Psychopharmacology (1996) 128 : 130–138

ORIGINAL INVESTIGATION

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Characterization of tobacco withdrawal symptoms: transdermal nicotine reduces hunger and weight gain

Received: 29 June 1995 / Final version: 22 April 1996

Abstract The accurate assessment of both tobacco withdrawal and the impact of the nicotine patch on withdrawal may be compromised by attrition of subjects, or by subjects smoking during withdrawal. To reduce these occurrences, 211 participants were provided with intensive cessation counseling while trying to quit smoking with either nicotine (21 mg) or placebo transdermal patches. Subject attrition was low, with 80.5% of participants continuing through the 5-week study period. Abstinence rates were also high over this period (75% and 61% in active and placebo groups, respectively). In this multisite, double-blind trial, withdrawal severity was assessed using a nine-item daily self-report questionnaire, and abstinence was confirmed via CO monitoring. Abrupt smoking cessation increased multiple tobacco withdrawal symptoms/signs including craving for cigarettes, irritability, anxiety, appetite, sleep disruption, difficulty concentrating, restlessness, depression, and impatience. Treatment with transdermal nicotine reduced craving for cigarettes, anxiety, irritability, and appetite, as well as weight gain (1.85 versus 2.88 kg mean gain over 4 weeks in active and placebo groups, respectively).

Key words Nicotine · Tobacco withdrawal · Transdermal nicotine patch

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Introduction

Physical dependence upon a drug is inferred when abrupt cessation of drug use results in a withdrawal syndrome; hence, withdrawal is central to concepts of drug dependency. Abrupt cessation of tobacco use produces a reliable constellation of symptoms including increased appetite/weight, difficulty concentrating, irritability, decreased heart rate, etc. (Hughes and Hatsukami 1986). The expectation that cessation of tobacco use will result in many aversive symptoms may serve as a barrier to making attempts to quit. Moreover, given that the intensity of tobacco withdrawal symptoms often peaks during the first week post-quit (Fiore et al. 1994a), and some 65% of self-quitters relapse during the first week (Hughes 1992), it is tempting to posit a causal relationship between withdrawal severity and relapse to smoking. However, this relationship has not been observed in a consistent fashion (DHHS 1990). Given present knowledge, it is difficult to determine if this lack of consistency reflects a true lack of association or methodological shortcomings.

One major methodological concern in the study of tobacco withdrawal has been the selection of an appropriate group for study. A common approach in smoking cessation clinical trials has been to evaluate all randomized participants, regardless of their smoking status after their quit date. This has the advantage of increasing the generalizability of the findings, since analyses are not restricted to the small subsample of participants that typically succeed in maintaining abstinence. However, by including all randomized participants, results may be contaminated because some participants will smoke during withdrawal, possibly blunting their symptoms. If the study involves a comparison of nicotine replacement and placebo during withdrawal, analytic and interpretive strategies may be further complicated. Typically, in such studies, more placebo participants smoke than do participants

receiving nicotine replacement. Thus, contamination by smoking would vary across groups.

There is a possibility that in previous studies, the characterization of nicotine withdrawal or nicotine patch effects was affected by post-withdrawal smoking. In one study (Hatsukami et al. 1988), participants were randomly assigned to attempt total abstinence or reduce their smoking by 50%. The latter group reported less severe withdrawal ratings on such dimensions as weight, number of wakenings, and anger-hostility than did the abstainers. Similarly, Fiore et al. (1994a) found that those smokers who lapsed spontaneously in a nicotine patch clinical trial reported weaker withdrawal symptoms than did abstinent subjects. However, it is impossible to characterize the effects of post-cessation smoking with certainty, since one report associates such smoking with *increased* smoking withdrawal symptoms (ICRFGPRG 1993), while Hughes and Hatsukami (1986) found no difference in withdrawal ratings between abstinent subjects and those smoking a few cigarettes per day.

An alternate approach has been to assess tobacco withdrawal by examining only those participants who are abstinent after the quit date. While this eliminates the possible confounding effects of concomitant smoking, abstinence rates during the critical first few weeks after quitting may be low. Moreover, by excluding non-abstinent participants from data analysis, the characterization of tobacco withdrawal depends on data from a small, and possibly unrepresentative, group of smokers. Additionally, if some participants receive nicotine replacement in the study while others receive placebo, the participants receiving placebo may be more likely to smoke, and thus be excluded from analyses. This might result in the nicotine replacement condition being confounded with participant type (e.g., severely dependent participants would be abstinent only in the nicotine replacement condition).

The problems noted above not only hinder the characterization of the tobacco withdrawal syndrome, they also may obscure or distort the assessment of treatments designed to reduce withdrawal. For instance, when participants are largely abstinent during withdrawal, participants receiving the nicotine patch have less withdrawal than do placebo participants; if smoking is relatively frequent during withdrawal, the patch may have less discernable impact (Fiore at al. 1994a).

There is little doubt that the nicotine patch does reduce many symptoms of tobacco withdrawal such as negative affect and inability to concentrate (Daughton et al. 1991; ICRFGPRG 1993; Levin et al. 1994; Richmond et al., 1994; Stapleton et al. 1995). However, additional research has the potential to yield a clearer picture of the impact of the patch on withdrawal. One unresolved issue concerns whether the patch can reduce both the withdrawal symptoms of appetite and hunger, as well as counter the weight gain that typically follows smoking cessation. Nicotine gum has been effective in this regard (Emont and Cummings 1987; Gross et al. 1989; Nides et al. 1994), but most studies suggest that the patch is not (Tonnesen et al. 1991; Stapleton et al. 1995; although cf. Sachs et al. 1993)

The impact of the patch on weight gain is of both theoretical and clinical significance. If withdrawal-induced weight gain is due to a readjustment of a body-weight regulatory value (Schwid et al. 1992), then the patch should reduce hunger and counter weight gain as does nicotine gum. Moreover, if the patch can be shown to delay weight gain following cessation, this may encourage additional smokers to try to quit (Klesges et al. 1988; Gritz et al. 1989). The current study should be a sensitive test of the impact of the patch on hunger and weight because of its unique design features (low drop-out and high cessation rates).

An additional reason for conducting this study was to obtain information on the timecourse of individual withdrawal symptoms as they are affected by nicotine patch therapy. Most clinical trials involving the patch report information on composites of withdrawal symptoms (Daughton et al. 1991; TNSG 1991; Sachs et al. 1993; Richmond et al. 1994) and so do not yield information on how individual symptoms are affected. Numerous clinical trials have evaluated the impact of the patch on the symptom of craving, but report only aggregates of other symptoms. Virtually all such research reports reveal that patch therapy reduces craving at some time over the first 1–6 weeks post-cessation (Abelin et al. 1989; Tonnesen et al. 1991; Levin et al. 1994; Richmond et al. 1994). However, the impact of the patch on other withdrawal symptoms has been more variable. Several studies have shown that patch therapy reduces scores on aggregates of withdrawal items – at least over the first several weeks post-cessation (Daughton et al. 1991; TNSG 1991; Sachs et al. 1993). Other studies reported either no significant impact of patch therapy on aggregate scales [ICRFG PRG 1993 (for abstainers); Tonnesen et al. 1991] or provided too few data to permit evaluation (Abelin et al. 1989).

Specific information on patch therapy's impact on individual withdrawal symptoms should provide useful information for treatment planning and counseling. Many smokers attempting to quit request information on the likely duration of particular withdrawal symptoms. In essence, they want to know how long withdrawal symptoms are likely to remain elevated over baseline levels. Information on individual symptoms is important because there is heterogeneity in the symptoms that smokers find most troubling or noxious (Hughes and Hatsukami 1986). The present study not only provides information on which particular withdrawal symptoms are ameliorated by patch therapy, but also the duration (up to 1 month) that individual symptoms remain above baseline levels.

Materials and methods

Participants

Participants were recruited at two sites (Madison, Wisc, and Minneapolis, Minn;) by means of newspaper advertisements and local press releases. An initial telephone screening for inclusion and exclusion criteria was conducted; qualified respondents were invited to a group orientation meeting where study details were explained. The study was designed to recruit participants who were truly tobacco dependent (and thus likely to experience withdrawal symptoms), and sufficiently motivated to remain abstinent. Therefore, inclusion criteria consisted of the following: smoking no fewer than 20 cigarettes per day; a minimum of 1 year of regular tobacco use; at least one previous quit attempt of a minimum of 24 h; experiencing at least four self-reported tobacco withdrawal symptoms [by DSM-III-R (APA 1987) criteria] in a previous quit attempt; and expressing a commitment to stop smoking and a willingness to comply with study requirements. Exclusion criteria included: allergy or hypersensitivity to nicotine or transdermal adhesives; use of other nicotine-containing products; history of a generalized skin disorder; concomitant use of other pharmacologic smoking cessation aids; recent myocardial infarction; history of serious cardiovascular disease; history of severe hepatic or renal impairment, or active peptic ulcer, or serious endocrine disorder; ongoing therapy with a psychotropic agent for a diagnosed mental disorder; ongoing therapy with an anxiolytic agent; use of an investigational drug; concomitant abuse of alcohol or other drugs; inability to provide informed consent; weight of less than 45.35 kg; pregnant and/or lactating females, or females of childbearing potential not using a medically accepted form of birth control. Qualified participants provided informed consent and were scheduled for a medical screening visit, which included a physical examination, ECG, an expired CO sample, a saliva sample for cotinine assay, and a urine pregnancy test for females of childbearing potential. A total of 211 participants were enrolled (99 in WI, 112 in MN). The study protocol was reviewed and approved by the appropriate Institutional Review Board at each site.

Participants who passed the medical screening visit were randomly assigned to active or placebo treatment in a double-blind manner, stratified on the basis of their Fagerstrom Test of Nicotine Dependence (FTND; Fagerstrom 1978) score (high > = 7, low < 7). No attempt was made to recruit equal numbers of high- and low-dependence participants as assessed by the FTND.

Study design

The study was a 5-week, multisite, randomized, double-blind, placebo-controlled clinical trial. A quit date 7–14 days after the medical screening visit was selected. For the 7 days prior to the quit date, participants were instructed to smoke normally and to record the amount they smoked as well as to complete daily diaries.

Participants reported to the study center on the evening before their quit date. At this visit, and once per week thereafter data were collected on vital signs, adverse events, concomitant medications, and self-reported smoking status for the previous week (confirmed by expired CO level < = 10 ppm). Participants were randomly assigned to either active or placebo treatment at the time of the pre-quit visit. Adjuvant treatment consisted of group counseling for groups of 8–12 participants, with each group lasting 1 h. In addition to the pre-quit visit, groups met three times in each of the first 2 weeks following the quit date, and twice in both the third and fourth week post-quit (for a total of 11 group sessions). Groups were conducted by trained smoking cessation group counselors, working from a standardized treatment manual containing topics appropriate to specific phases of the cessation process. Joint training in group facilitation was held for all counselors prior to the beginning of the study to ensure uniform delivery of treatment. Once the study was underway, ongoing consultation was conducted both face-to-face (within sites) and by telephone (between sites).

Pharmacologic treatment began the morning following the pre-quit meeting (Quit Date) and consisted of 21 mg transdermal nicotine systems (Habitrol, Ciba-Geigy) or an equivalent placebo system (placebo patches contained approximately 13% of the nicotine found in the active patches in order to maintain adequate blinding). Participants were instructed to apply a new patch every morning to a clean, nonirritated portion of the torso or arms, below the neck and above the waist. Patches were worn for 24 h.

Participants completed two different smoking withdrawal symptom questionnaires every day for 35 days: a modified Minnesota Nicotine Withdrawal Scale (MNWS; Hughes and Hatsukami 1986) and the Center for Tobacco Research and Intervention Smoking Withdrawal Scale (SWS). The former scale was modified to reflect the DSM-IV (APA 1994) criteria for nicotine withdrawal symptoms, rather than the DSM-III-R criteria, and was rated on a 0–4 scale. This scale was the primary outcome measure, and results are reported below; the latter is a new scale that is in development. Because results from the two scales were highly similar, and because the SWS has not yet been validated, we present the MNWS results in the present paper.

Biological assays

Carbon monoxide levels were assessed by having participants take a deep breath and hold it for 20 s before exhaling in to a carbon monoxide monitor (Bedfont Scientific, Upchurch, UK). Levels < = 10 ppm (expired breath level minus ambient CO level) were considered to be confirmatory of self-reported abstinence. When self-report conflicted with measured CO, a second expired CO sample was obtained, and the lower value of the two was used as the CO level for purposes of confirming self-reported abstinence. Participants were eligible to earn $25 for having a CO value < = 10 ppm at each of the four data collection visits during the treatment phase of the study.

Saliva samples for assessment of cotinine levels were obtained at visit 1 (baseline) and at visit 3 (after 1 complete week on patch). Participants dropped a sterile cotton dental roll into their mouth and held it there for 5 min, after which it was expectorated into a plastic vial. Vials were sealed and placed in a sample freezer until they were analyzed. All analyses were conducted by the University of Minnesota Epidemiology Laboratory using a gas-liquid chromatography technique.

Statistical analysis

Baseline participant characteristics for active nicotine patch versus placebo patch participants and for population comparability between sites were evaluated with independent groups Student's *t*-tests for continuous-level variables and χ^2 tests of independence for categorical variables. Patch efficacy and tolerability analyses were based on intent-to-treat. Nicotine patch efficacy was evaluated by means of 2 (active patch versus placebo patch) × 2 (abstinent versus smoking) χ^2 tests of independence computed at the end of each week of patch treatment. Tolerability was evaluated by means of 2 (active patch versus placebo patch) × 2 (adverse dermatologic event occurrence versus absence) χ^2 tests of independence. Withdrawal symptom data were collected daily during patch treatment but, for purposes of analysis, a weekly mean was computed for each of the nine MNWS items at each of the 4 weeks of treatment. In addition, a mean composite score consisting of the mean of the nine MNWS withdrawal items was computed at each of the four weeks of treatment. The influence of withdrawal per se was assessed in placebo participants via *t*-tests for dependent means. Withdrawal was indicated when MNWS scores for the post-quit weeks were significantly elevated over baseline scores. The nine MNWS

withdrawal items and the composite score were also analyzed in a three-factor analysis of covariance (ANCOVA) model consisting of a patch treatment factor (active patch versus placebo patch), a Fagerstrom Test of Nicotine Dependence (FTND) factor (FTND score < = 7 versus FTND score > = 7), and a site factor (WI versus MN). For each withdrawal item and the composite score at each week, the ANCOVA model tested main effects and all higher-order interactions after adjusting for baseline values. ANCOVA assumptions were also tested. Finally, Pearson correlation coefficients were computed to test the relationship between the MNWS scales (each of the nine items and the composite score) and cotinine measures (absolute cotinine level and percent cotinine replacement computed as: week 1 cotinine level divided by baseline cotinine level) after 1 week of patch treatment. Two-tailed tests of statistical significance were used in all analyses.

Table 1 Baseline participant characteristics by treatment group. Standard errors in parentheses. Groups did not differ on any of the listed variables (using Student's t statistic or the χ^2 test; $P > 0.15$)

Variable	Active patch ($n = 105$)	Placebo patch ($n = 106$)
Sex (% female)	52.4	55.7
Age	42 (0.97)	40.4 (0.96)
Race (% white)	97.1	98.1
Cigarettes/day	29.4 (0.92)	30.9 (1.00)
Fagerstrom score	6.8 (0.16)	6.8 (0.13)
Weight (kg)	76.6 (1.76)	77.2 (1.53)
Cotinine (ng/ml)	520.3 (21.63)	497.6 (21.65)
CO level	28.6 (0.95)	30.6 (1.04)

Results

An initial analysis was conducted to test for possible baseline population differences between treatment centers. No statistically significant differences ($P < 0.05$) emerged from this analysis; therefore, data from the two centers were pooled to test for potential randomization differences. Table 1 presents the baseline characteristics of participants in the active and placebo groups. No statistically significant differences were observed between the two groups. Of the 211 participants randomized to a treatment condition, 170 completed the 5-week study phase (80.5%). Of the 41 participants who failed to complete the study, 36.6% were assigned to active patch treatment and 63.4% were assigned to the placebo condition. There was a significant difference in attrition rates between the two sites: eight participants (four active, four placebo) failed to complete the study in WI, while 33 participants (11 active, 22 placebo) did so in MN. Because the two sites differed in attrition rates, all statistical tests comparing active and placebo participants tested for site differences (see ANCOVA description above). Significant site differences are noted below.

Abstinence

The combination of patch therapy and intense group smoking cessation therapy produced high rates of abstinence. Using an intent-to-treat analysis, 80% of the sample were completely abstinent at the end of the first week of treatment, 73% at the end of the second week, 70% at the end of the third week, and 68% at the end of the study. The percentage of participants abstinent in each group across study weeks 1–4 was: active patch = 87, 78, 76, and 75%; placebo patch = 74, 68, 64, and 61%.

Tolerability

In general, the patch was well tolerated. Only six of 211 participants (2.8%) discontinued the study due to adverse patch reactions (two active, four placebo). The most common side effect was headache, reported by 32.4% of active patch users and 23.6% of placebo patch users [χ^2 (1) = 2.03, $P = 0.16$]. Erythema at the patch site was reported by 22.9% of active and 10.4% of placebo users [χ^2 (1) = 5.94, $P < 0.05$]. A number of participants reported general sleep disruption, but there was no difference between treatment conditions [11.4% active versus 14.2% placebo; $\chi^2(1) = 0.35$, $P = 0.55$]. More marked sleep-related symptoms (insomnia, nightmares, unusual dreams) were reported by about 6% of the sample, and there were no significant differences between active and placebo conditions. No serious adverse events occurred during the study.

Change in withdrawal symptoms from baseline

To assess possible changes in withdrawal symptoms from baseline, uncontaminated by nicotine replacement or concurrent smoking, only ratings from abstinent placebo participants were analyzed. Such participants did experience a significant degree of withdrawal (defined as an increase in mean symptom ratings from baseline to the first week post-quit). Table 2 presents the results of the within-subjects comparisons; as shown, all the differences were significant, except for craving. Because it was possible that a weekly average was insensitive to the impact of withdrawal on craving, baseline craving was compared with each daily mean for craving over the first 7 days post-quit. Craving was significantly elevated above baseline during the first 3 days post-quit (ts = 6.41, 4.49, and 2.57, Ps < 0.05), but not thereafter. (Table 2 also presents equivalent change scores in abstinent active patch participants for means of comparison).

Figure 1 presents the means for four withdrawal items and the total score over the 4 treatment weeks for both active and placebo groups. In order to gauge the impact of tobacco withdrawal, t-tests were used to compare mean scores for each post-cessation week with the baseline value. These tests revealed that five of the

Table 2 Mean changes in symptom ratings (first week post-quit – baseline) among abstinent placebo ($n = 78$) and active ($n = 91$) patch participants

Symptom	Placebo mean difference	*t*-Test value	Active mean difference	*t*-Test value
Craving for cigarettes	0.22 (0.12)[a]	1.76[b]	−0.03 (0.11)	−0.28[b]
Irritability/ frustration/anger	1.00 (0.11)	9.24**	0.49 (0.11)	4.47[d]
Anxiety	0.81 (0.10)	7.80[d]	0.36 (0.11)	3.25[c]
Difficulty concentrating	1.12 (0.12)	9.34[d]	0.63 (0.09)	7.07[d]
Restlessness	0.95 (0.12)	7.94[d]	0.72 (0.10)	7.02[d]
Increased appetite	1.28 (0.12)	10.43[d]	0.97 (0.10)	9.33[d]
Disrupted sleep	1.03 (0.12)	8.45[d]	1.12 (0.12)	9.22[d]
Depression	0.62 (0.11)	5.43[d]	0.43 (0.09)	4.77[d]
Impatience	0.84 (0.12)	7.25[d]	0.51 (0.10)	5.12[d]
Total score	0.89 (0.09)	10.28[d]	0.59 (0.08)	7.63[d]

[a] Standard errors in parentheses
[b] n.s. ($P > 0.05$)
[c] Student's t at $P < 0.01$
[d] Student's t at $P < 0.0001$

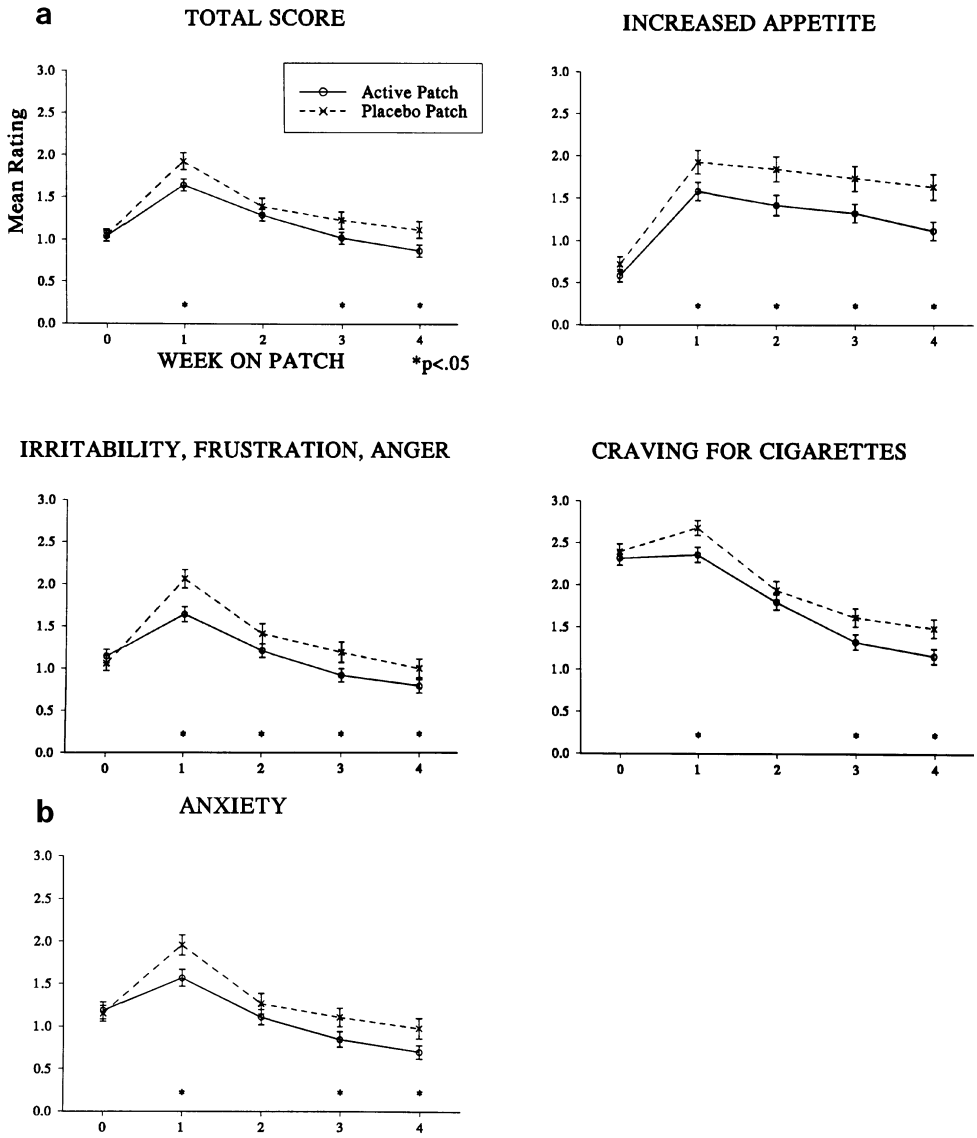

Fig. 1a,b Weekly mean self-reported withdrawal symptoms (plus SEM bars) in participants receiving active ($n = 105$) and placebo ($n = 106$) patch treatment. Symptoms were rated on a scale of 0 (none) to 4 (severe)

symptoms and the total score had returned to baseline levels by the end of treatment, while two withdrawal symptoms remained significantly elevated: increased appetite ($t = 6.74$, $P < 0.0001$) and disturbed sleep ($t = 4.63$, $P < 0.0001$). Craving for cigarettes ($t = -7.01$, $P < 0.0001$) and anxiety ($t = -2.11$, $P < 0.05$) had declined below baseline by the end of treatment.

Effect of transdermal nicotine replacement on withdrawal symptoms

Analyses of nicotine replacement effects on withdrawal symptoms were conducted with only abstinent participants (i.e., those participants whose ratings were not contaminated with concomitant smoking). The active nicotine patch reduced the severity of withdrawal symptoms. Expressed as a mean composite score of the nine MNWS items, abstinent participants wearing active patches had significantly lower symptom scores in weeks 1, 3 and 4 [Fs (1/159/139 and /135) = 8.00, 4.14, and 5.63, Ps < 0.01, 0.05, and 0.05, respectively]. Figure 1 displays the mean composite score over the 4-week treatment period. There were no consistent differences observed as a function of site or FTND factors in the ANCOVA model.

Examination of the nine individual withdrawal items revealed differences in the nature of the patch effect. Figure 1 presents weekly mean withdrawal ratings for participants receiving active and placebo patch treatment, grouped by individual item. The impact of the active patch on withdrawal symptoms varied considerably. For instance, active patch treatment significantly reduced irritability/frustration/anger [Fs (1/159/144/139 and /135) = 4.00–12.16, Ps < 0.05], and anxiety [Fs (1/159/139 and /135) = 10.17–4.56, Ps < 0.05] across all 4 treatment weeks. Some items showed significant differences only in the first week of treatment (e.g., difficulty concentrating, impatience), while others showed no reliable differences between active and placebo treatment across the study (e.g., restlessness, disrupted sleep, depressed mood). Active treatment also reduced craving for cigarettes [Fs (1/159/139 and /135) = 4.44–7.03, $P < 0.05$] in 3 of the 4 treatment weeks among participants receiving the active patch.

A particularly striking effect of active patch treatment was observed with the symptom of increased appetite (Fig. 1). Placebo participants reported a greater increase in appetite, and this divergence actually increased over the 4 weeks of treatment [Fs (1/159/144/139 and /135) = 4.25–7.59, Ps < 0.05]. This was also reflected in participants' weights. Average weights in the active patch group increased from 78.01 to 79.86 kg (an increase of 1.85 kg) from baseline to end of treatment, while the placebo patch group mean increased from 76.98 to 79.86 kg (an increase of 2.88 kg) during the same period (F[1,144) = 12.47, $P < 0.001$].

Another way to examine the impact of nicotine patch therapy is to measure the duration of withdrawal symptom elevation above baseline in both active and placebo patch groups. Table 3 depicts the number of weeks that withdrawal symptoms remained elevated over baseline (pre-cessation) levels for the majority of abstinent participants in each group. This table reveals that for most participants in each group, withdrawal symptom severity had dropped below pre-cessation levels by the third week post-cessation. Active patch participants showed more rapid declines than did placebo participants for the symptoms of craving, depression, and restlessness, as well as for the total score on the withdrawal scale.

Table 3 Treatment week at which > = 51% of participants reported a post-cessation withdrawal severity rating less than or equal to pre-cessation ratings

Withdrawal item	Active patch (n = 105)	Placebo patch (n = 106)
Irritability/frustration/anger	3	3
Anxiety	2	2
Craving for cigarettes	1	2
Depression	2	3
Increased appetite	>4	>4
Impatience	3	3
Difficulty concentrating	3	3
Disrupted sleep	>4	>4
Restlessness	3	4
Total score	3	4

There were no significant correlations between individual MNWS items or the global composite score and cotinine level expressed as either the absolute cotinine level after 1 week of patch therapy or the percent replacement (cotinine at visit 3/cotinine at visit 1).

Discussion

This research revealed that nicotine withdrawal (revealed by significant increases over baseline ratings) produced the following symptoms: irritability/frustration/anger, anxiety, difficulty concentrating, restlessness, increased appetite, sleep disruption, depression, impatience, and weight gain. Craving for cigarettes also increased, but the increase was short-lived, lasting only 3 days after withdrawal. The tobacco withdrawal syndrome was relatively brief for most smokers, with most symptoms decreasing below baseline within 1–3 weeks of quitting smoking. Only increased appetite, sleep disruption, and weight gain remained significantly elevated 1 month after quitting. In essence, affective or mood disturbance decreased while physical symptoms persisted.

Nicotine replacement therapy via the transdermal patch significantly attenuated the tobacco withdrawal symptoms of craving for cigarettes, anxiety, and irritability/frustration/anger over the 4 weeks of the study in comparison to a placebo patch. The nicotine patch also reduced ratings of impatience and difficulty concentrating, but only during the first week of quitting. Moreover, the active nicotine patch resulted in significantly lower appetite ratings and significantly less weight gain over the first month post-quit.

The value of these findings rests, in part, on our success in producing high levels of abstinence. Studies supplying data on abstinence typically report that a very

large percentage of participants smoke during the withdrawal period (e.g., 74% smoking within 2 weeks; Hughes et al. 1991). Similarly, studies attempting to characterize the effect of the nicotine patch on withdrawal typically exclude over half of their placebo participants from analyses due to smoking. For example, Levin et al. (1994) reported data on only 35% of placebo participants in the first week of withdrawal, and on only 16% of such participants in the fourth week of withdrawal. Other studies have also had significant smoking rates among placebo participants (Rose et al. 1990; TNSG, 1991; Fiore et al. 1994a). Therefore, while 39% of placebo participants in the present study had smoked at least one cigarette by the fourth week post-quit, the abstinence rates obtained were nevertheless quite high *relative* to other withdrawal studies conducted in outpatient settings [some studies have achieved higher abstinence rates in inpatient settings (Hatsukami et al. 1984) that may influence withdrawal ratings due to the absence of usual smoking cues, altered stress levels, etc].

Characterization of the tobacco withdrawal syndrome

Because the present study was unusually successful in producing abstinence and subject retention, it is important to compare its results with previous research directed at the same issues. For the most part, the present research replicated the results of earlier studies that characterized the tobacco withdrawal syndrome (Hatsukami et al. 1984; Hughes and Hatsukami 1986; Hughes et al. 1991; Hughes 1992). As with much of the earlier work, the symptoms of irritability/frustration/anger, anxiety, difficulty concentrating, restlessness, increased appetite/hunger, disrupted sleep, and impatience were all elevated due to tobacco withdrawal. While the absolute magnitude of the changes in withdrawal scores are small (Table 2), they are similar to those reported in the studies cited above. Two findings of the current research are particularly noteworthy, however. First, self-reports of depression were significantly elevated during the post-cessation period (see Table 3). Several prominent studies on tobacco withdrawal did not report data on depression (Hughes and Hatsukami 1986; Hughes et al. 1991), and other research showed that self-reports of depression did not increase following tobacco cessation (Hughes 1992). The current research suggests that depression severity is a sensitive index of tobacco withdrawal and does belong among the DSM-IV nicotine withdrawal criteria; it similarly supports the inclusion of impatience and disrupted sleep among those same criteria (Hughes 1994).

The second notable finding is that craving self-reports were significantly elevated in the immediate post-cessation period. The current diagnostic criteria for nicotine withdrawal do not include craving. In part, this reflects the fact that some previous studies of withdrawal did not find craving to be significantly elevated over baseline levels (Hughes 1992). The present data, and the data of other studies (e.g., Hughes et al. 1991; Tonnesen et al. 1991; Zinser et al. 1992; Tiffany 1994), suggest that withdrawal elevates craving reliably, but the effect is short-lived and follows a timecourse that is different from other nicotine withdrawal symptoms.

Other reasons have been offered for removing craving from the list of withdrawal symptoms (Hughes 1994). For instance, some research has failed to show evidence that nicotine administration reduces post-cessation craving (Hughes and Hatsukami 1986) and other research has shown that craving can be affected by nonpharmacological factors such as contextual cues (Baker et al. 1987). However, there is now overwhelming evidence that nicotine administration via transdermal patch significantly attenuates withdrawal-induced craving (Abelin et al. 1989; Fiore et al. 1994a; Levin et al. 1994; Richmond et al. 1994; Stapleton et al. 1995). Moreover, all of the withdrawal symptoms (difficulty concentrating, irritability, etc.) can be influenced by nonpharmacologic factors. Some confusion regarding the meaning of craving may arise from the fact that it is influenced by pharmacologic and nonpharmacologic events other than withdrawal (Baker et al. 1987), but this is also true of other withdrawal symptoms.

Characterizing the effects of transdermal nicotine

This research replicated many previous findings in that transdermal nicotine reduced a host of nicotine withdrawal symptoms: craving, anger/irritability/frustration, anxiety, impatience, and difficulty concentrating (Daughton et al. 1991; TNSG 1991; Sachs et al. 1993; Fiore et al. 1994a; Richmond et al. 1994; Stapelton et al. 1995). However, much of the earlier research did not examine the impact of the patch on individual withdrawal symptoms.

The emphasis of this study on individual withdrawal symptoms revealed the impact of the patch on hunger ratings and weight. Although there have been reports of diminished increase in hunger among participants using active patches (Levin et al. 1994), a more common finding has been no difference (Rose et al. 1990; Sachs et al. 1993; Westman et al. 1993; Fiore et al. 1994a). Failures to detect differences in previous studies may have been due to decreased statistical power caused by exclusion of smoking participants, or contamination of nicotine replacement effects due to inclusion of such participants (in the present study, the weight effect disappeared if nonabstinent participants were included in the analyses). Fear of weight gain following smoking cessation may cause some smokers to avoid quitting or provoke a relapse (Klesges et al. 1988). The ability of the patch to reduce feelings of hunger

and delay weight gain may encourage some smokers to try to quit, and may reduce relapse.

The timecourse of withdrawal symptoms presented in Table 3 may also have practical or clinical utility. First, it shows that the majority of smokers will experience relief from total withdrawal symptoms about a week earlier if they use the nicotine patch. Second, it agrees with earlier suggestions that withdrawal symptoms differ greatly in their course (Hughes 1994). Most symptoms decline steadily to below baseline levels in 2–3 weeks post-cessation. Others symptoms such as hunger and sleep disturbance persist for at least a month. Information on the timecourse of particular symptoms, and the impact of patch therapy on those symptoms, may be helpful in counseling.

Withdrawal severity and measures of dependence

This research agrees with some earlier findings in that withdrawal severity was unrelated to putative markers of nicotine dependence such as the FTND and pre-cessation cotinine levels (Hughes and Hatsukami 1986; Hughes et al. 1991; Hughes 1992). Such failures to find a relation between widely used dependence indices and withdrawal severity suggest that the concept of dependence, or its assessment, should be reappraised. Such a reappraisal might entail the systematic comparison of positive (West and Russell 1985) and negative reports.

Summary and conclusions

The clinical implications of this study, along with other studies (Fiore et al. 1994b; Orleans et al. 1994), are notable. First, for most smokers, nicotine withdrawal symptoms are brief, declining to below baseline levels within 2–3 weeks after individuals quit smoking. Second, the nicotine patch is effective in reducing nicotine withdrawal symptoms. In fact, compared to baseline levels in the first week using active patches, participants reported less craving, less anger/frustration/irritability, less anxiety, and less impatience than they reported prior to quitting [$ts(85) = 2.04–9.04$, $Ps < = 0.05$]. Third, the nicotine patch reduced both hunger and weight gain among participants who were successful at quitting. On average, active patch participants gained only 1.85 kg over the first month post-quit, compared to 2.88 kg for individuals on placebo patch. The effectiveness of the nicotine patch in reducing withdrawal symptoms and weight gain could be used to encourage smokers to make quit attempts, as smokers list withdrawal symptoms and fear of weight gain (Klesges et al. 1988) as principal impediments to making quit attempts. Finally, the results supported the inclusion of craving, depression, impatience, and sleep disturbance as criteria for nicotine withdrawal.

Acknowledgements The authors wish to thank the following persons for their invaluable assistance in the conduct of this research: Susan Kenford, Douglas Keehn, Valerie Stromquist, Donald Lynam, Richard Bauer, Kathy Longley, Helen Roemhild-Wilke, Pam Weber, and Gayl Martin. This research was supported by a grant from CIBA-GEIGY Corporation, Summit, N.J.

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