups of experimental participants: an active nicotine patch group and a placebo patch group. The two patch groups quit smoking midway through the study. On the basis of previous findings (Prosser et al., 1994; Wetter et al., 1995), we hypothesized that specific, objective indexes of tobacco withdrawal (i.e., polysomnographic assessment of sleep fragmentation) would be more sensitive to gender differences in response to NRT than would subjective self-report measures.

## Method

### Participants

Cigarette smokers ( $N = 34$ ) who were motivated and attempting to permanently quit were recruited through newspaper advertisements and other media announcements. Inclusion criteria were as follows: age 20–65 years; smoking history of at least 20 cigarettes a day for at least 1 year; expired air carbon monoxide (CO) level greater than 10 ppm; agreement to refrain from all alcohol use, illicit drug use, and sleep medication use during the first 2 weeks of the study; 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. 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; and previous use of a transdermal nicotine patch or use of an investigational drug within 30 days of study initiation.

### Procedure

Participants were randomly assigned to one of two experimental groups in a double-masked, randomized placebo-controlled clinical trial that investigated the effects of tobacco withdrawal and NRT. The two experimental groups included those participants who quit smoking and received placebo NRT (placebo patch group,  $n = 17$ ) and those who quit smoking and received active NRT (active patch group,  $n = 17$ ). Participants were told that the effects of nicotine withdrawal and the nicotine patch on objective measures of sleep were unknown and that the purpose of the study was to examine these effects.

After enrollment in the study, a quit day was scheduled and experimental participants underwent two overnight polysomnogra-

phy sessions during the week before quitting (7 and 5 days before their quit day) and three sessions during the week after quitting (Days 1, 3, and 5 after quitting). All five polysomnography sessions were conducted at the University of Wisconsin Specialized Center of Research in cardiopulmonary disorders of sleep.

### Polysomnography Data

At each sleep session, continuous polygraphic (Polygraph model 78; Grass Instruments, Quincy, MA) recordings were made of electrooculography; electroencephalography; electromyography of the submental musculature; electrocardiography (single lead); 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). The monitoring equipment permitted normal position changes during sleep. Sleep data were scored in 30-s epochs.

Sleep fragmentation, sleep stage distribution, and other general sleep measures were examined. Indexes of sleep fragmentation included awakenings per hour of sleep time and mean time between arousals. Awakenings per hour adjusted the total number of awakenings for total sleep time such that long duration awakenings or short total sleep times did not unduly distort the assessment of sleep fragmentation. Arousals were defined as a downward shift in sleep state from Stage 2, Stage 3, Stage 4, or REM sleep to either Stage 1 sleep or awake. An increase in sleep fragmentation is reflected by an increase in number of awakenings per hour and a decrease in mean time between arousals. Sleep stages (1, 2, 3, 4, and REM) were scored with standardized procedures (Rechtschaffen & Kales, 1968). Stage 3 and Stage 4 sleep were combined to yield a measure of deep sleep. Other general sleep measures were sleep latency, sleep duration, time awake after sleep onset, REM latency, and sleep efficiency. *REM latency* refers to the latency between sleep onset and the first episode of REM sleep. *Sleep efficiency* represents total sleep time expressed as a percentage of the time spent in bed with lights out.

Data from the first polysomnography session were not included in the analyses because the first night is considered an adaptation night (i.e., previous sleep laboratory research has documented that sleep tends to be more disturbed on the first night than on subsequent nights; Schmidt & Kaelbling, 1971; Thase & Kupfer, 1987). Thus, there were a total of four data points for polysomnographic sleep parameters: baseline (5 days before the quit day), Day 1 (quit day), Day 3, and Day 5.

### Self-Report and Other Data

Beginning 1 week before their quit date, all participants completed a diary twice daily at approximately 10:00 a.m. and 9:00 p.m. Both the morning and evening diaries assessed mood, urges to smoke, and hunger. The morning diary also included items assessing sleep.

The sleep self-report items included sleep latency, number of awakenings, time awake after sleep onset, sleep duration, sleep quality relative to sleep during the previous month (1 = *much worse than my average*; 5 = *much better than my average*), sleep quality on an absolute scale (1 = *extremely poor sleep, about the worst I can imagine*; 5 = *excellent sleep, solid and completely restful*), and 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*). Sleepiness was assessed by a single item (1 = *most alert*; 7 = *most sleepy*).

The diary also included the Profile of Mood States (POMS; McNair, Lorr, & Droppelman, 1992) and 11 items from the Questionnaire of Smoking Urges (QSU; Tiffany & Drobes, 1991). The POMS yields scale scores for anger, confusion, depression, fatigue, tension, vigor, and total mood disturbance. The QSU yields two scale scores: anticipation of pleasure from smoking (positive reinforcement urges) and anticipation of negative affect and withdrawal relief (negative reinforcement urges). Both the POMS and QSU have good internal consistency (McNair et al., 1992; Tiffany & Drobes, 1991). A single, well-validated item was used to assess hunger (Hughes & Hatsukami, 1986).

Diary data were collapsed across completion times and days to yield four data points that were temporally consistent with the polysomnographic 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). Consequently, each of the postcessation data points reflected the mean of the day of a polysomnographic session and the following day, whereas the baseline data point consisted of the mean of three consecutive days with the day of a polysomnographic session being the middle day.

Participants also provided breath samples for testing CO levels at each clinical contact, urine samples for testing cotinine at each polysomnography session, and completed additional testing and questionnaires.

### *Treatment*

NRT comprised either active nicotine patches (22 mg absorbed dose; PROSTEP, Lederle Laboratories) or placebo patches. Active patches delivered nicotine over a 24-hr period. Participants applied their first patch on the morning of their quit day (Day 1), applied a new patch within 1 hr of awakening each day, and wore each patch for 24 hr. In order to minimize smoking, participants received three prequit and three postquit smoking cessation counseling sessions during the data collection period (i.e., during the week before and the week after the quit date).

### *Data Analyses*

The primary hypothesis is supported when there is a three-way interaction among gender (between-subjects factor), patch status (between-subjects factor), and the pre- to postcessation trend in withdrawal across measurement timepoints (repeated measures factor). In other words, the hypothesis is supported when, across measurement timepoints, men benefit more from NRT relative to placebo than do women. Therefore, our analyses focused on the three-way interaction of Gender  $\times$  Group (patch status)  $\times$  Pre- To Postcessation Trend (repeated measures factor).

The repeated measures factor 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. The repeated measures effect was modeled by using two terms—linear and quadratic. Only linear and quadratic trends were tested and interpreted because we hypothesized that only these patterns of disturbances or improvements across sessions would be consistent with withdrawal and patch effects. For example, linear effects might represent a steady exacerbation or improvement in the outcome variable over time because of withdrawal or because of increasing blood nicotine levels from the active patch (Palmer, Buckley, & Faulds, 1992), whereas a peaking

and diminution effect would be consistent with the classic pattern found for most symptoms of tobacco withdrawal (i.e., a quadratic trend; Hatsukami, Dahlgren, Zimmerman, & Hughes, 1988; Hatsukami, Hughes, Pickens, & Sviki, 1984).

Generalized estimating equations (GEE) were used for all analyses. GEE is a multivariate generalization of quasi-likelihood for dependent data (Liang & Zeger, 1986). GEE was used because repeated measures from the same individual are expected to be correlated. In GEE, the standard errors of the regression coefficients are adjusted for the observed within-subject correlations. Failure to account for these correlations may lead to inflated Type I error rates. The adjusted standard error estimates were used to construct robust  $z$  statistics for testing whether the regression coefficients were significantly different from zero.

As noted above, the repeated measures factor was modeled by using two terms (linear and quadratic). Thus, for each outcome variable, a model was constructed that included terms for the main effects (gender, group [active or placebo patch], linear trend, quadratic trend), two-way interactions (Gender  $\times$  Group, Gender  $\times$  Linear Trend, Gender  $\times$  Quadratic Trend, Group  $\times$  Linear Trend, and Group  $\times$  Quadratic Trend), and three-way interactions (Gender  $\times$  Group  $\times$  Linear Trend, Gender  $\times$  Group  $\times$  Quadratic Trend). The two three-way interaction terms, representing the hypothesis of interest, were evaluated as a set in order to maintain alpha at .05 (i.e., both terms were tested simultaneously using a Wald statistic with alpha equal to .05). Under the null hypothesis of no interaction effect, this statistic has an asymptotic chi-square distribution, with two degrees of freedom. This analysis strategy is relatively conservative because it consists of a single test of the set of three-way interaction terms rather than separate tests of the linear and quadratic components, which could inflate the Type I error rate. The separate linear and quadratic components of the three-way interaction and differences between genders were evaluated only if the set was significant.

The distributions of a number of outcome variables were improved by log transformations prior to analyses. However, all figures depict raw data because the results of the analyses were similar when using log transformed or raw data and because of the greater ease of interpretability of the raw data.

## *Results*

### *Participants*

Table 1 displays participant characteristics by gender ( $N = 34$ ). There were no significant differences between men and women. Three placebo patch participants and 1 active patch participant smoked during the postcessation data collection period (i.e., between their quit day and the 6th day after quitting). Two participants smoked a single cigarette, 1 smoked 10 cigarettes on the quit day and none thereafter, and 1 smoked three cigarettes on the 4th day, seven cigarettes on the 5th day, and 26 cigarettes on the 6th day of quitting. Because exclusion of nonabstinent participants can bias the study sample as well as differentially bias the experimental groups when there are differential abstinence rates across groups, these participants were included in the analyses (i.e., the analyses were based on intention-to-treat). However, the results were unaffected by the inclusion or exclusion of these participants. All other participants were abstinent during the postcessation data collection period. Abstinence was defined as a self-report of no smoking since

Table 1  
*Participant Characteristics by Gender*

Characteristic	Women ( <i>n</i> = 17)	Men ( <i>n</i> = 17)
Active nicotine patch group, <i>n</i> (%)	9 (53)	8 (47)
Age (years)		
<i>M</i>	41.0	42.7
<i>SD</i>	11.6	7.4
No. of cigarettes per day		
<i>M</i>	30.0	31.0
<i>SD</i>	8.9	8.9
Fagerstrom Tolerance Questionnaire score		
<i>M</i>	7.1	7.1
<i>SD</i>	1.2	1.8
No. of previous quit attempts		
<i>M</i>	2.6	3.0
<i>SD</i>	2.3	2.4
Carbon monoxide level (ppm)		
<i>M</i>	26.2	27.8
<i>SD</i>	9.3	8.6

*Note.* There were no significant differences between men and women.

the quit day and a breath CO sample of < 10 ppm at each postcessation clinical contact (the 1st, 3rd, and 5th days of quitting). Data were missing for a single postcessation polysomnography session for 2 active patch participants, 1 because of illness and 1 because of equipment failure.

### *Polysomnography Analyses*

#### *Sleep Fragmentation*

The set of three-way interaction terms was not significant for mean time between arousals.

The Gender  $\times$  Group  $\times$  Repeated Measures interaction set was significant for awakenings per hour,  $\chi^2$  (2, *N* = 34) = 7.4, *p* < .05. The Gender  $\times$  Group  $\times$  Linear Trend interaction was also significant (*z* = -2.2, *p* < .05).

Among men, there was a significant Group  $\times$  Linear Trend interaction on awakenings per hour (*z* = -3.2, *p* < .001; see Figure 1) that reflected a significant linear reduction in awakenings per hour for the active patch group, (*z* = -3.7, *p* < .001). The linear trend for the placebo patch group was opposite in direction to that of the active patch group but was nonsignificant. Male active patch participants had fewer awakenings per hour relative to both male placebo patch participants and their own baseline values on the 3rd and 5th nights of quitting. Awakenings per hour at each postcessation timepoint were above baseline levels for male placebo patch participants.

Among women, there were no significant two-way interactions on awakenings per hour, nor were there any significant linear trends for the active and placebo patch groups when analyzed separately. Women did display a significant quadratic trend (*z* = -2.4, *p* < .05), and the quadratic trend was significant within the placebo patch group (*z* = -2.4, *p* < .05). Both active and placebo patch groups displayed a postcessation peak in awakenings per hour on Day 3 (see

Figure 1). Baseline differences between men and women on awakenings per hour were nonsignificant (*p* > .10).

#### *Sleep Stage Distribution*

The set of three-way interaction terms was not significant for Stage 1 percentage, Stage 2 percentage, Stages 3 and 4 percentage, or REM percentage.

#### *Other Sleep Measures*

There were no significant sets of three-way interaction terms for REM latency, sleep latency, or sleep duration.

*Time awake after sleep onset.* For time awake after sleep onset, there was a significant Gender  $\times$  Group  $\times$  Repeated Measure interaction set,  $\chi^2$  (2, *N* = 34) = 9.5, *p* < .01. Both the Gender  $\times$  Group  $\times$  Linear Trend (*z* = -2.3, *p* < .05) and the Gender  $\times$  Group  $\times$  Quadratic Trend (*z* = -2.5, *p* < .05) interactions were significant.

Among women, there was a significant quadratic trend (*z* = -4.7, *p* < .001), Group  $\times$  Linear Trend interaction (*z* = 2.6, *p* < .01), and Group  $\times$  Quadratic Trend interaction (*z* = 2.2, *p* < .05) for time awake after sleep onset (see Figure 1). The linear trends for the patch groups were opposite in direction, although both only approached significance (active, *z* = 1.8, *p* = .07, and placebo *z* = -1.9, *p* = .06). The quadratic trend for the placebo patch group was significant (*z* = -4.7, *p* < .001), whereas the quadratic trend for the active patch group was not (*z* = -0.7, *p* = .48). Thus, women in the placebo patch group displayed an increase in time awake after sleep onset that peaked on the first day of quitting and declined thereafter, whereas women in the active patch group displayed an increase in time awake across the study period (see Figure 1).

There was a significant linear trend for time awake after sleep onset among men (*z* = -2.1, *p* < .05), and the linear trend was significant within each patch group (active, *z* = -2.4, *p* < .05, and placebo, *z* = -2.1, *p* < .05). The two-way interactions and quadratic trend were not significant among men, nor was the quadratic trend significant for either the active or placebo patch group when analyzed separately. Both active and placebo patch groups displayed linear decreases in time awake after sleep onset across sleep sessions (see Figure 1). Baseline differences between men and women on time awake after sleep onset were nonsignificant (*p* > .10).

*Sleep efficiency.* There was a significant Gender  $\times$  Group  $\times$  Repeated Measure interaction set for sleep efficiency,  $\chi^2$  (2, *N* = 34) = 6.11, *p* < .05. The Gender  $\times$  Group  $\times$  Quadratic Trend interaction was significant (*z* = -2.3, *p* < .05) whereas the Gender  $\times$  Group  $\times$  Linear Trend interaction only approached significance (*z* = -1.8, *p* < .10).

Among women, there was a significant linear trend (*z* = -2.3, *p* < .05), quadratic trend (*z* = -6.2, *p* < .001), Group  $\times$  Linear Trend interaction (*z* = 2.1, *p* < .05), and

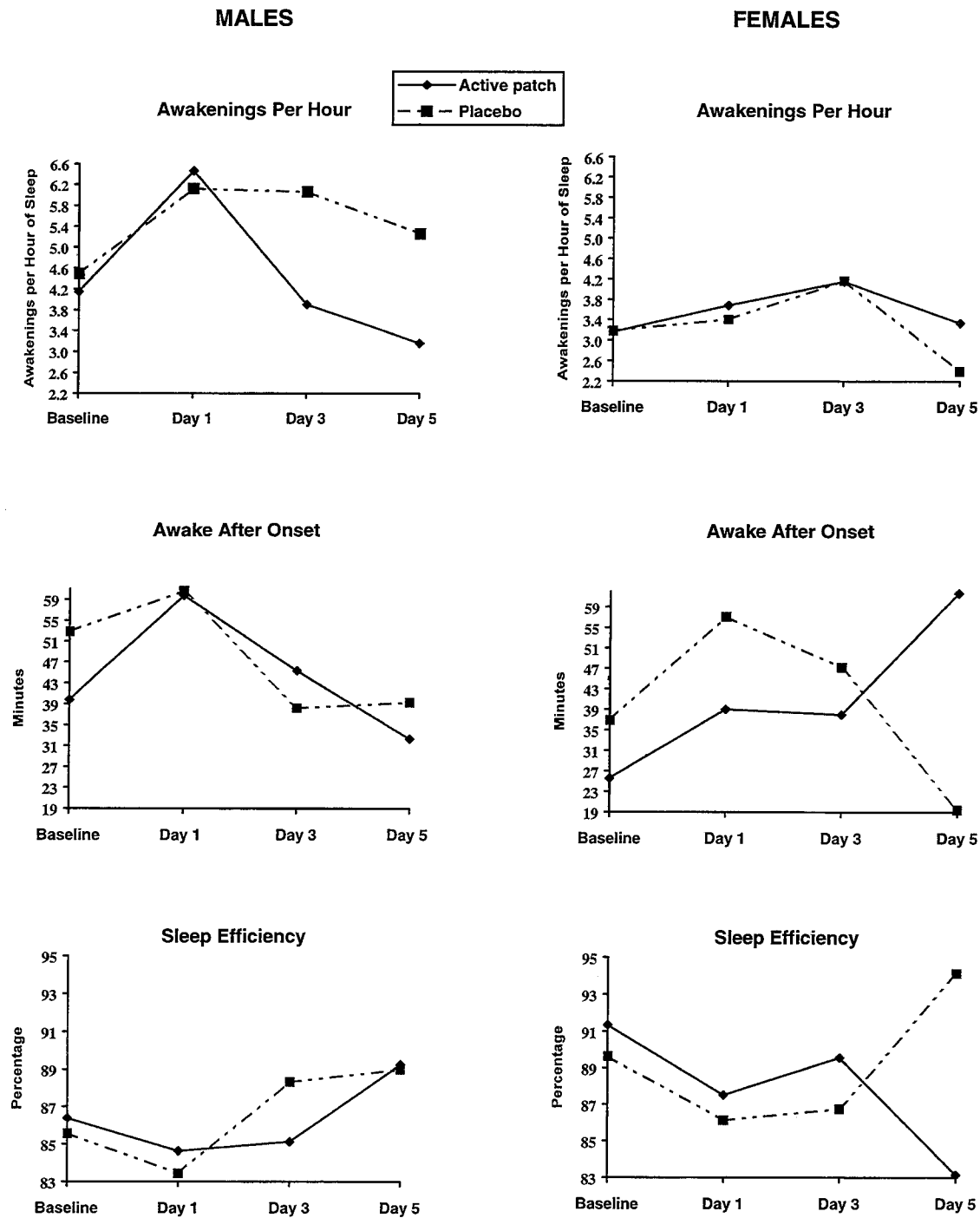


Figure 1. Polysomnographic measures of awakenings per hour of sleep time, time awake after sleep onset, and sleep efficiency for active nicotine patch participants (represented by diamonds) and placebo nicotine patch participants (represented by squares) by gender.

Group  $\times$  Quadratic Trend interaction ( $z = 2.6, p < .01$ ) for sleep efficiency. Women in the placebo patch group displayed a significant linear trend ( $z = 2.3, p < .05$ ) and quadratic trend ( $z = 6.2, p < .001$ ). Neither the linear nor the quadratic trend was significant among female active patch participants. As shown in Figure 1, after a small

decrease in sleep efficiency from baseline to the first and third days of quitting, female placebo patch participants experienced greater sleep efficiency by the fifth day after quitting than they did at any other timepoint. Active patch participants experienced no improvement in sleep efficiency over time. There were no significant effects on sleep

efficiency among men. Baseline differences between men and women on sleep efficiency were nonsignificant ( $p > .10$ ).

### *Self-Report Analyses*

#### *Mood*

The Gender  $\times$  Group  $\times$  Repeated Measure interaction set was not significant for any of the POMS scales.

#### *Urges to Smoke and Hunger*

The Gender  $\times$  Group  $\times$  Repeated Measure interaction set was not significant for positive reinforcement urges, negative reinforcement urges, or hunger.

#### *Sleep*

The Gender  $\times$  Group  $\times$  Repeated Measure interaction set was not significant for any of the self-reported sleep items.

### *Post Hoc Analyses*

One possibility that might account for gender differences in response to NRT is that NRT may produce higher postcessation blood levels of nicotine relative to body weight among women than men. This may be especially relevant in the case of the nicotine patch because dosing is fixed, despite women's smaller body weight (i.e., women cannot titrate their dosing by chewing fewer pieces of gum for example). Other factors that might account for gender differences in response to NRT include depression, age, and level of nicotine dependence. Therefore, we reran our analyses for those variables displaying significant gender differences in response to NRT (i.e., polysomnographic assessments of awakenings per hour, time awake after sleep onset, and sleep efficiency) while simultaneously controlling for baseline Beck Depression Inventory score (Beck, 1967), age, body mass index, cigarettes smoked per day at baseline, cotinine at baseline, cotinine fraction (postcessation cotinine/baseline cotinine) at Day 1, cotinine fraction at Day 3, and cotinine fraction at Day 5. The cotinine fraction reflects the percentage of baseline cotinine replaced by NRT (i.e., if NRT results in higher blood nicotine levels relative to baseline levels among women than among men, this should be reflected in a higher cotinine fraction). The results were unaffected by controlling for these variables.

### *Discussion*

Perkins (1996) recently hypothesized that nicotine reinforcement controls smoking to a greater degree among men than women and that consequently, NRT during smoking cessation may benefit men more than women. That is, for women, NRT may not compensate as well for the reinforcement lost through smoking abstinence. In the current research, data from several objective indexes of tobacco withdrawal were supportive of that prediction. Polysomnographic sleep parameters revealed two different types of NRT effects, and there were gender differences in these effects. NRT ameliorated withdrawal signs in men and exacerbated signs in women. Psychometrically valid and

reliable self-report measures of tobacco withdrawal, however, did not reveal gender differences in response to NRT.

### *Gender Differences in Response to NRT*

Our findings suggest that gender differences in NRT effects may occur by two distinct mechanisms. First, NRT may simply be less effective at suppressing certain withdrawal responses in women (see Hatsukami et al., 1995; Killen et al., 1990). For example, among men, both active and placebo patch groups displayed increases in sleep fragmentation on Day 1 of the postcessation period (see Figure 1). However, NRT appeared to exert a beneficial effect thereafter. There was a steady decline in fragmentation across subsequent withdrawal days for men in the active patch group, whereas men in the placebo patch group showed no such improvement. The improvement in sleep fragmentation with NRT was paralleled by the increase in steady-state blood nicotine level that occurs over the first 2 to 4 days of patch use (Palmer et al., 1992). Among women, there was a pre- to postcessation increase in sleep fragmentation, but no beneficial effect due to NRT. In fact, women receiving active NRT had slightly, albeit nonsignificantly, higher levels of fragmentation than did women receiving placebo treatment (see Figure 1).

Second, NRT may actually produce some iatrogenic effects in women. The sleep efficiency and time awake after sleep onset data revealed no effect of NRT among men but did suggest that there was a detrimental effect of NRT on women. There were significant withdrawal effects on sleep efficiency and time awake after sleep onset for women, and NRT appeared to exacerbate these effects (see Figure 1). Furthermore, like the improvement in fragmentation found among men who used the active patch, the exacerbation of withdrawal signs among women who used the active patch paralleled the rise in blood nicotine level found with continuous patch use (Palmer et al., 1992).

It is important to note that for each of the three polysomnographic variables displaying significant gender differences in response to NRT (i.e., awakenings per hour, time awake after sleep onset, and sleep efficiency), women in the placebo patch group displayed statistically significant withdrawal effects. Thus, our findings of greater benefit with NRT among men are not simply the result of NRT reducing a withdrawal effect that is present only in men. In addition, there were no significant main effects of gender on these variables nor were there significant two-way interactions involving gender. Furthermore, differences at baseline between men and women were not significant. Only the three-way interactions were significant, suggesting that our results are not the results of a generalized gender difference in sleep but rather they reflect gender-specific patterns of response to NRT. These findings are congruent with recent research demonstrating that the pattern of nicotine withdrawal response is motivationally significant, independent of the absolute magnitude and duration of withdrawal (Piasecki, Fiore, & Baker, 1998). Moreover, the results appear consistent with Perkins's (1996) conclusion that differential response to NRT is not due simply to a greater

biological sensitivity to nicotine among women (Grunberg et al., 1991). Although the sleep efficiency and time awake after sleep onset data are consistent with a greater sensitivity among women, the sleep fragmentation data are not.

### *Assessing Withdrawal and Response to Treatment*

It can be argued that results in a single response domain like sleep provide only a narrow, unrepresentative index of the impact of NRT, and it is certainly true that a thorough assessment of NRT effects requires assessment across diverse domains. For example, none of the self-report measures of withdrawal indicated that NRT effects differ by gender, despite the fact that a substantial number of significant withdrawal effects were found in these data—both men and women displayed significant withdrawal effects on the POMS tension, vigor, and total mood disturbance scales as well as on positive reinforcement urges and self-report sleep variables (number of awakenings, relative sleep quality, and absolute sleep quality; data not shown). Therefore, the relevance of our findings to NRT's clinical efficacy is unknown.

Nevertheless, sleep is a fundamental index of psychobiological disturbance (National Advisory Mental Health Council, 1995) that reflects disruption in a diverse array of behavioral, affective, cognitive, and physiological response systems (see Lacks & Morin, 1992; Naylor & Aldrich, 1994). It may be that objective sleep measures better capture the molar impact of tobacco withdrawal's many dimensions (e.g., physiological, psychological, social, behavioral) than do other types of withdrawal indexes. In other words, symptoms traditionally associated with psychopharmacologic models of dependence (e.g., craving), as well as perturbations in mood and cognition due to nonpharmacologic events, may be reflected in polysomnographic sleep parameters while eliminating the recall and response biases and errors that are inherent in self-report measures. Our results showed significant gender effects in response to NRT on polysomnographic assessments of awakenings per hour, time awake after sleep onset, and sleep efficiency. These three measures are reflective of general sleep quality, consistent with the notion that sleep disruption may be reflecting global disturbance that follows the classic withdrawal pattern over time rather than a specific pharmacological effect.

There is evidence that NRT yields better clinical outcomes among men than among women (Davis et al., 1994; Killen et al., 1990; Sachs & Leischow, 1992). However, it has been difficult to attribute this disparity to gender differences in specific actions of nicotine or to other characteristics that might mediate or moderate the relation between gender and outcome (Wetter et al., in press). The lack of progress in this area may be due, at least in part, to a heavy reliance on self-report measures. For example, a growing body of work suggests that self-reports may constitute insensitive indexes of drug actions or drug motivational states (Brandon, Wetter, & Baker, 1996; Hughes, Oliveto, & Terry, 1996; Perkins, Grobe, & Fonte, 1997; Robinson & Berridge, 1993; Tiffany, 1990). There are many

reasons that objective and subjective measures of withdrawal might disagree (e.g., different thresholds of response activation, the relative involvement of self-appraisal or memory processes, sensitivity of measurement instruments; Baker & Brandon, 1991). Our research certainly suggests that, in addition to self-report measures, it may be important to use objective behavioral or physiological measures when studying withdrawal processes and response to treatment. Such measures may point to ways that men and women differ in their response to nicotine—ways that could potentially be related to efficacy differences in the clinical impact of NRT.

### *Study Strengths and Caveats*

Postcessation smoking often precludes accurate assessment of withdrawal because participants with the most severe withdrawal may be especially likely to return to smoking. These participants are often dropped from further analysis, resulting in a potentially biased sample of smokers, or if included, the characterization of withdrawal is then contaminated by the effects of smoking. Furthermore, studies that examine NRT effects on withdrawal are often further confounded by differential abstinence rates between active and placebo patch groups, resulting in differentially biased samples across groups. A strength of the current study was that 88% of the participants were completely abstinent and 94% smoked one cigarette or less during the postcessation data collection period.

Unfortunately, the high abstinence rates were achieved through intensive counseling and a large amount of experimental contact, which may have reduced the generalizability of the results. Similarly, although participants were heavy smokers, the rigorous inclusion–exclusion criteria may have resulted in a more motivated and psychologically healthy sample than is typical of the general population of smokers trying to quit. It is also possible that the time frame of this study was too short for gender differences to emerge on self-report measures (Piasecki et al., 1998). In addition, the sample size is relatively small. Finally, our results are specific to NRT by a 24-hr patch, and the effects of using a 16-hr patch are unknown. Thus, replication of these results is required before definitive conclusions can be made regarding the differential impact of NRT among men and women.

Nevertheless, objective sleep measures did reveal gender differences in response to NRT, despite the fact that withdrawal severity may have been attenuated by the stringent selection criteria and the intensive behavioral treatment. However, it is also important to note that the effects of tobacco withdrawal and NRT appear to be largely restricted to measures of sleep fragmentation (Prosser et al., 1994; Wetter et al., 1995) and associated measures (i.e., sleep efficiency and time awake after sleep onset).

### *Conclusions and Future Research Directions*

Perkins (1996) proposed that the relative level of nicotine versus nonnicotine reinforcement was the critical mechanism in accounting for gender differences in NRT efficacy.



Although our results are compatible with this hypothesis, they are also compatible with other explanations. Our data are compatible with Perkins's notion in that if NRT compensates less well in women for the reinforcing efforts of smoking (nicotine as well as nonnicotine reinforcement), it may produce less amelioration of withdrawal and more adverse impact. However, our findings might also be attributed to the heterogeneity of nicotine reinforcement. That is, women might smoke more for the incentive properties of nicotine (Robinson & Berridge, 1993) and less for negative reinforcement, in part because nicotine may be less effective in reducing withdrawal in women (Hatsukami et al., 1995; Killen et al., 1990). Additional research is needed to elucidate further the mechanisms underlying gender differences in response to nicotine.

Our findings do provide a strong rationale for future research investigating the effects of tobacco withdrawal and treatment on objective measures of sleep. First, objective indexes of withdrawal phenomena might yield important information that is either not available to conscious awareness or not easily retrieved and synthesized and thereby have the potential to expand our understanding of basic withdrawal processes and address fundamental questions in addictive behaviors. Furthermore, objective indexes of withdrawal might benefit theory development and evaluation by providing a clinical outcome that is sensitive to treatment effects, can be assessed early in the quitting process, and is immune to recall errors and response biases. Research that uses objective measures of sleep might also yield insights that are useful in developing and evaluating treatments. For example, the efficacy of various antidepressants in changing specific sleep parameters has been related to their efficacy in reducing depression (see Benca, 1994).

Moreover, withdrawal-induced sleep disturbance and the effects of treatment on sleep may be motivationally significant. Withdrawal-induced sleep disruption may produce or exacerbate dysphoria and other withdrawal symptoms. Similarly, the attenuation of sleep disturbance with treatment may reduce these effects. Some data suggest that sleep disturbance is more difficult to tolerate than other drug withdrawal symptoms (Gossop, Bradley, & Brewis, 1982), and self-report evidence suggests that awakenings may predict relapse (Persico, 1992). Thus, the nature of sleep disturbance and its consequences during smoking cessation deserve further attention.

This study is important in several respects. To the best of our knowledge, it is the only study to date that has examined NRT effects on objectively assessed sleep measures, and it demonstrated that polysomnographic parameters convey information that is unavailable from well-validated measures of mood and urge to smoke. It also demonstrated that NRT may have different effects on objective versus subjective measures of withdrawal and underscored the importance of using multidimensional assessments. Sleep fragmentation appears to be a particularly valuable index of response to treatment because it is immune to subjective reporting biases, indicative of impaired daytime functioning, and may tap processes that are unavailable to self-report (Berry, Webb, Block, Bauer, & Switzer, 1986; Stepanski et al.,

1984). Finally, this study provides unique evidence that suggests that women may receive less benefit from NRT during smoking cessation than do men.

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