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Nicotine replacement: ten-week effects on tobacco withdrawal symptoms

Janet Gross [1, 2] **and Maxine L. Stitzer** [2, 3]

[1] The Johns Hopkins University School of Medicine, [2] Department of Psychiatry and Behavioral Sciences, 1235 E. Monument Street, LL50; Baltimore, MO 21202, USA, and [3] Francis Scott Key Medical Center, Behavioral Pharmacology Research Unit, D-5-West; 4940 Eastern Avenue, Baltimore, MD 21224, USA

Abstract. This study examined the long-term effects of nicotine replacement on tobacco withdrawal symptoms. Smokers ($N=40$ community volunteers) maintained biologically validated smoking abstinence under closely monitored conditions while chewing 2 mg nicotine gum (Nicorette; average of 6.9 pieces per day) or placebo gum during the first 10 weeks following smoking cessation. During the first post-cessation week symptoms of irritability, anxiety, impatience, restlessness, excessive hunger, difficulty concentrating, drowsiness, sleep disturbance and tobacco craving intensity were significantly lower in active as compared with placebo nicotine gum subjects. Symptoms of psychological distress including irritability, anxiety and impatience declined over time in placebo subjects and were suppressed by replacement therapy below placebo treatment levels only during the first 4–5 weeks after smoking cessation. On other items, most notably increased appetite and excessive eating, stable between-group differences persisted over the entire 10-week trial. The data suggest that use of active gum beyond the first 5 weeks post-cessation may be inconsequential as far as suppression of certain key symptoms of psychological disturbance is concerned, but more prolonged use of active gum would be advisable if the long-term nicotine replacement effects observed (e.g. decreased hunger) are relevant to smoking relapse prevention.

Key words: Smoking cessation – Tobacco withdrawal symptoms – nicotine gum – Nicotine replacement – Symptom time course

It is now widely acknowledged that the cluster of symptoms observed following cessation of smoking is largely due to the effects of nicotine withdrawal (US DHHS 1988). Several recent studies have defined the characteristics of tobacco withdrawal by examining the symptoms reported by smokers who initiated abstinence either under close monitoring while residing on a research ward (Hatsukami et al. 1984) or in their natural environment (Shiffman and Jarvik 1976; Gilbert and Pope 1982; Cummings et al. 1985; Hughes and Hatsukami 1986; West and Russell 1988). The symptoms that have been consistently identified and included in the DSM-III-R (American Psychiatric Association 1987) criteria for tobacco dependence are cravings for nicotine, irritability, restlessness, anxiety, difficulty concentrating, increased appetite or weight gain and decreased heart rate. Withdrawal symptoms are thought to be an important factor contributing to the high rates of early relapse characteristic of smoking quit attempts (Stitzer and Gross 1988). Our understanding of the natural time course and duration of tobacco withdrawal symptoms is currently limited. Previous studies have shown that the subjective and physiologic symptoms of discomfort begin within 24 h after smoking cessation (Gilbert and Pope 1982; Hatsukami et al. 1984; West and Russell 1988). Most subjective symptoms appear to peak within 48 h (Hatsukami et al. 1984) and then decline steadily during the first 3–4 weeks post-cessation (Cummings et al. 1985; West et al. 1987).

Evidence supporting the pharmacological basis of tobacco withdrawal syndrome comes from studies which have shown that nicotine replacement with the use of nicotine-containing chewing gum (Nicorette®) suppresses withdrawal symptoms in outpatient stop smoking clinic participants (Jarvis et al. 1982; Hughes et al. 1984; Schneider et al. 1984; West et al. 1984). These controlled studies, which provided valuable information about the short-term effects of nicotine replacement, found that newly abstinent smokers using active as compared to placebo gum reported fewer and less intense symptoms of psychological and somatic distress such as irritability, anxiety, restlessness, difficulty concentrating and impatience. While different studies have used different specific symptoms to define a withdrawal syndrome, the results are generally consistent with the DSM-III-R definition of tobacco withdrawal syndrome. Since the longer term therapeutic effects of nicotine gum are unknown, it is possible that the recommended period of 3 months of prescribed gum use in clinical populations may be either inadequate or excessive for effective withdrawal relief. An analysis of symptoms with appropriate control conditions for a longer time period would help to shed light on the role of withdrawal in relapse and aid in prescription practices of nicotine gum to optimize abstinence.

Previous studies of nicotine replacement effects on tobacco withdrawal symptoms have been variable in methodologic rigor. Critical elements of a well-controlled trial that have been used inconsistently in previous studies include a) biological verification of smoking abstinence, b) inclusion of a baseline smoking period during which dependent measures are assessed, c) inclusion of appropriate control comparisons such as placebo nicotine replacement ther-

Offprint requests to: M.L. Stitzer

apies, and d) biological assessment of nicotine exposure levels achieved with replacement therapy.

The purpose of the present study was to examine the time course and patterns of nicotine replacement effects on tobacco withdrawal symptoms in outpatient volunteers over 10 weeks, a longer post-cessation time period than has previously been studied. The present study provides additional information by ensuring continuous abstinence in study participants, measuring nicotine exposure levels during replacement therapy, and obtaining frequent self-reports of withdrawal symptoms based upon DSM-III-R criteria. The study enabled us to examine the time course and severity of the tobacco withdrawal syndrome during 10 weeks of verified abstinence and to determine the duration of nicotine replacement effects, which to date have not been described.

Methods

Subjects. Study participants were recruited from the community through local media to participate in a smoking cessation program involving nicotine gum, behavioral counseling and group support. Interested smokers who responded to advertisements were screened in brief telephone interviews and met the following inclusion criteria: aged 18–70, smoked at least ten cigarettes/day, motivated to quit smoking, not currently using any prescribed medications for psychiatric problems, residence within 15 miles of the hospital, and medically approved to chew nicotine gum (i.e., free from recent myocardial infarction, temporomandibular joint disease, gastric ulcers, pregnancy). One hundred and twenty-seven adults attended the introductory meeting; 87 (68.5%) of these attended the requisite three prequit meetings and were assigned to a gum condition. Depending on compliance from this point on, a subject was categorized as a dropout, an exclusion, or a completer. Over the 10-week trial there were 44 (50.6%) dropouts for reasons including: initial failure to quit smoking (30%), failure to show for appointments after quitting (9%), self-reported relapse to smoking (57%), hospitalization during the trial (2%), and failure to use gum (2%). Subjects were not dropped for isolated smoking slips (≤ 3 cigarettes within 24 h) which were followed by CO verified abstinence. Three subjects were excluded following detection of noncompliance with smoking abstinence ($N=2$) and/or gum use ($N=1$) based on biochemical analyses which were performed after the end of the study. Thus, 40 study completers remained for all subsequent analyses.

Pre-quit procedures. Subjects attended three smoking cessation classes over a 2-week period prior to receiving gum. Classes consisted of small group discussion about addiction and the hardships of quitting smoking, instruction on nicotine gum use, behavioral instruction in smoking cutdown, stimulus control of smoking cues, alternative behaviors for smoking, and relapse prevention. All subjects received "Freedom From Smoking in 20 Days" published by the American Lung Association as a behavior change guide. A battery of self-report measures, objective indices of cigarette smoke exposure, and body weight were obtained at the first meeting. The pre-quit smoking goal was to reduce cigarettes to five per day in preparation for 10 weeks of complete abstinence and daily gum use. At the third prequit meeting, subjects received a 1-week supply of gum under double blind conditions with instructions to quit smoking completely and begin chewing a minimum of 5 and maximum of 15 gum pieces per day.

Random assignment. Assignment to gum condition was double blind and random with stratification on sex, baseline body weight and baseline expired air carbon monoxide (CO) level. Subjects were deliberately over-assigned to the placebo condition (10:7) in anticipation of greater dropout from this condition.

Post-quit procedures. During the 10 weeks of abstinence, subjects reported to the laboratory twice weekly for biological and self-report data collection, replenishment of gum supply (105 pieces/week), and brief smoking cessation counseling with the experimenter. At each laboratory visit, subjects were weighed on a standard balance beam scale provided a breath sample for carbon monoxide (CO) analysis, returned unused gum from the previous week, and completed questionnaires. As an additional incentive for remaining abstinent, each breath carbon monoxide reading of 8 ppm or lower, as measured during laboratory visits, earned the subject a token towards a weekly cash lottery with prizes ranging from \$10 in postquit week 1 to \$75 in week 10.

Abstinence verification procedures. Carbon monoxide was used throughout the study as an objective confirmatory measure of smoking abstinence with 8 ppm or less coded as abstinent. For the CO analysis, subjects expired breath into a 1 l bag following a 20-s breath hold. The contents were analyzed for CO with a MiniCO Carbon Monoxide Indicator (Catalyst Research Corporation, Model 1000). Saliva samples from the first baseline meeting and from post-cessation weeks 1, 2, 6, and 10 were sent to an outside laboratory (Labstat, Toronto, Canada) upon completion of the study for gas chromatography analysis of cotinine levels and for colorimetric analysis of thiocyanate levels. Thiocyanate, a biochemical index of smoke exposure, is not influenced by nicotine gum exposure and was used post hoc to confirm smoking abstinence. In the present study, mean post-cessation values of 1600 μM/l or lower were coded as abstinent. Cotinine, a nicotine metabolite, was used to verify adequate levels of nicotine exposure in the active gum condition and corroborate abstinence in the placebo gum condition. Post-cessation values of 10 ng/ml or less were coded as abstinent. (One subject with a week 10 cotinine of 26 ng/ml but abstinent readings on CO and thiocyanate measures was included in analysis.) We employed a further procedure for abstinence verification: subjects were visited at their homes 2–3 times per week on weekday evenings and on weekend days for unannounced breath sample collections which were subject to later CO analysis. Each day of the week was selected with an equal probability for the home visits according to a predetermined random schedule.

Subjective report measures. A battery of subjective report measures was administered at baseline (2 weeks prior to quitting) and at laboratory visits for the 10 post-quit weeks. Only the measures pertinent to the discussion of withdrawal will be presented here. Other measures used in this study will be presented in a separate report (Gross et al. 1989).

The 15-item Smoking Withdrawal Questionnaire was used to assess degree of withdrawal discomfort (Hughes and Hatsukami 1986). Included in this measure were the DSM-III-R criteria for tobacco withdrawal syndrome in addition to a variety of somatic complaints. The withdrawal questionnaire included the following items: irritability, anxiety, impatience, difficulty concentrating, restlessness, excessive hunger, increased eating, drowsiness, headache, gastrointestinal problems, tremor, heart racing, sweating, dizziness, and insomnia/disturbed sleep. Subjects rated the severity of each symptom on a 4-point scale with 0 = none, 1 = slight, 2 = moderate, and 3 = severe. The question "How strong are your cravings for a cigarette?" was separated from the other withdrawal items on the questionnaire page but answered on the same 4-point scale. A total withdrawal score was calculated by summing scores on the 15 symptom items and the craving question.

Data analysis. Data were collected weekly or summarized for weekly intervals and analyzed in repeated measures analysis of variance or covariance for effects of active versus placebo gum condition, post-cessation time (Weeks), and gum condition × week interactions. Relevant baseline measures obtained at the first prequit class were used as the covariates. Post-hoc tests (Tukey's) were used to compare withdrawal report scores for the two treatment groups during the first and last treatment weeks (1 and 10). While one-tailed tests would be appropriate given the experimental hypothesis, the more conservative two-tailed tests of significance were used because of the small sample size and the large number of tests performed.

Results

Subject characteristics: study completers

Table 1 shows subject characteristics for study completers in the two gum conditions. Active and placebo gum subjects did not differ significantly at baseline on any of the demographic or smoking history variables. Active gum subjects reported using significantly fewer cigarettes per day than did placebo gum subjects [$t(38) = 2.8$, $P < 0.008$]. However, the groups did not differ on any of the biological indices of tobacco smoke exposure (i.e., breath carbon monoxide, salivary continine and salivary thiocyanate) at baseline assessment 2 weeks prior to quitting. Similarly, the two groups had comparable scores on 15 of the 16 withdrawal symptom items and on the total withdrawal score at baseline. Craving intensity was the one withdrawal item that differed for the two groups at baseline [placebo mean sore = 3.1; active = 2.4; $t(38) = 3.2$, $P < 0.003$].

Table 1. Baseline subject characteristics

	Active ($N = 20$)		Placebo ($N = 20$)	
	Mean	(SEM)	Mean	(SEM)
Demographics				
% Female	55.0		50.0	
Age	41.8	(2.2)	43.5	(2.1)
Smoking variables				
Years of smoking	24.0	(2.1)	24.3	(2.1)
No. previous quit attempts	2.1	(0.4)	2.9	(0.7)
Cigarettes per day*	25.5	(1.5)	33.9	(2.6)
Nicotine yield (mg)	0.8	(0.1)	0.8	(0.1)
Carbon monoxide (ppm)	37.9	(2.4)	42.0	(4.0)
Salivary cotinine (ng/ml)	336.9	(24.4)	303.8	(31.2)
Salivary thiocyanate (μmole/l)	3454.5	(286.9)	2977.5	(255.8)

* $P < 0.01$

Dropouts analysis

Analysis of variance for gum condition by dropout status was conducted with 84 subjects ($N = 40$ completers and 44 dropouts) who had been randomly assigned to one of the two gum conditions to determine whether any of the baseline subject variables contributed to dropping out of the study. There were more dropouts from the placebo ($N = 29$ of 49 assigned) than from the active ($N = 15$ of 35 assigned) gum condition. Dropouts, as compared to completers, were of lower socioeconomic status based on Hollingshead's (1975) index of social status ($P < 0.002$). The one baseline variable for which there was an indication of differential dropout by gum condition was baseline cigarettes per day (interaction: $P < 0.03$): active gum completers reported smoking fewer cigarettes per day than did active dropouts (25.5 versus 38 CPD) while for the placebo gum subjects there was no difference in baseline cigarette consumption between dropouts and completers (35 versus 34 CPD).

A second analysis was conducted to determine whether dropout was related to week 1 withdrawal scores. For this analysis, only the subgroup of dropouts who were abstinent at the first post-quit session (as determined by CO < 8 ppm) was included in the analysis (active $N = 10$; placebo $N = 16$). The analysis of covariance (baseline withdrawal score as the covariate) revealed a main effect for study completion status [$F(1,61) = 6.7$, $P < 0.01$] and a significant interaction between completion status and gum condition [$F(1,61) = 4.0$, $P < 0.05$]. Post-hoc analyses for the interaction showed that active gum completers had significantly lower week 1 withdrawal scores ($M = 9.6$) than did active dropouts ($M = 16.5$) and placebo dropouts ($M = 15.8$). Placbo completers had a mean score of 14.9.

Gum use

A gum count was determined from return of unused pieces at laboratory visits. As shown in Fig. 1, active gum subjects

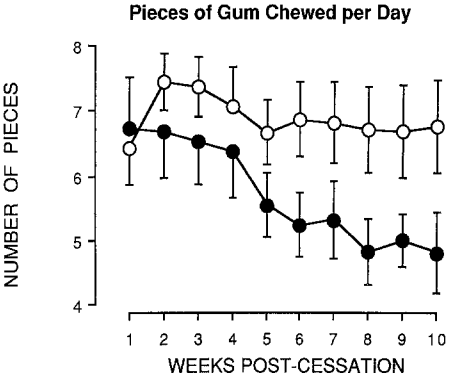

Fig. 1. Pieces of gum used per day (mean + SEM) is shown for active gum (*open circles*) and placebo gum (*closed circles*) subjects over 10 post-cessation weeks

used an average of 6.9 pieces per day throughout the study while placbo gum subjects gradually decreased from 6.8 during week 1 to 4.9 pieces per day by week 10. These trends were verified in statistical analyses. Using a repeated measures ANOVA, there was a significant gum condition × weeks interaction on the gum use measure: $F(9,342=2.1$, $P<0.03$. Cotinine analysis was employed to verify compliance with gum use. Active gum subjects achieved average cotinine levels (mean of weeks 2, 6 and 10) of 166.5 ng/ml (SEM = 15.9 ng/ml) which were stable throughout the study, while no significant salivary cotinine could be detected for placebo subjects ($M=3.0$, SEM = 1.4 ng/ml). Average salivary cotinine levels for active gum subjects were about half of values seen during smoking (Table 1).

Smoking abstinence

Smoking abstinence was verified by frequent breath sample carbon monoxide analysis and by periodic analysis of saliva samples for thiocyanate. Only 5% of the 1487 CO readings (lab visits plus home visits) obtained from study completers exceeded the abstinence cutoff of 8 ppm with no difference between the gum conditions. The mean number of self-reported smoking slips per subject during the 10-week trial did not differ between the two gum conditions (active: $M=$ 0.6, placebo: $M=0.8$). Average salivary thiocyanate levels, which did not differ between groups at any time, decreased from a mean baseline level of 3216 μM/l (SEM = 196) to a mean level of 1693 μM/l (SEM = 107) by post-cessation week 2 and further decreased to a mean of 1108 μM/l (SEM = 85) by post-cessation week 10. Given the assurance of smoking abstinence concurrent with appropriate nicotine and placebo gum use, the analysis of withdrawal symptoms was undertaken.

Total withdrawal scores

The study provided strong evidence for a gum effect on post-cessation withdrawal symptoms. It can be seen from Fig. 2 that total withdrawal scores for placebo subjects increased from baseline levels during the first post-cessation week, declined steadily through post-cessation week 5, and then remained stable for the remainder of the trial. In contrast, average total withdrawal scores for active gum subjects never increased from baseline but showed a gradual decline from baseline through post-cessation week 3 before stabilizing.

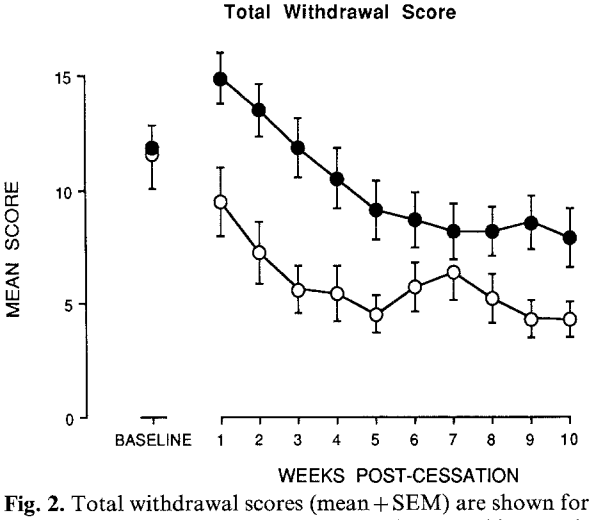

Fig. 2. Total withdrawal scores (mean + SEM) are shown for active (*open circles*) and placebo (*closed circles*) gum subjects at baseline and for 10 weeks after smoking cessation. Baseline data were collected 2 weeks prior to cessation, post-cessation scores were obtained weekly. Total scores represent the sum of scores on 16 symptom items, each of which was rated on a 4-point intensity scale from 0 = none to 3 = severe

Confirmatory analysis of the gum effect on total withdrawal score was performed using a repeated measures analysis of covariance (ANCOVA) with two covariates, baseline total withdrawal score and baseline cigarettes per day, with the latter included as a covariate because of significant group differences at baseline. The ANCOVA confirmed the finding that nicotine gum suppressed post-cessation reports of withdrawal symptoms [main effect for Gum Condition: $F(1,36)=10.5$, $P<0.003$]. A significant effect of Weeks [$F(9,342)=17.6$, $P<0.001$] and a significant Gum Condition × Week interaction [$F(9,342)=2.6$, $P<0.03$] were also observed. In post-hoc Tukey's tests active and placebo gum groups differed significantly at post-cessation weeks 1 and 10 ($P<0.01$).

Individual withdrawal symptoms

Withdrawal questionnaire items were individually analyzed to identify items with differential sensitivity or different time course of response to nicotine replacement. All but the items excessive hunger, sweating, insomnia/disturbed sleep, heart racing and bowel or stomach problems, showed a significant effect of weeks indicating declining scores over time. There were significant ($P<0.05$) main effects for gum condition on four items: excessive hunger, increased eating, restless and drowsiness. Four other items, difficulty concentrating, craving intensity, sweating and insomnia/disturbed sleep, showed borderline significance ($P<0.10$) for a main effect of gum condition. Finally, three items, anxious/tense, irritable/angry and impatient, showed significant interactions of gum condition with weeks. The 11 items with significant gum condition effects, borderline gum condition effects or a significant gum condition by week interaction were grouped into two categories characterized by transient versus stable between group differences

Transient effect pattern

As shown in Fig. 3, the three items with significant gum condition by week interactions were characterized by transient between group differences over time. Post hoc analysis confirmed that these items had significant group differences at post-cessation week 1 (placebo > active; $P<0.01$) and no group differences by post-cessation week 10. As can be seen in Fig. 3, item scores declined for both groups during the first 5 post-cessation weeks. Scores for the placebo group started higher and declined over a longer time course then scores for the active gum group; scores for the two groups were equivalent by week 5 (irritable/angry) or 6 (impatient; anxious/tense) and remained equal for the rest of the trial.

Stable effect pattern

Figure 4 shows adjusted means for the two items, increased eating and excessive hunger, that had the most highly significant main effect for gum condition. On these items, scores

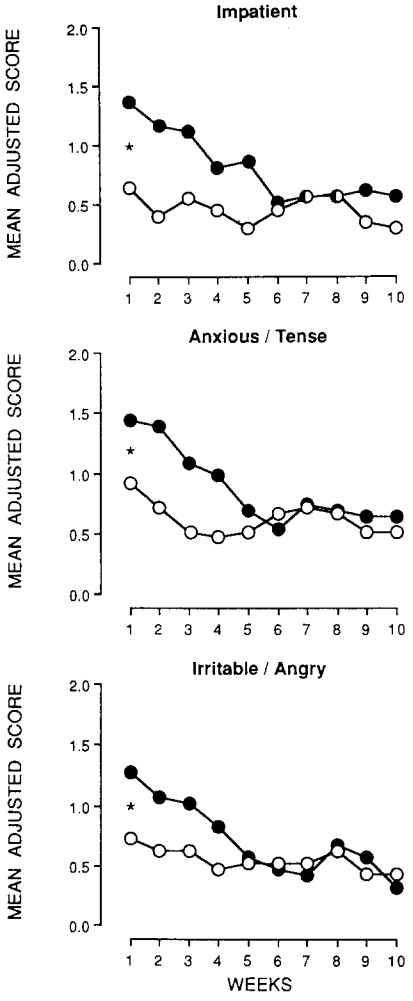

Fig. 3. Adjusted mean withdrawal scores for three individual tobacco withdrawal symptom items: impatient, anxious/tense and irritable/angry are shown for active (*open circle*) and placebo (*closed circle*) gum subjects over 10 post-cessation weeks. Adjusted scores are from an analysis of covariance with baseline cigarettes per day and baseline scores on the item shown as covariates. *Asterisks* indicate significant between-group differences from post-hoc tests conducted at post-cessation weeks 1 and 10

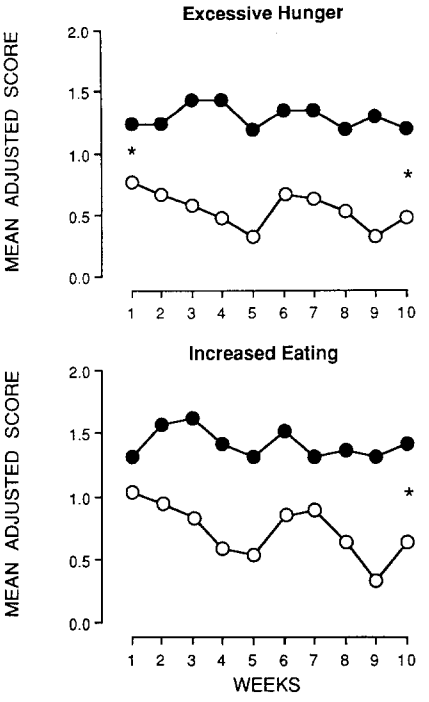

Fig. 4. Adjusted mean withdrawal scores for two individual tobacco withdrawal symptom items: excessive hunger, and increased eating are shown for active (*open circle*) and placebo (*closed circle*) gum subjects over 10 post-cessation weeks. Adjusted scores are from an analysis of covariance with baseline cigarettes per day and baseline scores on the item shown as covariates. *Asterisks* indicate significant between group differences from post-hoc tests conducted at weeks 1 and 10

for placebo treated subjects increased substantially from baseline levels (data not shown) and remained stably elevated throughout the trial. Scores for active gum subjects declined steadily over the first 5 post-cessation weeks then stabilized at levels well below those observed for the placebo group. Post-hoc tests indicated significant between group differences ($P<0.01$) at post-cessation week 10. The hunger but not the eating item also showed significant between group differences at week 1.

There were six remaining items with significant (restless, drowsiness) or borderline significant (difficulty concentrating, sweating, insomnia, craving intensity) main effects of gum condition. In general, scores declined over times for one or both groups on these items but scores for the two groups remained somewhat separated throughout the trial. Post hoc tests indicated that all these items except sweating had significant active versus placebo gum group differences at post-cessation week 1. Only two of these items (restless, sweating) had significant between group differences at post-cessation week 10.

Gum pieces per day. Effect on withdrawal scores

In order to assess the influence of dose (gum pieces per day) on withdrawal suppression, active gum subjects were divided post-hoc into those that chewed more than 6.5 pieces of active gum per day day on the average ($N=8$; mean $=9.2$ pieces per day) and those that chewed less than this amount ($N=12$; mean $=5.4$ pieces per day). These two active gum subgroups had similar total withdrawal scores throughout the trial. At post-cessation week 1, total withdrawal scores were 9.8 and 9.3 for the high and low gum use groups, respectively; total withdrawal score averages over the entire 10-week trial were 5.3 and 6.2 for the high and low gum use groups, respectively.

Gum identification

In order to assess the influence of expectancy of gum effects on withdrawal, subjects were asked at the final laboratory visit (week 10) to guess which gum they had been chewing. Active gum subjects had a 75% accuracy rate compared to a 50% accuracy rate among placebo subjects. A $2\times2\times10$ ANOVA with repeated measures on the third factor (gum condition $\times$ gum guess $\times$ total withdrawal score) assessed effects of gum identification on withdrawal symptoms over the 10 weeks of abstinence. There was no main effect of guessed gum condition nor was there a significant interaction between guess of gum condition and actual gum received.

Discussion

The present study has shown that nicotine replacement suppresses tobacco withdrawal symptoms after smoking cessation, an observation that is consistent with previous reports (Jarvis et al. 1982; Hughes et al. 1984; Schneider et al. 1984; West et al. 1984). Unique to the present study was a time course analysis of replacement effects on specific withdrawal symptoms over 10 consecutive post-cessation weeks. Further, the present study utilized rigorous methodologies to examine this long-range time course, including careful verification of smoking abstinence in study subjects as well as biological verification of nicotine replacement levels.

In the present study, there were significant differences between active and placebo gum groups at post-cessation week 1 on items reflecting irritability, anxiety, impatience, restlessness, excessive hunger, difficulty concentrating, drowsines, sleep distrubance and tobacco craving intensity. This pattern of effects is generally consistent with the results of previous controlled studies testing the anti-withdrawal effects of 2 mg nicotine gum over the first few post-cessation days and is most similar to patterns reported by Hughes et al. (1984), who showed significant drug-placebo differences on irritability, anxiety, impatience, restlessness and difficulty concentrating. The specific symptoms relieved by replacement therapy have been somewhat variable across studies, due in part to the use of different measurement instruments (West 1984).

With regard to the longer-term time course of withdrawal symptoms in placebo gum subjects, the pattern of change over time suggested that several of the most disturbing components of the tobacco withdrawal syndrome require about 5 weeks to resolve following smoking cessation. This lengthy time course of symptom resolution provides ample opportunity for withdrawal symptoms, acting either alone or in concert with other environmental stimuli and events, to contribute to early smoking relapse.

With regard to the time course of nicotine replacement effects, analysis of individual withdrawal scale items suggested two distinct patterns for such effects. The first pattern, most prominently observed for the three items showing a significant gum condition by time interaction (irritability, anxiety, and impatience), was characterized by a transient gum effect that disappeared by post-cessation week 5 or 6. This pattern of transient gum effects seen for items reflecting psychological distress suggests that continued nicotine replacement beyond this time would be unnecessary as far as treatment of these particular withdrawal effects is concerned.

A second pattern, observed for items showing a significant main effect of gum condition, was characterized by stable between-group differences over the enitre 10 week post-cessation period and is best illustrated by the time course of the symptoms excessive hunger and increased eating (Fig. 4). The pattern of stable between group differences over time suggests that appetite and eating changes are not part of a transient tobacco withdrawal syndrome but rather represent physiological states chronically altered by the presence versus absence of nicotine. Similar findings have been reported regarding heart rate changes following smoking cessation (West and Schneider 1988). The stable pattern of between-group differences observed for hunger and eating items is consistent with previous reports that appetite and eating may be chronically suppressed by nicotine exposure during smoking with removal of chronic nicotine thought to partially account for the weight gain that is commonly observed after smoking cessation (Wack and Rodin 1982; Fagerstrom 1987; Rodin 1987; Gross et al. 1989). It should be noted that chronic elevation of scores on the hunger and eating items accounted in large part for the persistent active versus placebo gum differences on the total withdrawal score measure seen in Fig. 2.

Several other withdrawal items showed significant (restless, drowsiness) or borderline significant (difficulty concentrating, sweating, disturbed sleep, craving intensity) effects of nicotine gum condition. In general, the pattern of changes over time for gum versus placebo conditions was intermediate to the transient and stable patterns discribed above. That is, item scores generally declined over the first 4–6 post-cessation weeks and then stabilized, but with scores for the placebo group continuing to be slightly higher than those for the active gum group. In general, these persistent between-group differences were not statistically significant, which calls their importance into question. However, it is possible that with a larger sample size more pronounced and stable between group differences would be evident on some of these items. The continued separation of group scores during post-cessation weeks 6–10 on items such as restless, drowsiness, difficulty concentrating and sweating may reflect chronically altered physiological states produced by continuing nicotine replacement that are unrelated to tobacco withdrawal. Alternatively, there may be persistent residual tobacco withdrawal symptoms that are suppressed by nicotine replacement during these late post-cessation weeks. A comparison of withdrawal scores obtained from both continuing smoker and nonsmoker control groups would be useful for interpreting the small residual differences in symptoms reported by placebo versus active gum subjects after 10 weeks of abstinence.

In the present study, subjective reports of craving intensity declined over time for both groups but subjects were still reporting craving at a "mild" intensity at 10 weeks post-cessation. This supports the notion that the craving symptom may require a longer time to resolve than other components of the tobacco withdrawal syndrome (West and Schneider 1987). Subjective reports of craving were lower for the active than for the placebo gum group throughout the trial, but the gum effect was not robust enough to result in a significant gum condition main effect. This is consistent with several previous reports in which nicotine gum has failed to significantly reduce reported craving for cigarettes (Hughes et al. 1984; Schneider and Jarvik 1984; West et al. 1984), suggesting that craving is more than a pharmacologic consequence of dependence. Consistent with this notion are the stimulus control theories which suggest that craving is part of a conditioned response resulting from expsoure to environmental or interoceptive (e.g. stress responses) smoking-related stimuli (Pomerleau 1981; Jasinski and Henningfield 1988; Stitzer and Gross 1988). It is also possible, however, that the lack of significant gum effects on craving in the present study could be due to inadequate nicotine replacement dosing levels or to use of an inappropriate or insensitive measure of the craving construct (Hughes and Hatsukami 1985; Koslowski and Wilkinson 1987).

It is interesting to note that withdrawal symptoms were adequately suppressed by active gum doses as low as five

pieces per day, which produced mean salivary cotinine levels of about 130 ng/ml (range in low gum users = 75–209 ng/ml). This could be due to the fact that subjects self-selected the amount of gum they used in relation to their own withdrawal intensity. Thus, subjects with greater withdrawal intensity may have chosen to use more gum. Additional studies would be needed to examine the efficacy of different nicotine replacement doses with subjects randomly assigned to dose conditions. Symptom suppression by low doses also suggests the possibility that effects were due to expectancies rather than pharmacology. A recent study (Gottlieb et al. 1987) suggested that therapeutic benefit from nicotine gum was related to subjects' belief about their gum treatment rather than to the actual content of the treatment. In the present study, however, beliefs at post-cessation week 10 about the content of the gum condition were not related systematically to withdrawal scores during the trial. Others have also shown that gum exerts an effect independent of the expected outcome (Hughes and Hatsukami 1985).

The analysis of dropout subjects has important implications for the generality of the present findings. Droput from the placebo condition appeared unrelated to either cigarettes per day during baseline or post-cessation withdrawal intensity in week 1. This suggests that the study obtained a relatively unbiased measure of withdrawal in placebo subjects. In contrast, active gum subjects who completed the trial reported smoking significantly fewer cigarettes per day at baseline than did any other subject subgroup. This raises the possibility that completers in the active gum condition were less dependent on tobacco prior to quitting. However, the biological measures taken during the study did not support subgroup differences in dependence levels. For example, carbon monoxide levels were similar across all study groups just prior to quitting, with mean CO values of 25.2 ppm for active droputs, 21.4 ppm for active completers, 22.8 ppm for placebo dropouts and 22.4 ppm for placebo completers. Further, CPD, on which the groups differed, was not related to withdrawal intensity.

The most intriging observation from the dropout analysis was that active gum dropouts showed significantly higher withdrawal scores during post-cessation week 1 than did active gum study completers. Indeed, withdrawal scores for active gum dropouts were comparable to those reported by the placebo subjects. This could be explained if active dropouts were not using the gum they had been given. However, mean daily gum use during the first 3 days following cessation was unrelated to dropout. Another good possibility that cannot be readily evaluated with the present data set is that active gum dropouts were not chewing the gum properly and thus not receiving adequate nicotine exposure.

The lack of post-cessation withdrawal suppression in active gum dropouts raises the possibility that some smokers are unresponsive to the withdrawal suppression effects of nicotine replacement and that study completers, in contrast, may represent a select subgroup of smokers for whom active gum treatment is effective. If this is true, then nicotine gum effects reported in the present study are clearly not applicable to all smokers. Nevertheless, the withdrawal suppression observed in study completers is entirely consistent with gum effects in other studies. Additional research will be needed to understand the reasons for early dropout from nicotine replacement therapy.

The present study adds important information to our understanding of nicotine replacement effects particularly with regard to the time course of withdrawal symptom suppression over an extended 10-week post-cessation period. We found evidence supporting a range of symptom severity and differential responsivity over time to nicotine gum. Stable between group differences persisted over 10 weeks post-cessation for symptoms of increased appetite and eating while symptoms of psychological distress, including irritability, anxiety and impatience, were transient and thus were suppressed by replacement therapy below placebo treatment levels only during the first 4–5 weeks after quitting. These data are pertinent to prescription practices for nicotine replacement and suggest that treatment beyond the first 5–6 weeks post-cessation may be unnecessary insofar as suppression of certain important symptoms of psychological disturbance is concerned. However, before the dosing duration question can be decided conclusively, more clinical research will be needed to determine whether nicotine replacement therapy confers any benefits beyond those directly related to suppression of transient withdrawal effects. For example, continued treatment would be indicated if long-term replacement effects, such as suppression of appetite and eating, reduced restlessness or increased alertness were shown to be effects that delay or prevent post-cessation relapse to smoking.

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