Psychopharmacology (2006) 184: 637–644
DOI 10.1007/s00213-005-0184-3

ORIGINAL INVESTIGATION

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Reduction of abstinence-induced withdrawal and craving using high-dose nicotine replacement therapy

Received: 2 January 2005 / Accepted: 27 August 2005 / Published online: 1 November 2005

Abstract *Rationale:* Decreasing withdrawal and craving during smoking cessation is a major aim of cessation medications. Prior studies have shown that Nicotine Replacement Therapy (NRT) decreases withdrawal symptom severity but have relied on retrospective reports and lacked robust measures of baseline symptoms or symptoms during unmedicated abstinence. *Objectives and methods:* We tested the effect of high-dose (35 mg) nicotine patch on withdrawal and craving during abstinence using real-time assessment with electronic diaries during ad libitum smoking, a brief period of experimentally directed trial abstinence, and the first 3 days of cessation. Subjects were 324 smokers randomized to high-dose nicotine patches or placebo. *Results:* Treatment with active patches reduced withdrawal and craving during cessation and completely eliminated deprivation-related changes in affect or concentration. *Conclusion:* High-dose NRT reduces withdrawal symptoms and craving and can eliminate some symptoms entirely.

Keywords Transdermal nicotine replacement · Withdrawal · Smoking cessation

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Introduction

For a nicotine-dependent smoker, abstinence results in nicotine withdrawal. The nicotine withdrawal syndrome (APA 1994; Hughes and Hatsukami 1986) includes irritability, difficulty concentrating, and restlessness; craving is also observed. These symptoms can appear within 2 h after the last use of tobacco, usually peak between 24 and 48 h after cessation, and last from a few days to a few weeks (Hughes et al. 1990). Nicotine craving and withdrawal symptoms contribute to smoking cessation failure (West et al. 1989; Piasecki et al. 2000; Shiffman et al. 1997a; Killen and Fortmann 1997; cf. Patten and Martin 1996). Accordingly, a major aim of cessation treatments such as Nicotine Replacement Therapy (NRT) is to reduce the severity of craving and withdrawal (Jarvik and Henningfield 1993). NRT reduces withdrawal (Hughes et al. 1989) and craving (Rose et al. 1985; TNSG 1991), but it has not been clear whether NRT can completely eliminate symptoms, which could account for its imperfect efficacy.

Existing studies of NRT and withdrawal relief have several limitations. First, clinical studies of NRT have relied on retrospective recall of symptoms, which are likely to be biased cognitive processes in recall (Hammersley 1994): for example, recall tends to be unduly affected by peak symptom severity (Redelmeier and Kahneman 1996), which will tend to exaggerate symptom severity. These biases operate even over short periods (Redelmeier and Kahneman 1996) and can therefore infect daily diaries. Further, paper diaries are often filled out retrospectively or in batches, which can reintroduce and even aggravate biases (Stone et al. 2002). In contrast, we present data collected by an electronic diary (ED) that collected data in

real time and sampled subjects' experiences throughout the day via Ecological Momentary Assessment (EMA; Stone and Shiffman 1994), which eliminates recall bias in self-reports. Subjects were not asked to recall past experience but only to report their current momentary state, which was sampled repeatedly throughout the day to characterize their condition.

A further limitation of prior studies is the lack of a basis for estimating the degree of symptom reduction for individuals—i.e., one does not know how severe symptoms might have been had the smoker abstained without NRT. In this study, we compare symptoms experienced while on NRT (and placebo) with those experienced during a prior unmedicated abstinence period. In this way, we are able to estimate the level of withdrawal a smoker would have encountered had they not been on NRT and thus more accurately quantify the reduction in symptom severity due to NRT.

Finally, studies have typically lacked robust estimates of baseline symptom intensity. Because nicotine withdrawal is marked by affective disturbances that resemble normal variations in mood, an accurate measure of baseline levels is essential to characterize withdrawal severity during abstinence and to assess when symptoms have subsided. This study investigates how much treatment with high-dose NRT decreases withdrawal and craving in abstinence. We used high-dose NRT (35 mg patches) because authors have expressed concern that currently approved doses (21 mg) may be too low for some smokers (e.g., Dale et al. 1995; Killen et al. 1999). We assessed whether NRT had the potential not only to reduce but also eliminate withdrawal symptoms.

Methods

Subjects

Subjects (n=324) were cigarette smokers recruited via advertising and fliers. Inclusion criteria were as follows: being between the ages of 21 and 65, smoking 15 or more cigarettes per day for at least 5 years, good health, and high motivation and confidence to quit smoking. Exclusion criteria were the following: regular use of noncigarette forms of tobacco, weight less than 110 lb, specific medical conditions that might interact with NRT use (e.g., uncontrolled hypertension), history of recent alcohol/drug abuse or mental illness, and current or recent use of cessation medications. Women who were pregnant, breast-feeding, or planning to become pregnant were also excluded.

Fifty-two percent of the subjects were women, and 85% were white. Subjects had a mean age of 39.34 years (SD=9.19), had been smoking for a mean of 21.95 years (SD=9.42), and smoked a mean of 24.29 cigarettes per day (SD=8.89). Subjects reported a mean of 4.01 attempts to quit smoking (SD=4.38) and had a mean score on the Fagerstrom Test of Nicotine Dependence (Heatherton et al. 1986) of 5.96 (SD=1.95). One hundred eighty-eight (58%) subjects were randomized to receive Active NRT, and 136 (42%) were randomized to receive placebo patches.

Procedure

Most of the methods for this study are described in greater detail in Shiffman et al. (in press). After providing informed consent, subjects used EDs to monitor their smoking, affect, and activities for 2 weeks prior to cessation. During the baseline period, subjects underwent a period of brief trial abstinence (TA), abstaining for 5 h, starting upon waking on day 9 of baseline (after overnight abstinence). EDs continued to monitor subjects' symptoms and craving through randomly scheduled assessments during TA. After TA, subjects resumed ad libitum smoking. On a designated quit day (day 1) 17 days after the start of monitoring, subjects were randomized to start using active or placebo patches and instructed to quit smoking completely. Assessments via EDs continued for 6 weeks after the quit day, during which time subjects continued to provide information about their affect, activities, and smoking.

Treatment

Subjects were randomized to treatment with 35 mg transdermal nicotine or Placebo within strata defined by smoking rate at entry (split at 20 cigarettes/day) and ED-monitored baseline craving intensity (split at 5.8 on a 10-point scale). By design, 30% more subjects were randomized to active patches, as compared with placebo patches (expecting that this would yield equal numbers of lapse events in the two groups). For the first 4 weeks of treatment, all subjects wore two patches, 22 and 15 cm^2, corresponding to NicoDerm CQ (GlaxoSmithKline Consumer Healthcare) 21- and 14-mg patches; for Placebo subjects, both patches were placebos.

Momentary assessments

Subjects were required to carry the ED with them throughout the waking day and to make an entry immediately after they smoked. In addition, ED prompted subjects randomly throughout the waking day for additional assessments. In both cases, subjects reported their smoking craving and affect (see below). This approach was similar to that used in previous EMA smoking studies (Shiffman et al. 2000a; Shiffman et al. 1997b).

Withdrawal and craving assessment The ED administered items designed to assess the intensity of subjects' craving and withdrawal. Assessments were completed on-screen, one item at a time. Craving was measured with a single 0- to 10-point item (Shiffman et al. 1997a). Mood ratings on a 0–10 scale were made for adjectives derived from the circumplex model of affect (Russell 1980), as well as items

relevant to nicotine withdrawal. Responses were used to form five scores: Positive Affect (items: happy, content, calm; Cronbach α=0.80); Negative Affect (frustrated, irritable, miserable, sad, worried; α=0.85); Arousal (reverse coded: sleepy, tired; α=0.95); Attention Disturbance (spacey, hard to concentrate; α=0.60); and Restlessness (jittery, restless, fidgety; α=0.84). Positive Affect and Negative Affect were standardized factor scores (mean=0, SD=1). Arousal, Attention Disturbance, and Restlessness were calculated as a mean of the raw item scores.

Analysis time points

Baseline ad libitum smoking (BSL1 and BSL2) Data collected from random prompts and cigarette records during days 4–7 were used as the first baseline period (BSL1), whereas those collected during days 11–14 were used as the second baseline period (BSL2). (We skipped days 8 and 10 to avoid any anticipation or carryover effects from TA on day 9.) Subjects completed a mean of 5.21 (2.04) randomly scheduled assessments each baseline day. Some analyses were based on the first five waking hours of the day, during which a mean of 1.90 (SD=0.88) random prompts were completed. On day 8 of baseline, a saliva sample was collected and analyzed for cotinine concentrations.

Trial abstinence (TA) Subjects were instructed to abstain from smoking (without the aid of any medication) for 5 h after waking on day 9, during which ED used random prompts to assess withdrawal and craving. The frequency of random prompting was enhanced during TA to ensure an adequate level of sampling (mean=3.15 assessments; SD=0.96).

Quit days 1–3 (days 1–3) Subjects were instructed to quit using their assigned medication on day 17. Subjects completed a mean of 1.61 (SD=0.67) randomly prompted assessments during the first 5 h of day 17 and 5.99 (SD=1.91) prompts throughout the day. For day 2, these figures were 1.86 (SD=0.84) and 6.00 (SD=1.74), and for day 3, 1.87 (SD=0.79) and 5.73 (SD=1.66). On the evening of their first day of abstinence, after approximately 19 h of abstinence and 11 h of patch wear, subjects provided a saliva sample for cotinine analysis.

Data reduction and analysis

To be eligible for analyses, subjects must have (a) provided baseline data, (b) reported abstaining during TA, and (c) abstained from smoking for the first 5 h of their quit attempt (day 1). Additionally, subjects must have remained abstinent during each relevant assessment day to obtain withdrawal measurements uncontaminated by smoking. (However, the results were essentially unchanged when the sample included those who had smoked.) Besides analyzing symptoms throughout the day, we also analyzed symptoms in the first five waking hours of the day to allow comparisons with TA. As shown in Table 1, 217 subjects were retained [67.0%; Placebo: 124 (57.1%); Active NRT: 93 (42.9%)]. Of the 107 excluded subjects, 56 (52.3%) smoked during TA, 47 (43.9%) smoked in the first 5 h of day 1, and 4 (3.7%) did not have baseline data.

Table 1 Number and proportion of subjects included in the analysis at each time point

	Number (%) of subjects		
	NRT	Placebo	Total
Day 1 (5 h)	124 (100)	93 (100)	217 (100)
Day 1 (all day)	118 (95.2)	72 (77.4)	190 (87.6)
Day 2 (5 h)	103 (83.1)	59 (63.4)	162 (74.7)
Day 2 (all day)	94 (75.8)	47 (50.5)	141 (65.0)
Day 3 (5 h)	84 (67.7)	43 (46.2)	127 (58.5)
Day 3 (all day)	76 (61.3)	40 (43.0)	116 (53.5)

Comparisons were conducted using Generalized Estimation Equations (GEE; Zeger et al. 1988). GEE are designed to account for the autocorrelation of data in repeated-measures designs.

Results

Cotinine analysis

At baseline, the Placebo group had a mean cotinine level of 333.56 ng/ml (SD=146.75). On day 1, their mean cotinine level was 170.64 ng/ml (SD=97.60), reflecting residual cotinine from smoking the day before quitting. The NRT group had a baseline mean level of 355.87 ng/ml (SD=170.06). This rose significantly to 400.46 ng/ml (SD=155.34) by the evening of day 1 [Fig. 1; $t(113)=3.45$, $p<.001$], indicating greater than 100% nicotine replacement. The difference between Active and Placebo groups at day 1 was significant: $t(180)=10.97$, $p<.001$.

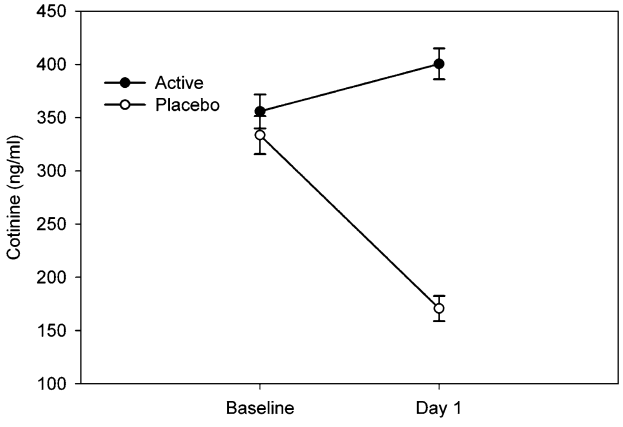

Fig. 1 Mean cotinine levels (ng/ml) at baseline and at day 1 for both the Active and Placebo groups. Standard error bars are shown

Effects of NRT on withdrawal and craving—analyses of all-day symptoms

Figure 2 displays the mean scores for the symptom measures, during the entire duration of BSL1, BSL2, days 1, 2, and 3, as well as TA. The two baseline periods did not significantly differ on Positive Affect, Negative Affect, or Restlessness (p values>.350). However, Craving and Arousal scores at BSL1 were slightly lower than BSL2 (p values<.001); Attention Disturbance score at BSL1 was

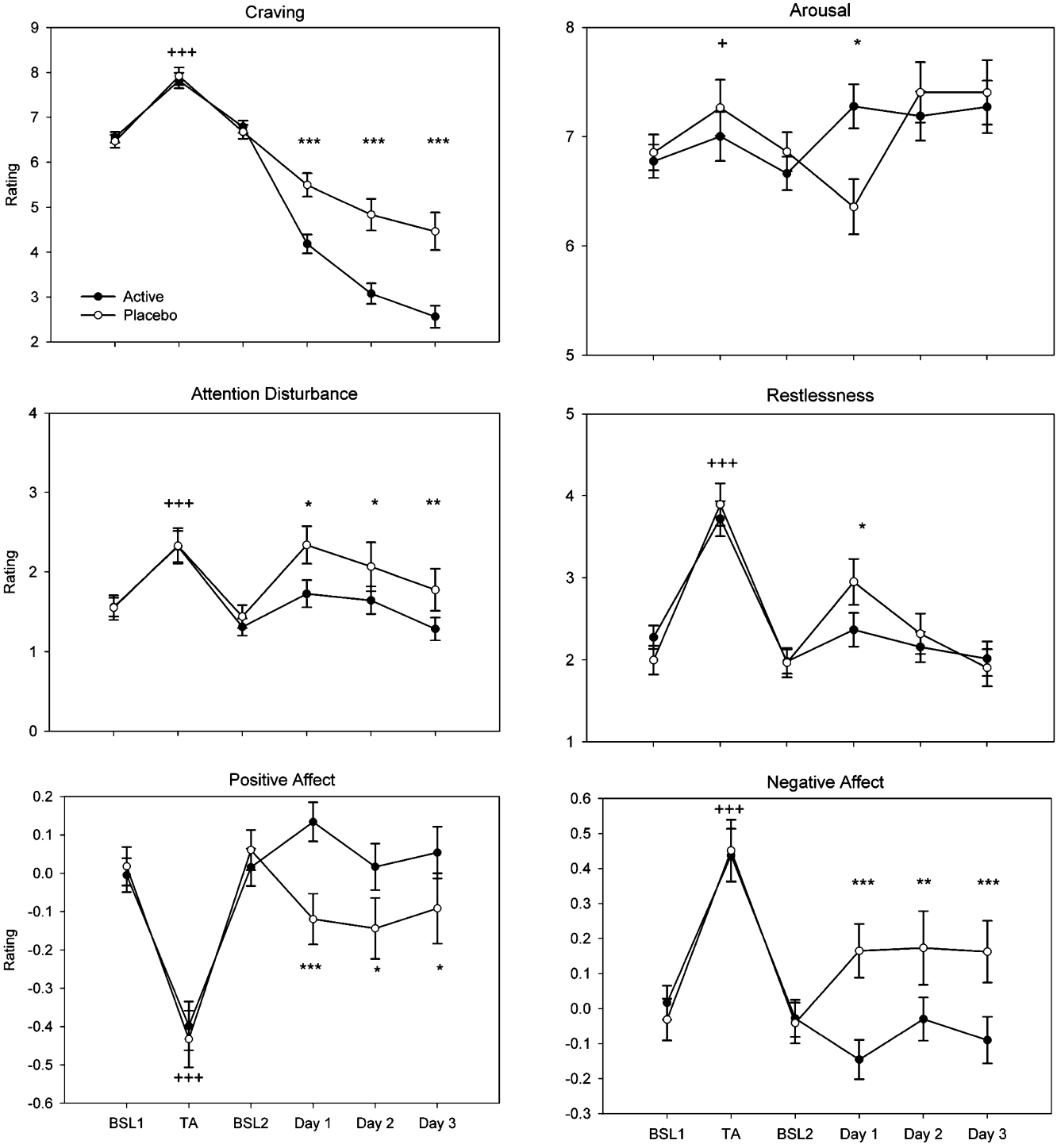

Fig. 2 Mean scores for the six withdrawal and craving variables measured during the two baseline periods (BSL1 and BSL2), the TA period, and during the first 3 days of abstinence. TA measurements were obtained only during the first five waking hours. Standard error bars are shown. *Asterisks* indicate significant differences between Active and Placebo groups (controlling for BSL1): *p<.05; **p<.01; ***p<.001. *Plus signs* indicate significant differences between BSL1 and TA periods (using only data gathered during the first five waking hours): ^{+}p<.05; ^{+++}p<.001

slightly higher than BSL2 (p<.001). We used BSL1 to represent baseline symptoms.

Without treatment (Placebo), abstinence resulted in withdrawal effects (Fig. 2), as indicated by symptom increases from BSL1 to days 1–3. On day 1, all symptoms showed significant changes from baseline (p values<.04). On day 2, Arousal, Negative Affect, and Positive Affect showed significant changes from baseline (p values<.05) but Restlessness and Attention Disturbance did not. On day 3, only Arousal and Negative Affect scores differed significantly from baseline (p values<.04). Across all 3 days, Craving scores were significantly lower than baseline (p values<.001).

Figure 2 shows that treatment with active patches markedly reduced the withdrawal effects. The effects of NRT on withdrawal severity were assessed by examining treatment group differences at days 1–3, while controlling for baseline levels. On day 1, subjects wearing the active patches (compared with those on Placebo) reported lower levels of Craving, Negative Affect, Attention Disturbance, and Restlessness and higher levels of Positive Affect and Arousal. Similar results were seen on days 2 and 3 but with no NRT effects on Arousal and Restlessness.

To test the effect of NRT on *absolute* severity of withdrawal, we compared day 1 and BSL1 scores within the Active treatment group to symptoms where the Placebo group had demonstrated significant withdrawal effects. The analysis showed that, with NRT treatment, there were no significant changes from baseline in Restlessness or Attention Disturbance scores. In addition, subjects demonstrated significantly *lower* Negative Affect and significantly *higher* Positive Affect and Arousal than during ad libitum smoking. Similar results were found when we compared levels of withdrawal and craving reported by the NRT group at days 2 and 3 to baseline levels: in no case was there a reliable increase in withdrawal symptoms.

Effects of abstinence and NRT on withdrawal and craving—analyses of the first 5 h of the day

Abstinence during TA resulted in marked changes from baseline for all six symptoms (Fig. 2). Compared with BSL1, during TA subjects reported higher Craving (p<.001), Negative Affect (p<.001), Attention Disturbance (p<.001), Arousal (p=.03), and Restlessness (p<.001) and lower Positive Affect (p<.001).

The TA period was a proxy measure of the degree of withdrawal smokers would experience if they attempted unmedicated cessation. As expected, for the Placebo group (for whom both TA and day 1 measures both represented unmedicated abstinence), TA and day 1 measures of Positive Affect, Negative Affect, Arousal, Attention Disturbance, and Restlessness correlated strongly (average r=0.57; all r values>0.53; all p values<.001). The correlation for Craving was weaker but still significant (r=0.26; p=.013). For subjects who were treated with high-dose NRT, the correlations were weaker (average r=0.45; all r values>0.29; p values<.002).

To assess the effects of NRT on withdrawal symptoms, while controlling for subjects' experiences during unmedicated abstinence, we included TA data as a covariate in the analyses of treatment group differences during the first 5 h of day 1. Including TA values added statistical control: subjects' TA scores accounted for significant variance in all symptoms (p values<.009) even when baseline data were already included in the model. Subjects on active patches reported lower Craving, Negative Affect, Attention Disturbance, and Restlessness and higher levels of Positive Affect and Arousal than those on Placebo. Similar results were seen at days 2 and 3.

Finally, to capture the degree of symptom relief provided by NRT, we compared the intensity of symptoms experienced during days 1–3 with those experienced during TA. As can be discerned in Fig. 1, on days 1, 2, and 3 of abstinence, Active NRT almost completely reversed the withdrawal effects seen in TA.

Nicotine replacement and symptom relief

On average, cotinine levels on day 1 on active patch were 25% higher than baseline levels. However, there was substantial variation, with individual values ranging from −55 to +174% (SD=45%). Cotinine levels did not significantly correlate with the level of withdrawal symptom relief (expressed as the difference between TA and BSL1 vs days 1 or 2 and BSL1) for any symptom (all p values>.2). Day 1 cotinine levels were derived from both the prior days' smoking and day 1 nicotine input from patch. To estimate the specific input from patch, we used a regression equation in the Placebo group (which had no input from patch) to model residual nicotine from the prior days' smoking and applied this to the active patch group to determine the incremental contribution from patch. Analyses using this value yielded the same results.

Discussion

Our results confirm that treatment with high-dose NRT significantly reduces withdrawal symptoms and craving resulting from smoking abstinence. While prior studies used retrospective weekly reports or falsifiable written diaries, this study relied on assessments collected in real time, multiple times per day, in subjects' real-world environments. The results confirm prior findings that NRT was effective in reducing craving and withdrawal symptoms, while further showing that high-dose NRT can eliminate symptoms altogether.

Our findings also differed in important ways from those previously reported based on retrospective methods. Most strikingly, the magnitude of symptoms reported during abstinence was smaller than typically reported, and some symptom levels had returned to baseline values after only a day or two of abstinence. The biases introduced by retrospective reporting used in prior studies might be expected to result in reports of higher intensity and to prolong the

duration of reported symptom elevations for two reasons. First, retrospective reports are unduly influenced by episodes of intense symptoms (Redelmeier and Kahneman 1996), which are commonly reported during abstinence (Shiffman et al. 1997a). Moreover, these episodic flare-ups of symptoms continue to occur even after the typical symptom level has subsided (Shiffman et al. 1997a), which may lead to the impression that symptoms continue unabated (see Shiffman et al. 1985). Secondly, retrospective reports are also influenced by the symptoms being experienced at the time of reporting (Teasdale and Fogarty 1979). Since daily summaries are typically solicited during the evening—when symptoms are at their peak (Shiffman and Jarvik 1976)—they may overestimate the actual experience over the entire day. Indeed, in this study, retrospective summary daily craving ratings collected each evening were significantly higher than the craving intensity reported in real time. Retrospectively collected data may exaggerate symptom intensity, and symptoms may be more modest and shorter lived than previously reported. Further exploration of these methodological effects, as well as of true symptom severity and duration, is needed.

We found that a 35-mg patch not only mitigated but actually eliminated any adverse change in affective tone (increased negative affect or decreased positive affect) or concentration. Importantly, because of the enhanced precision afforded by numerous assessments during each condition (>9,000 assessments), the design had good power to detect even very small changes from baseline (Cosby et al. 2003): we had 80% power to detect changes in affect only one twentieth as large as those seen during TA (i.e., 0.016 SD units). Thus, the lack of significant change from baseline suggests that symptoms had essentially been eliminated by NRT treatment.

The apparent suppression of some withdrawal symptoms may have been due to the complete nicotine replacement achieved by the 35-mg patch regimen. On average, cotinine concentrations rose by 25% at day 1, exceeding baseline levels. Our data suggest that slow infusion of nicotine can suppress some symptoms completely, despite the absence of the rapid bolus delivery of nicotine that marks cigarette smoking (Ross et al. 1991; Henningfield 1995). Bolus delivery may be most important to direct reinforcement from smoking or for the rapid relief of intense craving (Niaura et al. in press), rather than for the suppression of symptoms.

The seemingly complete suppression of symptoms by 35-mg patches is striking when considered alongside the findings on efficacy of high-dose patches. Even though NRT improved abstinence rates over placebo, 59% of our subjects treated on active patch lapsed while on active treatment (Shiffman et al. in press). Other analyses of even higher-dose patches (Dale et al. 1995) have similarly found the treatment superior to placebo and even to normal-dose patches, but still allowing substantial relapse. The question is why, if high-dose nicotine patches can completely replace baseline nicotine levels and relieve nicotine withdrawal, they still allow considerable relapse. One possibility is that, even when patch eliminates "background" or tonic symptoms, it does not protect smokers from phasic or acute responses to situational triggers that promote relapse (Shiffman et al. 1996). Tiffany et al. (2000) have documented that, even as they reduce overall background levels of craving, nicotine patches still leave smokers vulnerable to cue-induced cravings, which have been associated with smoking relapse episodes. Indeed, in this very sample, we also found that even high-dose patch did not protect smokers from cue-induced craving and did not facilitate recovery from such cue-provoked craving (Waters et al. 2004). Further, we found that vulnerability to cue-induced craving predicted subsequent relapse for smokers treated with the active high-dose patch. This suggests that the steady-state nicotine levels delivered by patch may be effective against background craving and withdrawal but leave smokers vulnerable to craving and relapse when they confront smoking cues.

Craving showed a different pattern from other symptoms. Like affective and cognitive symptoms, craving increased during TA, demonstrating its responsivity to deprivation (e.g., Maude-Griffin and Tiffany 1996; Payne et al. 1996; Teneggi et al. 2002). However, unlike other symptoms, craving dropped after quitting, even in the Placebo group; again, consistent with previous studies (Shiffman et al. 1997a; Shiffman and Jarvik 1976). Very likely, this reflects the way in which craving is influenced by perceived availability of smoking and by smoking itself. In the laboratory, craving is enhanced when smokers expect to smoke (Dols et al. 2002; Sayette et al. 2003). Quitting smoking essentially consists of a self-imposed "smoking-unavailable" condition and leads to a drop in tonic craving. Similarly, smoking itself may act as a priming stimulus that not only relieves craving acutely but also stimulates subsequent craving. Although craving decreases in abstinence, it can still be distressing (Shiffman et al. 1997a) and is an important factor in relapse (Shiffman et al. 1997a; Swan et al. 1996; West et al. 1989).

Expectations of smoking may also influence the severity of withdrawal symptoms, explaining why most symptoms were more severe during TA than on the actual quit day (analysis not presented), even for those on placebo (Fig. 2). However, the difference could also be due to the ameliorative placebo effect of wearing an inert patch or to order effects (since TA always came before the quit day). In any case, we found that symptom severity assessed during experimentally mandated unmedicated abstinence is relevant to subsequent withdrawal severity.

Our findings for subjective arousal were puzzling. Arousal increased during abstinence on TA but decreased briefly during actual quitting without NRT. Active patch protected smokers from a drop in Arousal on day 1, but this effect quickly dissipated by day 2. We know of no theory to explain this 1-day effect on arousal; it may be a chance finding. Withdrawal may not be accompanied by reliable changes in arousal, as indicated by mixed findings in the literature. Perhaps some smokers react with increased arousal while others show decreased arousal. Analyses of circadian trends in arousal, rather than mean levels, may reveal how withdrawal affects arousal.

Our findings on restlessness were surprising in a different respect. Although restlessness increased markedly during TA, it rose only modestly on the actual quit day and quickly recovered baseline levels by the second day of abstinence. The modest increases in restlessness are at odds with the finding that restlessness reliably increases during cessation (APA 1994), that nicotine patch can provide relief for restlessness (Shiffman et al. 2000b), and that restlessness is a particularly good predictor of smoking (Shiffman et al. 2002) and relapse (Shiffman et al. 1996). Better measures of restlessness may be needed to gain an understanding of this symptom.

Unlike some prior studies (e.g., Dale et al. 1995), we found no relationship between cotinine levels during treatment and observed symptom relief. Since subjects were on high-dose patches, most received adequate nicotine replacement (61% achieved at least 100% replacement at day 1), thus possibly blunting the relationship that might be observed when patch doses are lower.

This study adds to the prior literature on the effect of NRT on craving and withdrawal in several respects. First, we assessed withdrawal with real-time EMA methods rather than relying on retrospective summary measures, which can introduce bias (Hammersley 1994). Our analysis also had unusually robust controls for baseline levels of withdrawal symptoms and craving. We examined withdrawal at multiple time points before and after quitting, which allowed for a within-subject examination of NRT effects. Finally, we compared symptoms during cessation not only to symptoms during ad libitum smoking but also to symptoms experienced during a brief period of experimentally directed abstinence, allowing us to compare the severity of withdrawal experienced while on NRT (vs placebo) with unmedicated withdrawal.

At the same time, the methods used in this study had a number of limitations. First, we only examined a single dose of NRT, as compared with placebo. Accordingly, it is not clear which of the observed effects are due to the high-dose regimen and which might be seen, using these methods, even with approved doses of nicotine patch. A dose–effect curve for these effects would help establish the role of nicotine and nicotine dose in relieving symptoms. The intensive assessments used in this study could have led to reactivity, perhaps leading to more subdued symptom reports. However, studies (Hufford et al. 2002; Stone et al. 2003) have found little or no reactivity arising from EMA methods. The study was also limited by our use of a sample of relatively heavy, dependent smokers; however, these are typical for NRT studies. We studied a brief period of abstinence. While symptoms generally peak early in abstinence, we did not demonstrate whether the findings would be maintained during longer time frames. Finally, even though repeated measurements in the EMA design made for very precise estimates of symptoms, the sample sizes may have been too small to detect subtle residual elevations in symptoms.

In summary, we found that treatment with high-dose NRT significantly reduced, and in several cases completely eliminated, withdrawal symptoms and craving during smoking cessation. This raises the question of why NRT is not even more successful than it is and suggests that mechanisms other than tonic craving and withdrawal need to be considered as causes of relapse among smokers on NRT.

Acknowledgements This research was supported by Grant DA 06084 from the National Institute on Drug Abuse to Saul Shiffman. We are grateful to GlaxoSmithKline Consumer Healthcare (GSKCH) for providing nicotine and placebo patches for the study; GSKCH did not otherwise participate in the study or the paper. The authors acknowledge the assistance of Stephanie Paton and Celeste Elash in conducting this study; and Yolanda DiBucci and Qianyu Dang in manuscript preparation.

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