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Profiles in Discouragement: Two Studies of Variability in the Time Course of Smoking Withdrawal Symptoms

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Research has suggested that the time course of the smoking withdrawal syndrome is fairly invariant across smokers and that smoking withdrawal symptoms are weakly related to relapse. Withdrawal data from 2 clinical trials of the nicotine patch were analyzed to evaluate these characterizations. In both studies, patients were clustered according to the shapes of their withdrawal profiles across 8 weeks of treatment. In each study, 3 clusters with distinct temporal patterns of withdrawal symptomatology emerged. Clusters included both abstinent and lapsing patients, and patch dose was unrelated to cluster membership. Patients with "atypical" patterns of smoking withdrawal (e.g., late symptomatic elevations) were more likely to relapse than patients who showed a gradual elimination of withdrawal. Withdrawal shape, duration, and severity all contributed significantly to the prediction of relapse. Measures of negative affect closely tracked withdrawal symptoms over time within clusters. Topics for future smoking withdrawal research are discussed.

The withdrawal syndrome is a collection of characteristic symptoms or signs typically instigated by reduced intake of a dependence-producing drug following a period of sustained exposure. Most major definitions of addiction acknowledge that withdrawal symptoms are important pathognomonic signs (American Psychiatric Association, 1994; Edwards, Arif, & Hodgson, 1981). It was long axiomatic in clinical psychopharmacology that withdrawal symptoms are potent factors in the maintenance of drug dependence and in relapse to drug use (e.g., Eddy, Halbach, Isbell, & Seevers, 1965; Wikler, 1973). Although some recent models of drug motivation have deemphasized the importance of withdrawal symptoms, such models continue to afford them some role in drug relapse (e.g., Niaura et al., 1988; Vuchinich & Tucker, 1988).

Investigators have examined the impact of tobacco deprivation on dozens of behavioral, physiological, and psychological processes (for a review, see Hughes, Higgins, & Hatsukami, 1990). However, recent research has focused on a set of core symptoms for which there is evidence of reliability, validity, and clinical significance (e.g., Hughes, Gust, Skoog, Keenan, & Fenwick, 1991; Hughes & Hatsukami, 1986; Hughes, Hatsukami, Pickens, & Svikis, 1984). This syndrome includes urge/craving, irritability, difficulty concentrating, anxiety, depression/dysphoria, impatience, sleep disturbance, and hunger. Averaged across individuals, these symptoms are typically observed to increase sharply during the first week of deprivation, then decrease monotonically to values at or below baseline within 1 to 4 weeks (e.g., Cummings, Giovino, Jaen, & Emrich, 1985; Hughes, 1992). There is variability in this pattern across the different symptom types. For instance, urge/craving self-reports are unique in that they are sometimes found to be higher before cessation than after, and hunger self-report is sometimes elevated for many weeks after cessation (Hughes, 1992). However, in general, most smoking withdrawal symptoms appear to rise and fall within the 4-week period noted earlier.

Withdrawal plays a central role in conceptualizations of nicotine dependence and is often cited as the primary setting event for smoking relapse (Benowitz, 1991). Smokers themselves identify withdrawal symptoms as impediments to sustained abstinence (Cummings, Jaen, & Giovino, 1985). However, several findings challenge the presumed importance of withdrawal in the maintenance of smoking behavior. First, withdrawal is inconsistently related to both smoking relapse (e.g., Gritz, Carr, & Marcus, 1991; Hall, Havassy, & Wasserman, 1990; Kenford et al., 1994) and other indexes of nicotine dependence (Hatsukami, Hughes, & Pickens, 1985; Hughes, 1992). Second, several studies have demonstrated with withdrawal suppression, and treatment efficacy can be uncoupled (Hughes, 1993; Jorenby et al., 1995). Finally, if smoking withdrawal symptoms routinely decline 1 to 2 weeks after cessation, this suggests that withdrawal cannot account for a hallmark of addiction: the occurrence of relapse after weeks or months of abstinence (Brandon, Tiffany, Obremski, & Baker, 1990).

A New Approach to the Smoking Withdrawal Paradox

What accounts for the discrepancy between the theoretical and phenomenological prominence of withdrawal on the one

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hand and the weak and inconsistent research evidence on the other? One possibility is that conventional wisdom has fostered the use of data-analytic models that ignore important dimensions of the smoking withdrawal syndrome.

Current views of the smoking withdrawal syndrome have been shaped, no doubt, by earlier research on the withdrawal syndromes of other drugs. This research has identified characteristic withdrawal time courses in which symptoms wax and wane over temporally discrete intervals (e.g., Sellers & Kalant, 1982). The assumption of a prototypic temporal pattern of withdrawal has led to a common set of withdrawal assessment practices, namely, predicting outcome from cross-sectional measures of withdrawal distress or averaging ratings across individuals to describe the time course of various withdrawal symptoms (e.g., Cummings, Giovino, et al., 1985; Jorenby et al., 1996). By their very nature, these practices cannot reflect idiosyncratic patterns of withdrawal over time.

The present research is based on theoretical accounts of addiction that predict substantial heterogeneity in patterns of withdrawal across time. One such account suggests that withdrawal is an affective phenomenon (e.g., Baker, Morse, & Sherman, 1987; also see Tomkins, 1968). According to this view, the critical substratum of drug dependence is the impact of drug, drug deprivation, and drug cues on affective processing (e.g., the extent to which drug deprivation yields negative affect; Baker et al., 1987). In effect, drug dependence is defined in terms of the relation between drug use and a matrix of affective consequences.

The above perspective is supported by compelling evidence of a tight affect–addiction link (Brandon, 1994): For example, self-reports of smoking urge are consistently correlated with affect (Baker et al., 1987; Zinser, Baker, Sherman, & Cannon, 1992), negative affect is a potent setting event for relapse (Brandon et al., 1990; Shiffman, 1982), smoking status and smoking rate are both directly related to a positive history of affective disorder (e.g., Anda et al., 1990), and so on.

If affect constitutes the motivational core of withdrawal, this means that the withdrawal substratum is persistent, and its manifestation may be influenced by the host of pharmacologic and nonpharmacologic events that influence affect. Affective responses might be primed or modulated by falling drug levels, but they may also reflect the influences of other events (e.g., stressors) that are temporally remote from drug removal. If negative affect constitutes the motivational core of withdrawal, negative affect elicited by diverse instigators may activate drug motivational responses and be perceived or labeled as withdrawal. Whether such affective phenomena should be labeled withdrawal is an epistemic issue that is discussed subsequently.

A second line of theory, one emphasizing the associative elicitation of withdrawal responses (e.g., Siegel, 1983; Wikler, 1973), also suggests that the course of withdrawal should be highly variable. Such associative models predict that withdrawal should wax and wane in response to the presence or absence of reliable signals of either drug or drug withdrawal. These models, like the affect models of addiction, enjoy considerable empirical support. Numerous studies attest to the associative elicitation of responses that resemble withdrawal symptoms (Goldberg & Schuster, 1970; O'Brien, Testa, O'Brien, Brady, & Wells, 1977). In sum, a variety of theoretical perspectives and research literatures hint that smoking withdrawal may have a heterogeneous course.

In this article, we used withdrawal data from two clinical trials of the nicotine patch to evaluate individual differences in withdrawal trajectories. We hypothesized that a comprehensive assessment of the vicissitudes of smoking withdrawal would reveal the previously elusive links between withdrawal and indexes of smoking motivation (e.g., relapse). Specifically, we were interested in assessing whether the duration (number of days withdrawal symptoms were more severe than baseline levels) and the shape (the configuration of peaks and valleys in withdrawal) would improve the prediction of smoking relapse over and above traditional severity measures. Novelist William S. Burroughs (1957/1992) observed the motivational significance of prolonged withdrawal:

> When the addict seeks cure, he has, in most cases, already experienced withdrawal symptoms many times. He expects an unpleasant ordeal and he is prepared to endure it. But if the pain of withdrawal is spread over two months instead of ten days, he may not be able to endure it. It is not the intensity but the duration of pain that breaks the will to resist. (p. 245)

Study 1

The study of withdrawal dynamics entails a shift from the examination of withdrawal scores to a consideration of profiles of withdrawal symptoms across time. In Study 1, we examined withdrawal profiles from patients enrolled in a clinical trial of two nicotine patch doses. Patients who resembled one another in terms of profile shape were grouped together with cluster analysis.

We expected to find at least two groups of patients with distinctive withdrawal profiles. We hypothesized that for some smokers, drug removal (smoking cessation) would be the chief determinant of withdrawal symptoms. These smokers would be expected to display the prototypical withdrawal pattern. However, we predicted that for other smokers, withdrawal symptoms would be strongly influenced by events not temporally linked to cessation. Therefore, we expected to find one or more groups of patients with atypical withdrawal patterns that reflect significant withdrawal distress late in the postcessation epoch. Consistent with many theories, we believed that withdrawal motivates drug use and relapse; it may inflate the incentive value of the drug, serve as a setting event for negative reinforcement by drug use, and so on (e.g., Stewart, deWit, & Eikelboom, 1984; Wise, 1988). We believed that atypical withdrawal would be especially associated with relapse as such patterns might produce fatigue, discouragement, and hopelessness or might surprise individuals and therefore subvert effective coping. Also, because we hypothesized that negative affective processes would be responsible for the heterogeneity of withdrawal patterns, we explored the resemblance between profiles of postcessation negative affect per se and withdrawal profiles within each group. Finally, we compared the groups on a number of baseline characteristics, including measures of nicotine dependence.

Method

Patients

Study 1 was based on withdrawal data collected from patients (N = 504) enrolled in a randomized, double-blind, dual-site (Madison, WI,

and Rochester, MN) clinical trial designed to compare the efficacy of 44-mg and 22-mg nicotine patches when each was paired with one of three separate counseling treatments (Jorenby et al., 1995). Inclusion criteria were the following: (a) age ≥ 20 years; (b) history of smoking ≥ 15 cigarettes per day for at least one year; (c) good health, verified by medical exam and medical history; and (d) only one member per household enrolled in the study. Exclusion criteria were (a) cardiovascular disease, (b) pregnancy or lactation, (c) use of nonstudy nicotine replacement or tobacco products other than cigarettes, (d) chronic dermatologic disorders, and (e) use of an investigational drug within 30 days of the start of the study.

To be included in the analyses reported here, patients had to have completed at least 50 (91%) of the 55 daily withdrawal rating scales (see below). Inclusion in the analyses was not limited to patients who were completely abstinent during the treatment period.

Included and excluded patients were highly nicotine dependent, had smoked for many years, and had tried to quit unsuccessfully numerous times in the past. Excluded patients were significantly less likely to have been counted as abstinent at both the end of treatment, $\chi^2(1, N = 504) = 97.95$, $p < .00001$, and at 6-month follow-up, $\chi^2(1, N = 504) = 31.09$, $p < .00001$, and were much more likely to have dropped out of the trial before completing the entire protocol, $\chi^2(1, N = 504) = 36.89$, $p < .00001$. Excluded patients were also significantly younger than the included patients, $t(500) = 3.60$, $p < .001$, and reported significantly more past quit attempts than the included patients, $t(475) = 2.06$, $p < .05$.

Dosing Regimens

All patients were randomly assigned to one of the two patch doses. Patients assigned to the 44-mg group wore two 22-mg patches per day for the first 4 weeks, one 22-mg patch per day for the following 2 weeks, and one 11-mg patch per day for the final 2 weeks of the trial. Patients assigned to the 22-mg group wore one 22-mg patch and one placebo patch each day for the first 4 weeks of the trial, one 22-mg patch per day for the following 2 weeks, and one 11-mg patch per day for the final 2 weeks of the trial. Study personnel and participants were unaware of dose assignment.

Counseling

Within each dose group, patients were randomized into one of three counseling conditions. One third of the patients received no explicit counseling from study staff (but did report to the study center on a weekly basis for data collection), one third received a brief (15–20 min/session) individual counseling session during each of the 8 weeks of patch treatment, and the remainder received an intensive group counseling session (1 hr/session) each week of patch treatment.

Measures

Smoking withdrawal symptoms were assessed with a diary that contained a modification of the Minnesota Nicotine Withdrawal Scale (MNWS; Hughes & Hatsukami, 1986). At each weekly study visit, patients handed in completed MNWS forms for each day of the previous week and received additional blank MNWS forms as needed. Patients were asked to complete the MNWS each day, starting on the first day the patient attempted to quit smoking, and then continuing for an additional 54 consecutive days. The MNWS asked respondents to rate the severity of the following eight symptoms on a 4-point scale (0 = *not present*, 1 = *slight*, 2 = *mild*, 3 = *moderate*, and 4 = *severe*): desire to smoke, anger/irritability/frustration, anxiety/nervousness, difficulty concentrating, impatience/restlessness, hunger, awakening at night, and depression. These daily ratings were averaged across symptoms. A profile of global withdrawal severity was constructed for each patient. These profiles were the basis for all classification analyses (see below).[1]

Each diary page also asked patients to record the number of cigarettes they smoked that day. Weekly carbon monoxide (CO) breath tests were used to confirm patients' self-reports of abstinence.

At baseline, nicotine dependence was assessed with the Fagerstrom Tolerance Questionnaire (FTQ; Fagerstrom, 1978), and a brief demographic questionnaire was administered. Patients were asked to rate their mood at each of the eight weekly visits using the state version of the Positive and Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, 1988).

Missing Values

Only 197 patients (39%) completed the MNWS on all 55 days. Cluster-analytic classification requires that patients have a complete set of 55 withdrawal ratings. To maximize the generalizability of our findings and statistical power in our prediction analyses, we replaced missing values for patients who completed 50 or more withdrawal ratings. Of 151 patients meeting this criterion, the average number of missing ratings was 1.9. Missing ratings were replaced with the mean of ratings from the days adjacent to each missing day. Where ratings were missing for 2 or more consecutive days, a linear trend was assumed between the ratings on either side of the missing values. This interpolation was not possible for 11 patients, as they were missing either the first several ratings or the last several ratings. These patients were dropped from the analyses. Missing values were replaced for a total of 140 patients, yielding a total sample size of 337 for analysis.[2]

Data Analyses

Analysis of profiles: Conceptual issues and terminology. This investigation was primarily concerned with identifying and examining groups of patients who differed from one another in terms of the shape of their withdrawal symptom profiles after smoking cessation. Therefore, withdrawal scores were standardized within each case to remove the elevation and scatter (Cronbach & Gleser, 1953) from withdrawal profiles before clustering. This was done in preference to clustering raw profiles or profiles with only scatter removed because we believed that classification based on shape alone would constitute both a more stringent and more interpretable test of our hypotheses (Nunnally, 1962).

For various analytic and data presentation purposes (e.g., characterization of each cluster), it was useful to synthesize information from the profiles of related individuals into a single "group" profile. This was accomplished by averaging ratings from each time point across individu-

[1] Although previous research in this area has used ratings of individual symptoms in addition to global severity to predict outcome, all analyses reported in this article are based on global severity scores (severity averaged across symptoms). This strategy was selected because a series of principal-components analyses using symptom ratings collected at a variety of time points all suggested that a single dimension was sufficient to describe the withdrawal ratings provided by our patients. Coefficient alpha for the eight-item scale was .81.

[2] Although this data replacement procedure could conceivably bias the patterns of withdrawal symptoms that are recoverable from the data, it seems unlikely for two reasons. First, there was no obvious pattern to the missing values. For instance, missing values appeared to be distributed randomly across days, and it did not seem to be the case that missing withdrawal ratings coincided with smoking lapses. Second, our requirement that patients complete at least 50 ratings ensures that at least 91% of each patient's profile is based on his or her own report. In fact, among analyzed patients for whom missing values were replaced, the average number of valid ratings was 53, or 96%.

als belonging to the same cluster and constructing a profile on the basis of these means. Following Haggard, Chapman, Isaacs, and Dickman (1959), we use the term *criterion profile* to distinguish these profiles constructed from group means from the profiles of individuals.

In this initial investigation, a simple product–moment correlation between temporal profiles (i.e., between means at corresponding time points) was used to quantify profile similarity. Computed in this way, the correlation coefficient represents a straightforward and easily interpretable index of the extent to which two profiles share the same shape (Cattell, 1949; Haggard et al., 1959; Nunnally, 1962). To distinguish this interindividual pattern-matching index from the usual intervariable product–moment correlation, we refer to this coefficient as an "*S* correlation," following Cattell's (1951) taxonomy of correlational designs.

Cluster analysis. For each patient, we computed a global severity score for each day of the treatment period by averaging their ratings for the eight withdrawal symptoms. Because we were primarily interested in profile shape, we standardized withdrawal scores by case to remove the influence of elevation and scatter from the cluster solution (Cronbach & Gleser, 1953). The 337 sets of 55 standardized variables were then grouped through hierarchical agglomerative cluster analysis using the squared euclidian distance measure and Ward's (1963) minimum variance procedure. Decisions about the number of clusters to retain were accomplished by inspection of the dendrogram (Aldenerfer & Blashfield, 1984). In this procedure, then, clustering was based on a single measure (withdrawal) that was collected across repeated occasions (see Prochaska, Velicer, DiClimente, Guadagnoli, & Rossi, 1991).

Once final profiles were obtained, we undertook additional analyses to determine whether each cluster was homogeneous and whether profile assignment was reliable. *Intracluster consistency* or resemblance was computed by transposing the $N \times 55$ data matrix (55 repeated measures) for each cluster and computing Cronbach's alpha across individuals. *Cross-method agreement* was evaluated via *S*-technique factor analysis (SFA; Gorsuch, 1983) in which individual's scores on a single measure are factored across occasions. Of interest here was whether SFA and cluster analyses aggregated the same groups of individuals. We computed the SFA on only 55 randomly selected patients because the number of variables available constrains the sample size. Therefore, the profiles of these patients were both cluster analyzed and also submitted to SFA using principal-components extraction and varimax rotation. A three-group solution was specified for both types of analyses.

Baseline comparisons. After the final clusters were defined, the groups were compared on a number of baseline characteristics. The chi-square statistic was used for comparisons involving categorical variables. Significant omnibus tests were followed up with Bonferroni-corrected pairwise chi-square tests. One-way analyses of variance (ANOVAs), followed up with Bonferroni-corrected *t* tests, were used for comparisons involving continuously distributed variables. These tests were strictly a posteriori.

Negative affect. To test whether the clusters were characterized by distinctive patterns of affect during the treatment period, we conducted a profile analysis (Morrison, 1990). This hypothesis is tested by examining the significance of the Cluster × Week interaction in a repeated-measures ANOVA using the eight weekly ratings on the negative affect subscale of the PANAS (PANAS-N) as the repeated measure. We then computed intracluster *S* correlations between weekly MNWS criterion profiles and the weekly PANAS-N criterion profiles to quantify their resemblance.

Treatment outcomes. Two separate hierarchical logistic regression analyses were used to assess the predictive relation between cluster membership with respect to relapse. We sought to answer two main questions through these analyses. First, do traditional, cross-sectional measures of withdrawal severity predict outcome in our sample? Second, does consideration of other parameters of withdrawal (i.e., duration and profile shape) improve on prediction based solely on severity? We performed separate analyses using end-of-treatment (8-week) smoking and 6-month smoking as the dependent measures. Abstinence in these analyses was defined as a self-report of zero cigarettes during the 7 days preceding the assessment, confirmed by an expired CO of 10 parts per million (ppm) or less. In both analyses, counseling, site, and patch dose differences among the clusters were controlled at the first step. Week 1 severity, an average of each patient's global withdrawal scores from the first 7 days, was entered at the second step to test the predictive value of cross-sectional withdrawal measurement. The simple duration of withdrawal, defined as the number of days each patient reported a global withdrawal score in excess of the value they rated before cessation, was entered at the third step. Duration was entered before cluster membership in the regression analyses because it may have motivational significance in its own right; we also wanted to ensure that only the configural withdrawal information uniquely associated with a profile-based approach was being tested at the final step of the prediction models. Cluster membership was entered at the fourth step. Because we hypothesized that patients with atypical withdrawal profiles would be more likely to relapse than patients with typical profiles, the cluster membership data were coded so as to yield separate, single degree-of-freedom contrasts between each atypical group and the prototypical group in each analysis.

Influence of intratreatment smoking. We used two analytic strategies to assess the extent to which the different cluster profiles might be a product of smoking during the withdrawal period. First, clusters were compared on the proportion of members who lapsed during treatment using the chi-square statistic. Second, *S* correlations were computed between the criterion profiles of the lapsed and continuously abstinent patients within each cluster to quantify the degree to which these groups shared the same profile shape.

Influence of patch noncompliance. In this trial, complete records of each patient's adherence to the prescribed patch regimen were collected. These data allowed us to assess whether cross-cluster differences in the time course of withdrawal symptomatology simply reflected differing patterns of patch use. Two analytic strategies were used to assess this hypothesis. First, for each weekly study visit, we computed a separate chi-square test comparing the clusters on the proportion of members who reported intending to continue patch use. Second, we computed weekly noncompliance scores for each patient, representing the number of days per week that the patient reported not having applied a patch. To test whether the clusters differed on the basis of profiles of patch noncompliance, we submitted the weekly noncompliance scores to a profile analysis to test for a Cluster × Week interaction.

Results

Cluster Analysis

A three-cluster solution appeared to describe the withdrawal data well. Figure 1a displays the criterion profiles for these three groups in raw score form. For comparison, the criterion profile of the entire sample is also depicted in Figure 1b.

Cluster I comprises 207 patients. This group is characterized by steady improvement in withdrawal severity across the entire treatment period. This profile resembles the prototypical pattern found in the extant smoking literature, as well the criterion profile of the entire sample. Cluster II comprises 72 patients. This group shows gradual improvement over the first 3 weeks of the treatment period. After 3 weeks, Cluster II patients' withdrawal returns to the original, quit-day severity and fluctuates around this level for the remainder of the trial. Cluster III includes 58 patients. This group shows little change during the first 3 weeks of the trial, a decrease in withdrawal severity

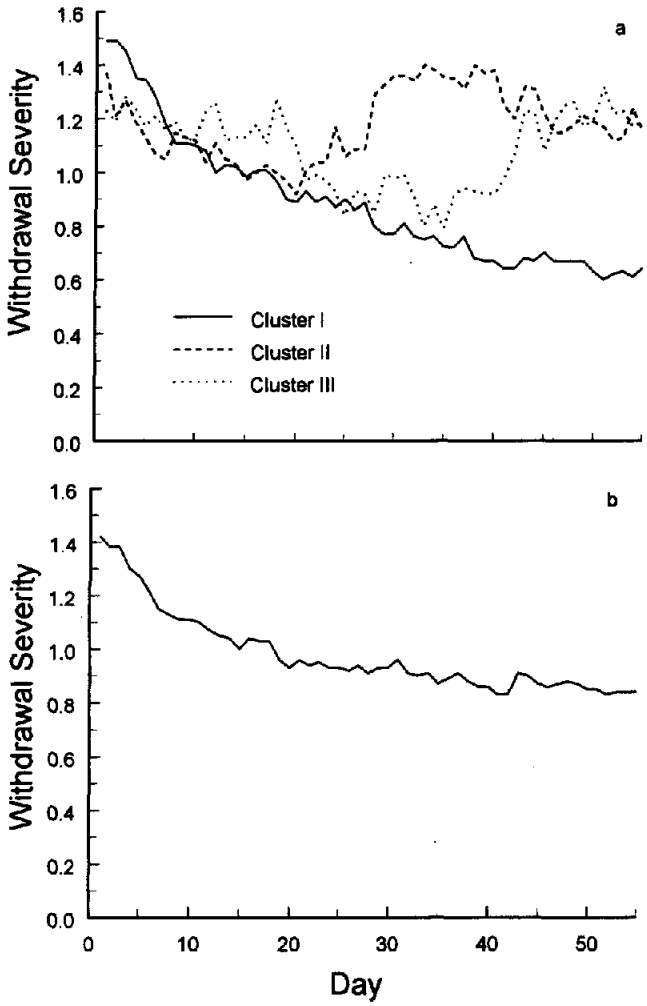

Figure 1. Raw-score criterion profiles of global withdrawal distress in Study 1 for (a) the three clusters and (b) the entire analyzed group. Averaged withdrawal scores can range from 0 to 4.

between Weeks 3 and 6, and a return to quit-day level during the final 2 weeks.

Cluster Solution Reliability

All three clusters had satisfactory internal consistency; alpha values for the three clusters ranged from .84 to .99. This indicates that, within clusters, patients tended to report high scores on the same days and low scores on the same days. In the cross-method agreement analysis, patients were assigned to a factor if they loaded $\geq .30$ on that factor, and this was their highest loading. Eleven of 55 patients were eliminated because the SFA revealed no loading that was $\geq .30$. For the remaining 44 patients, the cross-classification resulted in 84% agreement, yielding a kappa of .73.[3]

Baseline Comparisons

Table 1 summarizes comparisons among the clusters on baseline variables. As can be seen in Table 1, there were no differences among clusters in terms of patch assignment, counseling assignment, or study site. Cluster membership was related to gender, $\chi^2(2, N = 337) = 7.32$, $p < .05$; almost half of the patients in Cluster I were women, whereas 60% or more of Clusters II and III were women. Follow-up pairwise chi-square analyses revealed that only Clusters I and II differed on gender, $\chi^2(1, N = 279) = 6.17$, $p = .01$. The clusters did not differ from one another on the basis of age, cohabitation with a smoker, or years of education. A striking feature of Table 1 is that the clusters were indistinguishable from one another on all markers of nicotine dependence: FTQ scores, cigarettes per day, baseline expired air CO level, and number of previous quit attempts.

Negative Affect

A 3 (cluster) × 8 (week) profile analysis with PANAS-N scores as the repeated measure revealed a significant Cluster × Week interaction, $T^2(14, 580) = 0.21$, $p < .001$, indicating that the clusters had different profiles of negative affect during the treatment period. The shape of each cluster's negative affect profile was similar to its withdrawal profile. The *S* correlations between PANAS-N scores and MNWS ratings across the eight time points were moderate to high: Cluster I, $S = .89$; Cluster II, $S = .86$; and Cluster III, $S = .59$.

Treatment Outcomes

At the end of treatment, abstinence rates for Cluster I, II, and III were 76%, 56%, and 59%, respectively, $\chi^2(2, N = 337) =$

[3] One other method, *co-capturability analysis,* was used to assess profile reliability. A complete description of this technique is beyond the scope of this article; the interested reader may consult Moffitt, Caspi, Harkness, and Silva (1993). This analysis required the withdrawal scale to be split in half and both halves submitted to the same cluster analysis using Ward's (1963) method. Thus, each patient contributed two profiles for analysis, each profile being based on halves of the withdrawal scale. This analysis was repeated three times for 150 randomly selected patients, using a variety of splits of the withdrawal scale. The outcome of these analyses concerns the extent to which the two profiles from the same patient are assigned to the same cluster ("co-capturability") and the extent to which this assignment depends on the number of clusters retained. The results showed good co-capturability across a wide number of cluster solutions and across scale splits (e.g., kappas generally ranged from .65 to .75 when profiles were assigned to 2–10 clusters). The importance of this analysis is that it demonstrates that the reliability of profile assignment is dependent on neither a particular number of clusters being selected nor the aggregate effects of a small subsample of withdrawal items. Hunger and urge/craving have been shown to have time courses that are somewhat different from other withdrawal symptoms. One reviewer raised the concern that differences in the shapes of the obtained clusters might be attributable to differences in these unusual items rather than in total scale scores. Two analyses addressed this concern. First, one of the scale splits used in the co-capturability analyses included the hunger and craving items in the same four-item scale. Notably, satisfactory kappas (i.e., .65–.70) were obtained under these conditions, suggesting that reliability is not an artifact attributable to the inclusion of a small number of unusual items. To further assure ourselves that distinctive or unusual withdrawal profiles were not due to prolonged elevation of hunger or craving alone, we compared the different clusters in terms of individual withdrawal symptoms over the last 3 weeks of the withdrawal period. These analyses showed that the clusters were significantly different on all withdrawal symptoms, not just hunger, craving, or both.

Table 1
Comparison of Study 1 Cluster Groups on Baseline Variables

Measure	Cluster I (n = 207)				Cluster II (n = 72)				Cluster III (n = 58)			
	n	%	*M*	*SD*	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*
44-mg patch dose	110	53			36	50			28	48		
Counseling												
No contact	69	33			22	30			22	38		
Individual	72	35			25	35			11	19		
Group	66	32			25	35			25	43		
Wisconsin site	99	48			36	50			28	48		
Gender (female)[a]	100	48			47	65			35	60		
Live with smoker	88	43			27	38			24	41		
Age (years)			45.7	11.9			45.0	10.4			45.5	11.1
Years of education			14.2	2.3			14.5	2.7			14.4	2.2
FTQ score			7.2	1.8			6.9	1.8			7.3	1.8
Cigarettes per day			27.8	10.1			25.6	8.9			27.8	10.6
CO (ppm)			30.7	13.2			30.9	13.3			31.7	13.5
Prior quit attempts			2.9	2.5			2.6	2.2			2.8	1.7

Note. FTQ = Fagerstrom Tolerance Questionnaire; CO = expired air carbon monoxide; ppm = parts per million.
[a] Indicates groups significantly different from one another, $\chi^2(2, N = 337) = 7.32, p < .05$.

12.01, $p < .01$. Comparable figures for 6-month follow-up were 41%, 31%, and 24%, respectively, $\chi^2(2, N = 337) = 6.21, p < .05$.

Table 2 summarizes the results of the two hierarchical logistic regression analyses predicting relapse. At both follow-up time points, the Week 1 severity measure was a significant predictor of outcome. In both analyses, the duration variable significantly improved prediction when entered at the third step. At the end of treatment, cluster membership significantly improved the model when entered at the fourth step, and members of both atypical clusters were more likely to have relapsed than were members of Cluster I. At 6 months, only members of Cluster III were more likely to have relapsed than were members of Cluster I.[4]

Influence of Intratreatment Smoking

During the 8-week treatment period, 100 members of Cluster I (48%), 42 members of Cluster II (58%), and 38 members of Cluster III (66%) smoked at least one cigarette during the treatment period, $\chi^2(2, N = 337) = 6.28, p < .05$.[5] The omnibus difference was attributable to a difference in lapse rate between Clusters I and III, $\chi^2(1, N = 265) = 5.37, p < .05$.

Figure 2 depicts separate mean profiles for patients who lapsed and patients who were continuously abstinent throughout the treatment period. As can be seen from the figure, the profiles of lapsed and continuously abstinent participants were similar to one another. This similarity was reflected in the S correlations: Cluster I, $S = .96$; Cluster II, $S = .84$; and Cluster III, $S = .65$.

Influence of Patch Noncompliance

At the first three study visits during the treatment phase of the trial, all patients included in the classification analyses reported intending to continue patch use. The clusters did not differ in terms of the proportion of members intending to cease patch use at any of the remaining visits: all chi-squares were nonsignificant. A profile analysis comparing groups on the pattern of missed patches revealed neither a significant main effect for cluster, $F(2, 334) = 1.54$, *ns*, nor a Cluster × Week interaction, $T^2(14, 656) = 0.02$, *ns*. Thus, it appears unlikely that idiosyncratic patterns of patch noncompliance are wholly responsible for the variability in withdrawal time course.

Study 2

In Study 2, withdrawal data were drawn from a placebo-controlled clinical trial of the nicotine patch. This new sample permitted us to replicate the major findings of Study 1—that individual differences in the course of smoking withdrawal symptoms exist and that withdrawal profiles are both tracked by negative affect and related to clinical outcomes. In addition, Study 2 allowed us to redress a serious constraint on the generalizability of Study 1's results: All patients in Study 1 received active nicotine replacement therapy. Study 2 included patients receiving placebo treatment and therefore permitted us to determine whether atypical profiles are restricted to patients receiving nicotine replacement therapy.

[4] In both studies, cluster membership remained a significant predictor of outcome in both logistic regression analyses when Week 1 severity and duration were omitted from the model. Additionally, in both studies, cluster membership remained a significant predictor in both analyses when profile elevation (mean severity across the entire 55 days) was entered instead of Week 1 Severity at Step 2.

[5] Profile analyses using cigarettes per day as the dependent measure and limited to the subsample of patients with complete smoking records were performed for both studies as a further check on the influence of intratreatment smoking. In both studies, the main effect for cluster and the Cluster × Time interaction were not significant, providing further support for the suggestion that cross-cluster differences in withdrawal patterns are not attributable to different smoking patterns.

Table 2
Summary of Hierarchical Logistic Regression Analyses Predicting Relapse at Two Follow-Up Time Points in Study 1

Predictor	Wald	*df*	*p*	Odds ratio
End of treatment				
Step 2				
Wk 1 severity	10.10	1	.002	1.82/point
Step 3				
Duration	5.99	1	.014	1.02/day
Step 4				
Cluster	12.98	2	.001	
II	9.82	1	.002	2.74 vs. Cluster I
III	7.53	1	.006	2.52 vs. Cluster I
Six months				
Step 2				
Wk 1 severity	7.92	1	.005	1.70/point
Step 3				
Duration	6.48	1	.011	1.02/day
Step 4				
Cluster	4.75	2	.093	
II	1.59	1	.207	1.48 vs. Cluster I
III	4.07	1	.044	2.03 vs. Cluster I

Note. Step 1 in both analyses comprised study site, patch dose, and counseling variables. End of treatment: Step 1, model, $\chi^2(4, N = 337) = 14.72, p < .01$; Step 2, model improvement, $\chi^2(1, N = 337) = 10.37, p < .01$; Step 3, model improvement, $\chi^2(1, N = 337) = 5.99, p = .01$; Step 4, model improvement, $\chi^2(2, N = 337) = 13.35, p = .001$. Six months: Model $\chi^2(4, N = 337) = 4.75$, *ns*; Step 2, model improvement, $\chi^2(1, N = 337) = 8.38, p < .01$; Step 3, model improvement, $\chi^2(1, N = 337) = 6.67, p < .01$; Step 4, model improvement, $\chi^2(2, N = 337) = 4.96, p = .08$. Wk 1 severity = average of withdrawal ratings from first 7 days of treatment. The reference category for the single degree-of-freedom contrast for the cluster variable is Cluster I. The odds ratios for the severity and duration measures reflect the odds for a one-unit increase on these continuous measures (severity can range from 0 to 4, duration can range from 0 to 55). For all measures, higher values of the odds ratios indicate a higher probability of relapse, and their magnitude reflects the independent effect of the predictor when patients are equated for all other variables simultaneously in the model.

Method

Patients

In Study 2, withdrawal data were collected from patients ($N = 393$) enrolled in a randomized, double-blind, multisite (Madison, WI; Columbia, MO; Rochester, MN; Scottsdale, AZ; and Jacksonville, FL) placebo-controlled clinical trial of a 22-mg nicotine patch. The results from the Wisconsin site are presented in greater detail in a report by Fiore et al. (1994, Study 1). Inclusion criteria for this trial were as follows: (a) age = 21 to 65 years, (b) history of smoking >15 cigarettes per day during the past year, (c) expired air CO level of 10 ppm or greater, and (d) motivation to quit smoking. Exclusion criteria were (a) cardiovascular disease, (b) pregnancy or lactation, (c) use of psychotropic drugs, (d) current symptomatic psychiatric disorder, (e) current alcohol or drug abuse, (f) chronic dermatologic disorders, and (g) use of an investigational drug within 30 days of the start of the study.

As in Study 1, patients had to have completed at least 50 (91%) of the 55 daily withdrawal rating scales to be included in the analyses. This requirement eliminated 169 patients, leaving 224 (57%) for analysis.

Included and excluded patients were highly nicotine-dependent and had smoked for many years. Excluded patients were less likely than included patients to be abstinent at both 8-week follow-up, $\chi^2(1, N = 393) = 45.68, p < .0001$, and 6-month follow-up, $\chi^2(1, N = 393) = 17.78, p < .0001$. Excluded patients were also significantly more likely than included patients to have reported a history of depression, $\chi^2(1, N = 393) = 7.07, p < .01$. Included and excluded patients were similar in terms of most major demographic and study-related variables. Excluded patients were differentially distributed across study sites, $\chi^2(4, N = 393) = 15.07, p < .01$, with the lowest rate of exclusion being 30% and the highest exclusion rate being 60%. No other statistically significant differences between the two groups were found.

Dosing Regimens and Counseling

Half of the patients were randomly assigned to receive active nicotine patches, and the other half were assigned to the placebo patch group. Patients in the active group wore one 22-mg patch per day for the first 4 weeks of the trial, one 14-mg patch per day during Weeks 5 and 6, and one 7-mg patch per day during the final 2 weeks of the trial. Patients in the placebo group wore patches of equivalent size and appearance

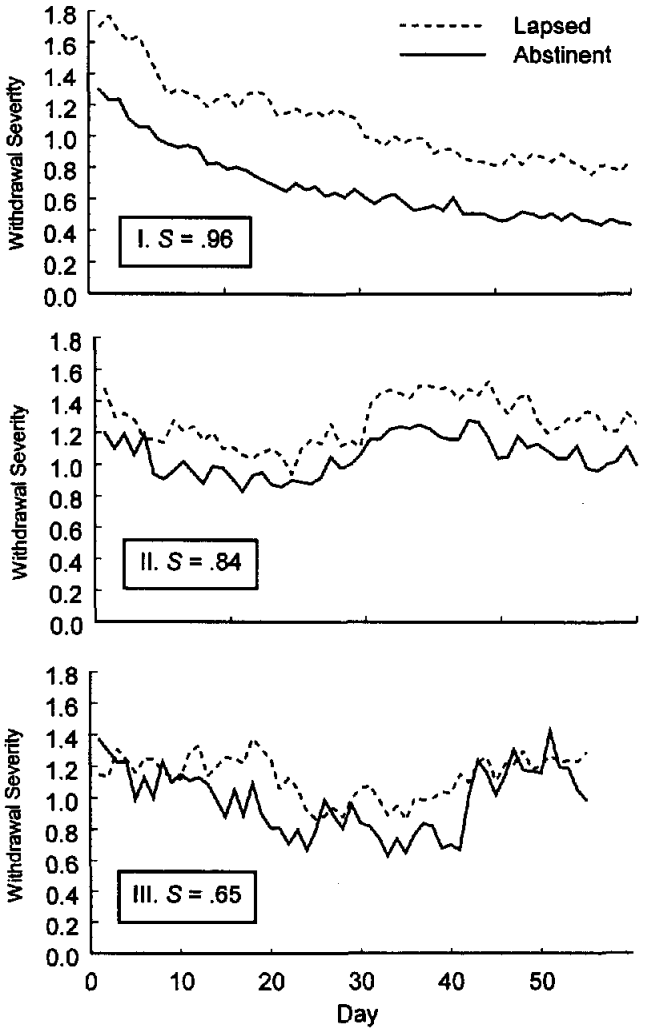

Figure 2. Raw-score criterion profiles of withdrawal severity for lapsed and abstinent patients within each cluster (I, II, and III) in Study 1. Averaged withdrawal scores can range from 0 to 4.

that contained no nicotine. Both patients and study personnel were unaware of dose assignment. All patients in this trial participated in group counseling (approximately 1 hr/session) at each of the eight weekly visits to the study site.

Measures

All measures used in Study 1 were included in Study 2. In addition, two depression history measures and two biochemical measures were examined in Study 2. During a baseline medical screening, we assessed depression history by asking whether (a) the patient had ever had a period when she or he felt depressed most of the day nearly every day and (b) the patient had ever been treated for depression. Plasma levels of nicotine and cotinine were also obtained at baseline.

Missing Values

Of 224 patients with 50 or more valid MNWS ratings, 151 (67%) provided complete withdrawal data. Missing MNWS values were replaced in the same manner as in Study 1 for the remaining 73 patients. These 73 patients were missing an average of 1.7 withdrawal ratings.

Data Analyses

The data analyses in Study 2 paralleled those of Study 1, with the following exceptions. First, because cross-cluster differences in gender distribution were found in Study 1, planned pairwise comparisons of cross-cluster gender composition were performed in Study 2 without Bonferroni adjustment. Second, because counseling was held constant across patients in the Study 2 trial, this variable was not entered in logistic regression models predicting treatment outcome. Third, the relation between patch noncompliance on cluster assignment was not assessed in Study 2. Fourth, data on cluster reliability are not presented.[6] Finally, as a check on the influence of patch dose on cluster construction, we performed a subsidiary cluster analysis limited to patients given placebo patches. Classification of placebo patients in the whole-sample and placebo-only analyses was then compared as a test of the influence of nicotine replacement on cluster outcomes.

Results

Cluster Analysis

As in Study 1, a three-cluster solution appeared to describe the withdrawal data well. Figure 3 displays the profiles for these groups in raw score form.

Cluster I comprised 71 individuals and was characterized by steady improvement over the course of the trial. Cluster II comprised 31 individuals. This group reported a gradual increase in withdrawal severity during the treatment period. Cluster III comprised 122 individuals. Members of Cluster III reported a small improvement during the first 2 weeks of the trial, after which their withdrawal ratings remained fairly constant.

Baseline Comparisons

Table 3 summarizes comparisons among the clusters on a number of baseline variables. As can be seen from the table, a significant group difference emerged only for study site, $\chi^2(8, N = 224) = 23.45, p < .01$. Planned pairwise gender comparisons revealed that Cluster III contained a significantly higher proportion of women compared with Cluster I, $\chi^2(1, N = 193) = 4.77, p < .05$. Notably, the clusters did not differ in terms of patch assignment, $\chi^2(2, N = 224) = 4.21, ns$.

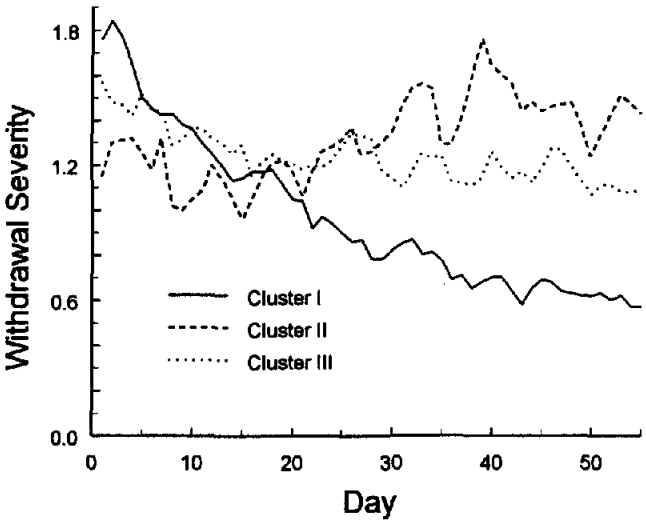

Figure 3. Raw-score criterion profiles of global withdrawal distress for the three clusters in Study 2. Averaged withdrawal scores can range from 0 to 4.

Placebo-Only Cluster Analysis

Data from patients given placebo patches were submitted to a separate cluster analysis, and three clusters were retained. We then compared cross-classification agreement for placebo patients for the placebo-only and total sample cluster analyses. The kappa coefficient for this comparison was .77, suggesting that the presence of patients given active nicotine replacement therapy was not necessary for the specific clusters derived from the primary cluster analysis to be recovered from the data.

Negative Affect

A 3 (cluster) × 8 (week) profile analysis using PANAS-N scores as the dependent variable revealed a significant Cluster × Week interaction, $T^2(14, 400) = 0.13, p < .05$, indicating that the clusters were characterized by distinct profiles of negative affect across the treatment period. Within each cluster, negative affect criterion profiles closely paralleled withdrawal severity criterion profiles; as in Study 1, intracluster S correlations between PANAS-N affect profiles and MNWS profiles were moderate to high: Cluster I, $S = .98$; Cluster II, $S = .59$; and Cluster III, $S = .80$.

Treatment Outcomes

At the end of treatment, abstinence rates for Clusters I, II, and III were 75%, 29%, and 52%, respectively, $\chi^2(2, N = 224)$

[6] Coefficient alpha was computed on the transposed data matrix in Study 2 as it was in Study 1. This revealed that clusters possessed good internal consistency across days: Alpha values ranged from .80 to .98 across the three clusters. Co-capturability and cross-method agreement analyses were not conducted because the basic cluster-analytic procedures were the same as those evaluated in Study 1.

Table 3
Comparison of Study 2 Cluster Groups on Baseline Variables

Measure	Cluster I (n = 71)				Cluster II (n = 31)				Cluster III (n = 122)			
	n	%	*M*	*SD*	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*
Active patch	30	43			17	55			70	57		
Site[a]												
Wisconsin	27	38			3	9			26	21		
Missouri	6	8			7	23			20	16		
Minnesota	23	32			12	39			34	28		
Florida	10	14			2	6			30	25		
Arizona	5	7			7	23			12	10		
Gender (female)	28	39[b]			16	52			68	56[b]		
Depression treatment	8	11			3	10			11	9		
Past depression	11	15			4	13			23	19		
Age			43.0	9.3			46.3	13.1			43.1	10.2
FTQ score			7.0	1.7			7.2	1.9			7.0	1.8
Cigarettes per day			30.6	9.8			27.5	6.9			28.4	8.4
CO (ppm)			31.3	14.2			26.1	11.9			27.8	13.3
Years smoked			25.0	8.8			27.7	13.3			24.4	9.8
Plasma nicotine (ng/ml)			21.2	9.7			23.4	8.1			14.5	1.3
Plasma cotinine (ng/ml)			286.7	123.3			290.3	98.9			292.2	138.6

Note. FTQ = Fagerstrom Tolerance Questionnaire; CO = expired air carbon monoxide, ppm = parts per million.
[a] Groups significantly different from one another, $\chi^2(8, N = 224) = 23.45, p < .01$. A posteriori pairwise comparisons were not performed. [b] Planned pairwise comparisons on gender composition revealed that these groups differed from one another, $\chi^2(1, N = 193) = 4.77, p < .05$.

= 20.08, $p < .0001$. Comparable figures for 6-month follow-up were 41%, 7%, and 27%, respectively, $\chi^2(2, N = 224) = 12.81, p < .01$.

Table 4 summarizes the results of the two logistic regression analyses predicting relapse. As in Study 1, severity and duration measures for Week 1 were significant predictors of outcome at both follow-up time points. Cluster membership was a significant predictor in both analyses when entered at Step 4. At end of treatment, members of both atypical clusters were significantly more likely to have relapsed than were members of Cluster I. At 6-month follow-up, members of Cluster II remained significantly more likely to have relapsed than members of Cluster I.

Influence of Intratreatment Smoking

During the 8-week treatment period, 50 members of Cluster I (70%), 25 members of Cluster II (81%), and 98 members of Cluster III (80%) smoked at least one cigarette during the treatment period, $\chi^2(2, N = 224) = 2.74$, *ns*.

As in Study 1, there was a high degree of correspondence between the profiles of lapsed and abstinent patients within each cluster: Cluster I, $S = .96$; Cluster II, $S = .72$; and Cluster III, $S = .80$.

General Discussion

Several theoretical perspectives, including models implicating affective processes in addictive phenomena, suggest that exacerbations of withdrawal symptomatology need not be instigated solely by declining drug levels. We therefore predicted that classification analyses would recover patterns in which exacerbations of smoking withdrawal were noncontingent with initial smoking abstinence. Certainly, we hypothesized that some patients would display abstinence-contingent withdrawal. We believed that this pattern would resemble the pattern commonly described in the literature—that of a brief initial increase, followed by steady amelioration over time. In addition, we expected to find one or more patterns in which withdrawal symptoms worsened or remained elevated outside the immediate postcessation period. Because this research was motivated by a model of addiction that attributes a core dimension of withdrawal to negative affective processing, we predicted that patterns of negative affect would closely track withdrawal profiles. Finally, based on the belief that withdrawal has motivational significance (e.g., as a setting event for negative reinforcement), we predicted that patients with worsening or unremitting withdrawal profiles would be more likely to relapse than patients who showed the prototypic pattern. These basic predictions were borne out by our results.

We clustered patients according to the shape of their withdrawal profiles in two separate and distinct data sets. In both data sets, we found multiple patterns of smoking withdrawal. In both studies, two of the recovered withdrawal patterns were markedly different in shape from those typically reported in the smoking withdrawal literature when ratings from all participants are averaged together. Figure 1 illustrates the profound masking effect that the practice of averaging withdrawal data has in smoking cessation trials. Figure 1b suggests that withdrawal peaks in the first postcessation week and declines monotonically thereafter. Figure 1a reveals that only the 207 patients in Cluster

Table 4
Summary of Hierarchical Logistic Regression Analyses Predicting Relapse at Two Follow-Up Time Points in Study 2

Predictor	Wald	*df*	*p*	Odds ratio
End of treatment				
Step 2				
Wk 1 severity	8.24	1	.004	1.88/point
Step 3				
Duration	20.34	1	<.001	1.05/day
Step 4				
Cluster	13.95	2	<.001	
II	13.77	1	<.001	8.54 vs. Cluster I
III	4.53	1	.033	2.24 vs. Cluster I
Six months				
Step 2				
Wk 1 severity	8.02	1	.005	2.03/point
Step 3				
Duration	9.39	1	.002	1.06/day
Step 4				
Cluster	8.77	2	.013	
II	7.68	1	.006	20.36 vs. Cluster I
III	2.59	1	.108	1.81 vs. Cluster I

Note. In both analyses, Step 1 comprised study site and patch dose variables. End of treatment: Step 1, model, $\chi^2(5, N = 224) = 20.90$, $p < .001$; Step 2, model improvement, $\chi^2(1, N = 224) = 8.67$, $p < .01$; Step 3, model improvement, $\chi^2(1, N = 224) = 22.31$, $p < .0001$; Step 4, model improvement, $\chi^2(2, N = 224) = 15.52$, $p < .001$. Six months: Model, $\chi^2(5, N = 224) = 17.62$, $p < .01$; Step 2, model improvement, $\chi^2(1, N = 224) = 8.68$, $p < .01$; Step 3, model improvement, $\chi^2(1, N = 224) = 10.35$, $p = .001$; Step 4, model improvement, $\chi^2(2, N = 224) = 14.63$, $p < .001$. Wk 1 severity = average of withdrawal ratings from first 7 days of treatment. The reference category for single degree-of-freedom contrasts for the cluster variable is Cluster I. The odds ratio for the severity and duration measures reflect the odds for a one-unit increase on these continuous measures (severity can range from 0 to 4; duration can range from 0 to 55). For all measures, higher values of the odds ratios indicate a higher probability of relapse, and their magnitude reflects the independent effect of the predictor when patients are equated for all other variables simultaneously in the model.

I from Study 1 (61%) actually displayed this pattern. Figures 1 and 3 illustrate a second interesting point: Ratings from all patients cohered early in the quit process but diverged in later weeks. Certainly drug removal is a powerful cause of smoking withdrawal symptoms. The divergence in withdrawal trajectories after the first weeks of the trials, however, suggests that idiosyncratic factors are capable of moderating the later expression of withdrawal symptoms.

Our findings not only demonstrate the heterogeneity in the course of smoking withdrawal but also suggest that atypical withdrawal profiles may be quite common. A large proportion of each sample was classified into atypical clusters: 39% of Study 1 patients and 68% of Study 2 patients. The discrepancy between the estimates of prevalence of atypical withdrawal profiles is intriguing but difficult to account for with the present data. The trials differed from one another in counseling and nicotine patch interventions and smoking lapse rates. Not one of these variables was, by itself, significantly related to withdrawal pattern. Additional research is needed to characterize factors responsible for withdrawal heterogeneity.

Atypical profiles of withdrawal may be quite general among smokers. Indeed, atypical clusters included patients treated with high-dose patch therapy, patients given standard patch treatment, and patients treated with placebo. Similarly, atypical clusters included patients given no behavioral support, patients given brief individual counseling, patients who received intensive group counseling, patients who were continuously abstinent, and patients who smoked during treatment. Although the two studies incorporated an array of nicotine dependence indexes (FTQ scores, plasma nicotine and cotinine, CO levels, cigarettes per day), the time course of withdrawal was variable across these dimensions. Thus, although the present research verifies that atypical withdrawal profiles are general, real, and consequential, it argues against a number of intuitively appealing explanations for their occurrence.

Both studies revealed robust relations between criterion profiles of negative affect and withdrawal ratings. These findings are consistent with the affect-laden nature of the withdrawal measure and are predicted by addiction models holding that critical withdrawal response elements arise from activity in neural systems subserving negative affect (e.g., Baker et al., 1987). Although the particular research strategies adopted in this research arose from a specific affect-based model of addiction, it is important to note that the results are consistent with other models that recognize the strong links between affective responding and addiction. One could argue that our findings should not be surprising, given that early research characterizing the smoking withdrawal syndrome incorporated standard mood measures (e.g., Hatsukami, Hughes, Pickens, & Svikis, 1984), measures of withdrawal and mood are strongly intercorrelated (Hall et al., 1990), and prior factor-analytic studies have found that parcels of affective items account for the majority of variance in withdrawal scales (Hughes, 1992; Hughes et al., 1991; Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996). However, the present research is unique in showing that exacerbations and remissions in withdrawal symptoms mirror the temporal dynamics of negative affect. One could attribute this correspondence to criterion contamination—the overlap in content between withdrawal and affect measures. However, this claim should not overshadow the fact that a great deal of programmatic research has led to this construct overlap (e.g., Hughes et al., 1990).

The strong relations between negative affect and smoking withdrawal found in both studies suggest that measures of constructs linked to negative affect, especially postcessation negative affect, may be relevant to predicting withdrawal-related and clinical outcomes. The two depression history variables included in Study 2 did not show significant relations with cluster membership. However, some patients with positive histories of depression were eliminated because of incomplete data, and this may have masked a relation between depression history and withdrawal profile.

We hypothesized that, if variability in the time course of withdrawal existed, assessment of withdrawal parameters other than severity should improve prediction of relapse. This prediction was borne out by our analyses. The duration of withdrawal (number of days after cessation that withdrawal was elevated) was a strong predictor of relapse in all logistic regression models. Although the odds ratios for duration in Tables 2 and 4 may appear small (they range from 1.02 to 1.06), this is attributable

to the fact that the variable was scaled in single-day units. Thus, for every one-day increase in the duration of withdrawal, the risk of relapse increases 1.02–1.06 times. The predictive power of duration makes some intuitive sense; as the "abstinence agony" is prolonged, the motivation to stay quit is sapped. Because of its computational simplicity and predictive potency, duration would appear to be an important withdrawal parameter to assess in future research.

Cluster membership (i.e., the shape, or trajectory of withdrawal) also improved prediction of relapse even after the predictive information due to withdrawal duration and severity was statistically controlled. Notably, one atypical cluster in each study (Cluster III in Study 1 and Cluster II in Study 2) relapsed more frequently than members of the prototypical cluster at both time points. The criterion profiles of both of these groups reveal late-onset exacerbations in withdrawal. This suggests that a worsening of withdrawal weeks after quitting has a particularly negative effect on patients' motivation to maintain abstinence.[7] It is clear that much remains to be learned about the specific roles played by withdrawal duration and shape in smoking relapse. Nonetheless, the present research suggests that withdrawal profiles contain information that may help elucidate the causes of relapse.

Prior research has shown withdrawal severity to be a sporadic and weak predictor of smoking relapse. However, in the present research, withdrawal severity was a strong and consistent predictor of relapse in all prediction analyses. What accounts for this discrepancy? One possibility stems from the fact that, unlike many studies of the withdrawal–relapse relation, we included patients who lapsed during the treatment period in our prediction analyses. Because intratreatment smoking is highly associated with eventual relapse (e.g., Gourlay, Forbes, Marriner, Pethica, & McNeil, 1994; Kenford et al., 1994), the common practice of eliminating patients who lapse may constrain both withdrawal and outcome data and limit predictive relations.

Although cluster membership did not appear to be a simple function of intratreatment smoking, it is axiomatic that smoking has some impact on withdrawal. For example, comparison of the criterion profiles of lapsed and abstinent patients within the same cluster (see Figure 2) reveals that lapsed patients reported more severe withdrawal. Of course, causal primacy is unknown in this instance. Lapsing patients may have been destined to experience more severe withdrawal, and this may have precipitated their lapses. Prior research has yielded conflicting findings regarding the impact of smoking on withdrawal (e.g., Hatsukami, Dahlgren, Zimmerman, & Hughes, 1988; Shiffman, 1979). It is intriguing to speculate that smokers may differ in their sensitivity to withdrawal after smoking reexposure. In other words, there may be a subgroup of smokers for whom postcessation cigarette use stokes withdrawal, leading to atypical withdrawal patterns and an increased risk of relapse. This could represent a mechanism that accounts for the high rates of relapse associated with smoking reexposure (e.g., Gourlay et al., 1994; Kenford et al., 1994). At present, this surmise is purely speculative.

The fact that postcessation smoking typically begins within 1–2 weeks of the quit attempt suggests that lapses preceded withdrawal exacerbations for most patients with atypical profiles. However, the data available to us do not permit us to explore definitively the temporal relations between withdrawal fluctuations and postcessation smoking. Characterizing this relation will require further research.

In both studies, women were overrepresented in the atypical clusters. This finding is intriguing because some evidence suggests that women are less successful at smoking cessation than are men (e.g., Bjornson et al., 1995; Swan, Ward, Carmelli, & Jack, 1993). Most prospective studies have not uncovered gender differences in withdrawal severity (Hatsukami, Skoog, Allen, & Bliss, 1995; Svikis, Hatsukami, Hughes, Carroll, & Pickens, 1986). Our results suggest that gender differences in withdrawal dynamics, as opposed to withdrawal severity, may contribute to the higher relapse rates among women. A gender difference in withdrawal dynamics could be due to differential sensitivity to nicotine replacement therapy (Hatsukami et al., 1995), menstrual cycle effects (O'Hara, Portser, & Anderson, 1989), and gender differences in the prevalence of affective disorders (e.g., Gritz, Nielsen, & Brooks, 1996).

A number of questions regarding atypical withdrawal patterns are raised but left unanswered by this research. For instance, given the correlational nature of this research, it is impossible to determine from our results whether late withdrawal symptoms per se cause relapse or whether some third variable (e.g., stress level) influences withdrawal ratings and directly causes relapse. Furthermore, atypical withdrawal patterns were found in both trials, but the shapes of these atypical profiles differed across the two studies. This challenges the hypothesis that distinct profiles reflect only neurophysiologic reactions to abstinence that generate exacerbations and remissions of withdrawal symptoms at particular postcessation time points. The captured profiles may indeed reflect events that have little temporal contingency with drug removal. For instance, recrudescent withdrawal may reflect increased levels of stressors that might occur at any time after cessation. In this case, captured profiles would change somewhat from sample to sample, depending on fortuitous occurrences of events. However, the fact that in both studies women were more likely to display atypical profiles suggests that enduring individual differences do influence profile dynamics.

One could argue that the reports of late (i.e., more than 4 weeks postcessation) symptomatic distress observed in the present research do not represent valid smoking withdrawal symptoms. A great deal of evidence suggests that the particular symptoms assessed in the present research are sensitive to nicotine manipulations. For instance, these symptoms increase after cessation or smoking reduction (e.g., Hughes & Hatsukami, 1986), are reversed by nicotine administration (e.g., Hughes, Hatsukami, Pickens, Krahn, et al., 1984; Jorenby et al., 1995), and occur after cessation of nicotine replacement (Hatsukami, Skoog, Huber, & Hughes, 1991). Thus, at least in their initial manifestation, these symptoms conform to conventional beliefs regarding withdrawal symptomatology (Jarvik & Hatsukami, 1989). Nevertheless, it could be argued that late-onset exacerba-

[7] Statistical redundancy with the duration variable may delimit statistical relations between other profile types and relapse. When logistic regression models were repeated without entering the duration variable at Step 3, the performance of the remaining atypical clusters in prediction analyses was improved. We thank an anonymous reviewer for pointing out to us the importance of examining the duration of withdrawal.

tions of these symptoms should not be labeled withdrawal. For instance, late-onset exacerbations may be influenced by the host of variables related to negative affect (e.g., stressors, coping style, and personality), and therefore the expression of these symptoms might be fairly independent of pharmacologic events (i.e., drug removal). Thus, these exacerbations would not conform to a definitional criterion of the withdrawal syndrome. What seems important in deciding this issue is to determine whether drug/nicotine withdrawal produces a prolonged sensitivity to affective instigators or stressors. The fact that similar affective patterns have not been described in nonwithdrawing individuals (Larsen & Kasimatis, 1990) suggests that withdrawal may be causal. Finally, regardless of how they are labeled, atypical affective and withdrawal patterns are significant phenomena if they play a role in motivating relapse and thereby sustain addictive drug use.

Several limitations of the data must be acknowledged. First, we relied on a relatively brief self-report measure of withdrawal in this research. This withdrawal assessment approach has become standard practice in this field (Shiffman, 1988). However, it is clear that the symptoms included in this scale do not exhaust the domain of smoking abstinence effects (Hughes et al., 1990; Shiffman, 1988). Particular signs, especially nonaffective components of the withdrawal syndrome (e.g., weight gain), may yield unique families of profiles across a given postcessation period. This is consistent with the suggestion of Kalant, LeBlanc, and Gibbins (1971) that the symptoms of psychological dependence (such as those measured here) have a more prolonged time course than do the symptoms of physical dependence (e.g., neurologic withdrawal signs). Future research not only should examine profile heterogeneity across distinct response domains but also should target the motivational significance of profile heterogeneity in these different domains.

Two sampling issues also constrain the generalizability of our findings. First, both studies consisted of patients who volunteered for intensive cessation programs. Only a small proportion of the smoking population is willing to undergo such treatment (Fiore et al., 1990). However, the limited research examining withdrawal symptoms in unaided quitters has revealed a prototypical pattern similar to that seen in clinical samples (Gritz et al., 1991; Hughes, 1992). Second, we limited our analyses to those patients who completed at least 50 daily withdrawal ratings, eliminating a substantial proportion of patients from each sample. However, given that excluded patients were more likely to relapse and (in Study 2) more likely to report a history of depression, it is possible that excluding patients may have actually served to underestimate the prevalence of atypical withdrawal patterns.

Research designed specifically to assess negative affect and withdrawal dynamics in smokers both pre- and postcessation may augment our understanding of the heterogeneity of smoking withdrawal. Important questions to be addressed by such research include the following: Do precessation patterns of negative affect presage postcessation withdrawal dynamics? What personal and environmental variables are associated with unusual affect and withdrawal dynamics? Is the specific withdrawal function form similar across individual quit attempts? Such research may ultimately enrich our understanding of motivational processes involved in smoking and smoking relapse.

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