Journal of Abnormal Psychology
2002, Vol. 112, No. 1, 14–27


0021-843X/02/$12.00 DOI: 10.1037/0021-843X.112.1.14

# Smoking Withdrawal Dynamics: II. Improved Tests of Withdrawal–Relapse Relations

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In this article, the authors assessed whether continuously scaled symptom parameters derived from growth models (T. M. Piasecki et al., 2003) are linked to smoking at long-term follow-up by using data from a large-scale clinical trial ($N = 893$). Results revealed that higher withdrawal intercepts, positive linear slopes, and greater volatility were all positively associated with relapse, and cigarette coefficients (indicating smoking-induced withdrawal reduction) were negatively related to relapse. In models keyed around the first lapse to smoking, those destined to lapse reported more severe withdrawal during abstinence, and withdrawal patterns discriminated groups defined according to lapse duration. The findings complement earlier heterogeneity studies in implicating the pattern of changing withdrawal symptoms over time as a factor strongly associated with smoking relapse.

Relapse is the fundamental problem in smoking research and in addictive behavior more broadly (Marlatt, 1985). The great majority of smokers attempting to quit eventually succumb to relapse—despite strong motivation to quit, despite success in resisting smoking for days, weeks, months, or years, despite a host of salient, tangible reasons for maintaining abstinence, and despite having weathered the aversive initial manifestations of withdrawal. Although a variety of treatments can produce very high rates of initial cessation, no treatment reliably staves off relapse in a majority of those trying to quit (Fiore et al., 2000).

Relapse is a vital phenomenon from a scientific as well as from a clinical perspective. It remains a working target of research because so little is known about its causes or origins. Clearly, researchers would be in a better position to craft more effective treatments if they had a better understanding of the processes that conspire to provoke relapses back to smoking (Piasecki & Baker, 2001). In this article, we take a new look at an old question: Do aversive withdrawal symptoms contribute to smoking relapse? Answers to this question are germane to theories of drug motivation as well as to the design and implementation of clinical smoking cessation treatments.

## Prediction of Relapse by Withdrawal: Rationale

Classic psychopharmacologic theory holds that withdrawal symptoms reflect unopposed neural adaptation to chronic levels of drug in the body. Because the nervous system has adapted to the presence of drug, drug removal disrupts the adapted systems, giving rise to aversive symptoms. Drug replacement restores homeostasis, eliminating the symptoms. Under classic theory, drug dependence disorders are thought to be relapsing conditions, at least in part, because aversive withdrawal symptoms punish abstinence and renewed drug self-administration ameliorates the aversive symptoms producing negative reinforcement (e.g., Benowitz, 1991; Henningfield & Goldberg, 1988; Schachter, 1978; Zinser, Baker, Sherman, & Cannon, 1992).

*Editor's Note.* Maxine Stitzer served as the action editor on this article.—TBB

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This report is based on a portion of a dissertation submitted by Thomas M. Piasecki in partial fulfillment of the requirements of the degree of Doctor of Philosophy at the Department of Psychology, University of Wisconsin—Madison under the supervision of Timothy B. Baker. Portions of these findings were presented at meetings of the Society for Research on Nicotine and Tobacco, Arlington, Virginia, February 2000, and the Academy of Behavioral Medicine Research, Mont-Tremblant, Quebec, Canada, June 2000. This research was supported in part by National Institute on Drug Abuse Grant DA07580-03, National Cancer Institute Grant CA84724-02, and a grant from GlaxoWellcome, Research Triangle Park, North Carolina. Preparation of this article was facilitated by a grant from the University of Missouri Research Board.

We thank Scott Leischow, Mitchell Nides, Stephen Rennard, J. Andrew Johnston, and their colleagues at collaborating sites in the clinical trial from which data were drawn.

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Data on smoking withdrawal symptoms do indeed seem consistent with classical pharmacologic withdrawal models. For instance, withdrawal assessment instruments tap symptoms that are frankly aversive, reliably exacerbated by nicotine deprivation in dependent smokers, and ameliorated by renewed smoking (e.g., Hatsukami, Dahlgren, Zimmerman, & Hughes, 1988; Hughes, 1992).

It is important to note, however, that items on withdrawal scales tap negative affect; this accounts for the largest proportion of variance in such instruments (Hughes, 1992; Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996; Welsch et al., 1999). Therefore, it is likely that affective items capture variance that is influenced by both pharmacologic and nonpharmacologic events. Affects can certainly be influenced by nicotine manipulations (e.g., Zinser, Fiore, Davidson, & Baker, 1999), but they are also affected by situational factors (e.g., stressors or conditioned stimuli) and personal characteristics (e.g., psychopathology or personality). Because smokers expect smoking to relieve naturally occurring negative affect (Brandon & Baker, 1991), it is reasonable to predict that scores on affect-laden smoking withdrawal instruments will be related to smoking relapse even if they do not reflect pharmacologic withdrawal. Diverse instigators could additively or interactively raise withdrawal symptom scores, but whatever the specific cause or causes for elevated scores in a given instance, smoking would be (or would tend to be perceived) as an effective countermeasure.

Thus, there are reasons to believe that withdrawal instruments should serve as *integrative readouts* of the motivation to smoke and should predict smoking relapse. However, considerable research attempting to predict relapse from withdrawal scores has yielded generally disappointing findings (see Patten & Martin, 1996, for a review). We have speculated that statistical conventions in withdrawal research may undercut the predictive power of withdrawal instruments in subtle ways (Piasecki, Fiore, & Baker, 1998; Piasecki et al., 2000). For example, researchers often choose to represent withdrawal scores using single occasion "snapshots" in prediction models. This approach makes sense if one assumes that pharmacologic processes are the overwhelming influence on withdrawal scores and that pharmacologic processes have very similar time courses across individuals.

Single-occasion measures appear inappropriate, however, if one acknowledges that symptom scores are influenced by both pharmacologic and nonpharmacologic factors. Not only might withdrawal symptoms be multiply determined but also the likelihood that the various factors that influence withdrawal scores are quasi-randomly distributed means that we cannot specify a priori the kinds of functions that symptom waveforms might take. Motivational information might be contained in aspects of the pattern of scores over time. If postcessation withdrawal patterns are indeed heterogeneous, then sensitive tests of the connections between withdrawal and relapse must use methods that can represent a wide array of symptom patterns over time.

In past research, we captured withdrawal patterns over time through the use of dynamic cluster analysis (Piasecki et al., 1998, 2000). Although this technique was useful in reflecting the diversity of withdrawal patterns over time (e.g., the shapes of symptom profiles), it is not ideal as a method for exploring the motivational impact of withdrawal: the relations between symptom dimensions and relapse. One limitation is that potentially separable symptomatic dimensions (e.g., trajectory or scatter) are confounded or ignored by that technique. Another disadvantage is that clusters are categorical and do not permit the assignment of continuous scores. Despite these limitations, our research did show that cluster membership was associated with relapse likelihood (Piasecki et al., 1998, 2000). If a smoker's withdrawal profile belonged to a cluster with persistent or rising withdrawal symptoms, then that individual faced a higher risk of relapse than did smokers with decreasing symptoms.

In a companion article (Piasecki et al., 2003), we described the use of hierarchical linear growth models (Bryk & Raudenbush, 1992) to derive a set of comprehensive, continuously scaled withdrawal parameters that might supplant cluster groupings as indices of withdrawal symptom dynamics. These methods were applied to withdrawal symptom data from a recent, large-scale smoking cessation trial (Jorenby et al., 1999). In contrast to clustering, growth modeling produces continuously scaled parameters of symptomatic distress, and their motivational implications are interpretable a priori. Moreover, unlike cluster analysis, growth modeling techniques can produce pattern indices for participants who are missing a limited amount of diary data, reducing the need to exclude participants or impute missing scores.

Clear motivational relevance for relapse can be hypothesized for four of the five parameters derived from this technique. Higher intercept values (indicating greater mean symptom severity), positive *slopes* (suggesting worsening symptoms over time), and greater symptomatic *volatility* (more unsystematic scatter) should each be positively related to smoking relapse because they signal severe, worsening, or volatile/chaotic negative affect. Logically, such negative affect should set the stage for negative reinforcement. A negative *cigarette coefficient* indicates that symptoms tended to be reliably lower on days when smoking occurred than would have otherwise been predicted by the overall fitted trend. Thus, negative cigarette coefficients may index the operation of escape–avoidance contingencies that are central to a negative reinforcement account. We predicted, therefore, that negative cigarette coefficients would be related to relapse. Motivational relevance of the final parameter, *quadratic trend* coefficients, which model curvature of the function describing withdrawal over time, is less clear. For instance, either a strong positive coefficient (U-shaped curve) or a strong negative coefficient (humped curve) could indicate the presence of an unusual and distressing symptom pattern. Thus, although quadratic trends have advantages for model fitting, we did not predict that individuals' quadratic coefficients would necessarily be related to relapse.

One major aim of this article was to evaluate whether these withdrawal score parameters are related to relapse in the manner predicted above. We tested this proposition in logistic regression analyses using follow-up smoking data from the clinical trial in which the withdrawal parameters were derived. These models evaluated whether withdrawal patterning contributes unique information about relapse proneness when other reputed predictors of relapse risk (e.g., sex, or nicotine dependence) or stable individual differences in pre-quit symptomatology were controlled.

A second aim was to examine the temporal interplay between withdrawal score patterns and smoking lapses. Because they presumably represent a pivotal moment in the cessation attempt when motivational processes fostering relapse are translated into active drug use, first lapses to smoking may provide a uniquely informa-

tive touchstone for evaluating the role of withdrawal in the return to smoking (Hedeker & Mermelstein, 1996; Shiffman et al., 1996). An underlying premise of this research (and major models of drug motivation in general; e.g., Benowitz, 1991; Solomon & Corbit, 1973) is that people smoke in response to withdrawal exacerbations; that is, withdrawal symptoms precede smoking, thereby constituting the basis for negative reinforcement. The relapse prediction models described above do not directly test this underlying principle. Specifically, the relapse prediction analyses were not designed to isolate the temporal sequencing of withdrawal and smoking events as they unfold during the process of relapse. Thus, it is possible that relapse-relevant trajectory information in withdrawal scores is an artifact of postcessation smoking. For instance, smoking lapses could boost withdrawal symptoms such as craving through priming mechanisms (e.g., Stewart, deWit, & Eikelboom, 1984). If this were the case, then it could be argued that most or all of the predictive relation between relapse and withdrawal is due to withdrawal serving as a proxy for smoking (lapsers). Because some of the importance of our findings derives from the notion that severe or worsening withdrawal precedes smoking lapses, we addressed this issue in a focused analysis. If withdrawal does set the stage for negative reinforcement by smoking, one should see evidence of particularly severe, increasing, or unremitting withdrawal preceding the first lapse to smoking, no matter when the lapse occurs in real time.

## Method

### *Parent Trial Participants*

Data were drawn from a four-center (AZ, CA, NE, WI), double-blind, fully factorial clinical trial evaluating the 21-mg nicotine patch and bupropion for smoking cessation (Jorenby et al., 1999). A total of 893 smokers were randomly assigned to one of four treatment groups, with preferential assignment to treatments involving active medication: placebo patch + placebo pill ($n = 160$), nicotine patch + placebo pill ($n = 244$), bupropion + placebo patch ($n = 244$), bupropion + nicotine patch ($n = 245$). Both sexes were approximately equally represented in the sample; 467 (52%) participants were women, and 426 (48%) were men. Smokers enrolled in the trial were similar to those of other clinical trial samples (Hughes, Giovino, Klevens, & Fiore, 1997). They tended to be in their early 40s ($M = 43.3$ years, $SD = 10.8$), tended to be heavily nicotine dependent (as assessed by the Fagerström Tolerance Questionnaire [FTQ; Fagerström, 1978]; $M = 7.4$, $SD = 1.7$), tended to smoke heavily in the year prior to enrollment ($M = 26.6$ cigarettes per day, $SD = 9.5$), tended to have started regular smoking in their teens ($M = 17.3$ years, $SD = 4.1$), and tended to report a history of several unsuccessful major quit attempts ($M = 2.8$, $SD = 3.3$). Random assignment was successful in the parent trial; treatment groups did not differ on these or other baseline variables.

### *Procedure*

The trial consisted of three phases: a 1-week baseline phase, a 9-week treatment phase, and a follow-up phase that extended to 1 year after the initiation of therapy. Participants were screened, completed a battery of self-report measures, and received brief individual counseling during the baseline phase. Participants began taking assigned pills during the 1st week of the treatment phase and continued to take them for the remainder of the 9 weeks. For smokers assigned to active bupropion, this translated into 3 days of 150-mg bupropion per day, followed by 8.5 weeks of bupropion at 150 mg b.i.d. Placebo bupropion participants took the same number of equivalent-appearing tablets. Placebo or active patch therapy began for all participants on the eighth day of the treatment phase and continued for the remainder of the treatment phase. Thus, all participants took tablets from Days 1–63 of the treatment phase and wore patches on Days 8–63. Day 8 served as the quit date for all participants. The design and primary outcomes of the parent trial are discussed in greater detail by Jorenby et al. (1999).

*Daily diary measures.* In the trial described above, smoking withdrawal symptoms and smoking behavior were assessed with a daily diary. Each diary page contained a modification of the Minnesota Nicotine Withdrawal Scale (MNWS; Hughes & Hatsukami, 1986), which asked respondents to rate the following nine symptoms on a scale from 0 to 4 (0 = *absent,* 1 = *slight,* 2 = *mild,* 3 = *moderate,* 4 = *severe*): craving for cigarettes, depressed mood, difficulty falling asleep, awakening at night, irritability/frustration/anger, anxiety, difficulty concentrating, restlessness, and increased appetite. Each diary page also contained a space for participants to record the number of cigarettes smoked that day. Participants were instructed to enter a value of zero on days they did not smoke. Participants were instructed to complete a diary page just before going to bed each night so that they could reflect on the entire day's experience when providing their responses. At each weekly study visit, participants returned completed diaries from the past week and received blank diaries to be completed each day between visits. Participants completed the diaries daily for 1 week prior to cessation and for 11 weeks after the quit date. Daily withdrawal and smoking data from the first 8 postcessation weeks were the focus of the present research (see below).

*Long-term abstinence–relapse definition.* The outcome to be predicted in logistic regression models was long-term abstinence or relapse, defined by biochemically corroborated self-reports of continuous abstinence from 10 weeks postcessation through 6-month follow-up. The long-term abstinence criterion was constructed using point-prevalence smoking status assessments collected at 10 weeks, 12 weeks, and 6 months after the quit date. Participants were counted as abstinent at a given follow-up if they provided a self-report of zero cigarettes in the 7 days prior to the assessment and provided a breath sample with a carbon monoxide concentration of 10 ppm or less. To be counted as abstinent in the present analyses, a participant had to have been confirmed abstinent at all three follow-up assessments. All other participants were counted as relapsed, including individuals who could not be reached for follow-up or who refused to provide breath samples. Note that the 10-week follow-up assessment occurred 2 weeks after the last withdrawal assessment used in the growth models, and the abstinence definition at 10 weeks required only 1 week of biochemically corroborated abstinence. Thus, even lapsers who smoked during the last week in which withdrawal was modeled could conceivably have stopped smoking and been counted as abstinent in these analyses.

*Lapser–abstainer split.* Data from a companion article (Piasecki et al., 2003) indicated that there were robust differences between participants who lapsed and participants who were continuously abstinent on all withdrawal parameters derived using data from the first 8 weeks of the postcessation period. This suggests that withdrawal parameters may be a causal factor in smoking status differences and that functional relations between withdrawal and relapse might differ across groups. Thus, the sample was stratified according to the occurrence of postcessation smoking using data from daily cigarette tallies from the first 8 weeks of the cessation attempt.

A total of 893 participants attended a screening session and were randomized to a treatment group. Four of these individuals did not return for additional sessions or complete any withdrawal assessments. Of the remaining 889 participants, 418 provided a complete series of cigarette tallies, with 194 of these reporting complete abstinence and 224 reporting at least one smoking event. Of the 471 subjects with one or more missing cigarette tally in their diaries, 318 reported smoking at least one postcessation cigarette in the completed ratings. This left 153 participants with an incomplete series of cigarette reports, with all completed reports indicating zero smoking. Following the spirit of intent-to-treat conventions, these individuals were assigned to the lapsed or abstinent groups according to the

extensity of missing data; participants with 3 or fewer missing ratings were deemed abstainers, and those with 4 or more missing values were assigned to the smoking group. This rule assigned 63 participants to the abstinent group and 90 to the lapse group. In sum, 257 (29%) participants were counted as continuously abstinent over the first 8 weeks of cessation, and 632 (71%) participants were counted as lapsers.

*Growth parameter derivation.* In a companion article (Piasecki et al., 2003), daily data from the first 8 postcessation weeks were used in growth models to derive parameters describing individual differences in distinct withdrawal dimensions. The derivation of these parameters is described in greater detail in Piasecki et al. (2003). Briefly, a base family of growth parameters (intercept, linear, quadratic) was derived in the mixed sample of lapsers and abstainers, and this set of parameters was expanded to include a time-varying cigarette covariate in the subsample of lapsers. Parameters derived from growth models were supplemented with a volatility statistic that gauged symptom variability or scatter. Volatility was computed as the average squared deviation of raw symptom scores from the corresponding predicted values derived from the Level 1 growth model (see Piasecki et al., 2003). Volatility estimates in the lapser-only submodel were computed around the smoking-covaried Level 1 function; thus, any systematic effects of postcessation smoking on withdrawal scatter are removed from these scores.

## *Predicting Relapse from 8-Week Withdrawal Parameters*

*Logistic regression analyses.* A series of logistic regression analyses was performed to assess whether withdrawal parameters were associated with clinical outcomes. In all analyses, relapse was the dependent measure; abstainers were assigned a value of 0 and relapsers a value of 1. Thus, analyses were keyed to detecting relapse risk rather than abstinence.

Separate logistic models were performed using three partially overlapping samples to provide a comprehensive view of withdrawal–relapse relations. The first model was conceptually similar to prior cluster analytic tests (Piasecki et al., 1998) and used data on the base family of parameters (intercept, slope, quadratic, volatility) as predictors in the full (mixed lapser–abstainer) sample. A second model tested the value of the expanded set of withdrawal parameters (i.e., base family plus cigarette coefficient) within the subsample of lapsers for which they could be estimated. Finally, the base family of parameters was tested in a logistic regression model limited to those who abstained continuously (see *Lapser–abstainer split*) across the withdrawal assessment period (8 weeks). The abstainer-only models provide a conservative test of predictive power of the derived withdrawal parameters. Metric concerns such as lowered relapse rates, constrained range of variability in withdrawal patterning, and smaller sample size would all be expected to conspire to undercut withdrawal–relapse relations in a sample of 8-week continuous abstainers. Note that, although postcessation smoking is represented in a variety of ways in the analyses reported in this article (e.g., lapser–abstainer groupings, cigarette coefficients, analyses keyed around the first lapse, etc.), the logistic regression models did not explicitly control for the amount of postcessation smoking with a specific predictor variable (e.g., number of cigarettes reported). If withdrawal differences are causal in provoking lapses to smoking, statistically controlling for postcessation smoking could handicap the ability to show predictive relations between withdrawal measures and long-term relapse.

For each participant grouping, logistic regression modeling followed a fixed analytic plan. Treatment assignment, study site, and other baseline variables that might account for relapse vulnerability were entered at the first step, and withdrawal measures were entered at a second model step. From the array of available baseline measures (Piasecki et al., 2002), we selected seven variables that tend to be related to relapse in clinical research (e.g., Kenford et al., 2002). Participant *sex* was represented by a 0–1 dichotomous variable, with men assigned a score of 1. Lifetime history of major depression was assessed at screening using the Mood Disorder module of the *Structured Clinical Interview for DSM–IV* (Spitzer, Williams, Gibbon, & First, 1994) and was also represented by a 0–1 dichotomous variable. In a smoking history questionnaire, participants were asked to provide the past year's smoking rate (in cigarettes per day). Additional information about smoking heaviness was gathered through expired carbon monoxide (in ppm) and serum cotinine (ng/ml) samples gathered at a baseline clinic visit. Finally, participants completed the FTQ (Fagerström, 1978) and the Negative Affect subscale of a past-week version of the *Positive and Negative Affect Schedule* (NPANAS; Watson, Clark, & Tellegen, 1988) at baseline. An additional measure of baseline withdrawal severity was also included in prediction models to control for any potentially stable individual differences in the severity of symptoms existing prior to the cessation attempt. This measure was constructed by averaging MNWS ratings from the first 4 days of diary recording during the pre-quit period. The first 4 days (i.e., vs. all 7 pre-quit days) were selected for two reasons. First, these ratings were relatively distal from the quit date and were thus unlikely to reflect nuisance variance such as anticipatory anxiety associated with the impending quit attempt. Second, a relatively large number of participants failed to complete MNWS ratings on Days 6 and 7 of the pre-quit period (e.g., only 32 participants had missing ratings on Day 5, but 92 had missing ratings for Day 7); eliminating these days from the composite prevented these participants from being eliminated from logistic models.

In all analyses, withdrawal variables were entered together as a block. Thus, tests of the statistical significance of individual withdrawal parameters (e.g., Wald statistics and odds ratios) assess the unique or independent effect of each. Continuous predictors, including the withdrawal variables, were standardized prior to analysis. Thus, odds ratios (ORs) associated with each may be interpreted as the change in the odds of relapse associated with a one-standard-deviation increase on the measure. A series of split-half replications (not shown) was conducted to examine the consistency of prediction for all models. Results from these models revealed good consistency of prediction across split-halves and were similar to the results obtained from the full sample. Results were also similar when baseline control variables were omitted from the models (data not shown).

Sample sizes varied across logistic regression models owing to missing data on the baseline covariates and to the distinctive requirements of the two growth models used to derive withdrawal parameters. Growth parameters could be fitted for 257 during-treatment abstainers, but 13 of these individuals were eliminated from logistic models because of missing data on the baseline variables, yielding an effective sample size of 244 abstainers. When the base family of withdrawal parameters (i.e., excluding the time-varying cigarette coefficient) was fit in the mixed sample, growth parameters could be estimated for 579 lapsers. Of these, 28 were missing data on one or more baseline variables and were eliminated from the full-sample logistic model. The resulting 551 lapsers and the 244 abstainers with complete data yielded an effective sample of 795 for the full-sample logistic model. The growth model limited to lapsers included a time-varying cigarette coefficient; using this expanded model, growth parameters could only be fitted for 539 lapsers. Of these, 25 lapsers were missing data on one or more baseline variables, yielding an effective sample size of 514 for the lapser-only analysis.

Because the subgroups of lapsers and abstainers were self-selected and could differ in important ways, we compared the subgroups included in logistic models on a number of baseline variables for descriptive purposes (Table 1). Descriptive statistics from the full-sample model are also provided in Table 1, but owing to nonindependence of the mixed sample with the lapser and abstainer subsamples, statistical comparisons of the mixed sample versus subsamples were not performed. Briefly, analyzed lapsers were more likely than abstainers to have been assigned placebo or patch only and were less likely than abstainers to have been assigned either treatment involving bupropion. The lapser group contained a significantly higher proportion of women than the abstainer group. Lapsers tended to be younger and have higher cotinine levels, higher FTQ scores, higher

Table 1
*Baseline and Demographic Characteristics of the Lapser, Abstainer, and Full Samples Used in Logistic Regression Models Predicting Relapse*

| Measure | Abstainers ($n$ = 244) | Lapsers ($n$ = 514) | Full sample ($n$ = 795) |
|---|---|---|---|
| Treatment group | | | |
| Placebo | | | |
| % | 8.6** | 22.0** | 17.6 |
| *n* | 21 | 113 | 140 |
| Bupropion | | | |
| % | 33.2** | 23.2** | 26.9 |
| *n* | 81 | 119 | 214 |
| Patch | | | |
| % | 23.4* | 31.3* | 28.3 |
| *n* | 57 | 161 | 225 |
| Combination | | | |
| % | 34.8** | 23.5** | 27.2 |
| *n* | 85 | 121 | 216 |
| Race (White) | | | |
| % | 94.3 | 93.4 | 93.3 |
| *n* | 230 | 480 | 742 |
| Sex (female) | | | |
| % | 47.1* | 55.8* | 52.5 |
| *n* | 115 | 287 | 417 |
| History of depression | | | |
| % | 16.8 | 18.5 | 17.5 |
| *n* | 41 | 95 | 139 |
| Age (years) | | | |
| *M* | 45.5** | 42.7** | 43.5 |
| *SD* | 10.5 | 10.7 | 10.8 |
| Cigarettes per day | | | |
| *M* | 25.9 | 27.0 | 26.6 |
| *SD* | 9.4 | 9.7 | 9.6 |
| Cotinine | | | |
| *M* | 336.1** | 373.7** | 360.3 |
| *SD* | 153.6 | 179.0 | 171.3 |
| Carbon monoxide exhaled | | | |
| *M* | 27.9 | 29.5 | 29.0 |
| *SD* | 10.7 | 11.4 | 11.2 |
| FTQ | | | |
| *M* | 7.0** | 7.5** | 7.4 |
| *SD* | 1.7 | 1.7 | 1.7 |
| NPANAS | | | |
| *M* | 1.4** | 1.5** | 1.5 |
| *SD* | 0.4 | 0.5 | 0.5 |
| Baseline withdrawal severity | | | |
| *M* | 4.4* | 5.3* | 5.1 |
| *SD* | 4.3 | 5.1 | 4.9 |

*Note.* Data are listed for participants with complete data on all covariates used in each multivariate logistic regression model (see Table 2). The "full sample" column contains more participants (795) than would result from summing the lapser and abstainer subsamples (758). This occurs because an additional withdrawal parameter (the cigarette coefficient) was fitted for the lapsers, and some lapsers did not provide enough data to estimate this additional parameter; they could be included in the full sample model because they provided sufficient data for estimating the reduced set of parameters fit for the full sample. Statistical comparisons refer to the differences between abstainer and lapser subgroups. FTQ = Fagerström Tolerance Questionnaire; NPANAS = Negative subscale of the Positive and Negative Affect Schedule.
* $p < 05$. ** $p < 01$.

NPANAS scores, and higher baseline levels of withdrawal relative to abstainers.

## *Patterns of Withdrawal Before and After Smoking Lapse*

*Subgroups.* To have sufficient withdrawal data to model withdrawal parameters, we limited this exploratory set of analyses to participants ($n$ = 152) who reported an unequivocal first lapse after at least 5 consecutive days of abstinence, and an equal number of continuous abstainers (the matched abstainer group, MA) selected at random from the complete abstainers identified in the lapser–abstainer split (see above). Thus, the total analyzed sample size was 304. Of the remaining 585 participants from the parent trial, 105 were during-treatment abstainers who could not be

included for lack of a suitable matched lapser, and 480 were lapsers. Of these, 378 were excluded due to reporting a lapse during the first 5 days of the quit attempt, and 102 returned smoking logs with too many missing entries to identify definitively if, or when, a first lapse to smoking occurred.

Participants who lapsed were further subdivided into two groups that differed with respect to the outcome of the lapse event. The *protracted lapse* (PL) group consisted of 28 smokers who smoked at least one cigarette per day for 3 or more consecutive days after the first lapse day, a pattern of consistent smoking which may be interpreted as a serious threat to the cessation attempt. The *transient lapse* (TL) group comprised the remaining 124 smokers who slipped but reported complete abstinence on at least one of the first 3 post-lapse days, a pattern of smoking that might be interpreted as a more fleeting setback to the cessation attempt than the PL pattern.

*Temporal windows and rationale.* To compare and contrast withdrawal patterns for each group of smokers across the span of the cessation attempt, separate symptom growth curve models were built for four distinct 5-day intervals. The *Baseline* analysis modeled symptoms across the 5 days immediately preceding the quit day. The *Early* analysis modeled symptomatic change across the first 5 days of the cessation attempt, including the quit day (i.e., Days 1–5 in real time). Two analyses were keyed around a behavioral event, the first lapse to smoking (or a matched day for MA controls; see later) rather than to a uniform point in real time. The *Pre-lapse* model tested symptomatic change across the 5 days preceding the day of the first lapse to smoking. The *Post-lapse* model characterized symptom growth during the 5 days immediately following the day of the first lapse. The lapse day itself was not included in either analysis so as to avoid ambiguity about the temporal relations between the lapse and the symptom reports. The median latency to first lapse in the sample submitted to this analysis was 16 days and ranged from 6 to 45 days.

*Data collation.* Data were organized for modeling following the procedure described by Hedeker and Mermelstein (1996). Briefly, a data set was constructed containing withdrawal ratings for 5 days on either side of the lapse event for lapsers and a matched group of continuously abstinent controls. Each participant in the lapse group was matched with an abstinent participant, and withdrawal ratings from corresponding epochs in real time were selected for analysis from the matched abstinent participants. For instance, if two lapse group members smoked their first cigarette(s) on Day 17, Days 12–16 were considered their pre-lapse ratings. Two members of the abstinent group would then be selected randomly (without replacement), and these individuals' ratings from Days 12–16 would be considered as pre-lapse ratings. Thus, although there was considerable individual variability in terms of the postcessation latency of pre- and post-lapse ratings (due to variability in the timing of lapse events), a statistical yoking of MA controls to lapse group members minimized any distortion of cross-group comparisons on withdrawal by broad temporal trends in symptomatology. Once an MA subject was yoked to a lapse subject, that MA subject was used in data analyses of all four temporal windows. Note that MA participants were yoked to lapsing participants on a random basis. That is, participants were matched in terms of the data points selected for comparison, not matched in the classic sense of selecting groups that were equated on particular baseline variables. We did not match lapsers and abstainers on baseline characteristics because lapsers and abstainers are clearly self-selected "natural categories," and it was unclear whether baseline matching would distort meaningful differences in withdrawal between groups. Instead, we tested for naturally arising differences in subgroups on baseline variables; such differences may help explain differences in withdrawal experience and cessation outcomes.

Baseline and Early data sets were constructed by simply collating withdrawal ratings from the 5 days before and 5 days after the quit date (the Early model includes quit date data) for all analyzed participants.

*Growth models.* Separate growth models were built for each window. In each model, the dependent measure was withdrawal severity, defined as the raw sum of items on the MNWS. At Level 1, individuals' symptom growth was modeled as a quadratic function.[1] Two dummy-coded variables were constructed to represent TL and PL status (0 = *nonmember*, 1 = *member*); these were used as the only predictors in all Level 2 models. Thus, Level 2 models assessed the modal pattern of symptom growth for MA participants and the magnitude of any systematic deviations from this pattern associated with each lapse group.

HLM allows for flexible handling of cases with missing withdrawal ratings (e.g., Bryk & Raudenbush, 1992), but subjects who failed to complete any ratings during the period of interest (e.g., individuals who became discouraged and refused to complete further ratings after lapsing) could not be included in particular analyses. Thus, the sample size varied across growth models, with smaller samples for the Post-lapse and Late windows. Participants could be included in an analysis if they provided only a single valid rating in a given window, but this was relatively rare; in all analyses and subgroups, the mean number of missing ratings was less than 1, and the most frequent number of missing values among those with incomplete records was 1.

*Post-lapse smoking and withdrawal.* An additional growth model was built, using data from lapse group members from only the Post-lapse window, to characterize the acute consequences of renewed smoking on the course of withdrawal. In this analysis, the Level 1 model was identical to that described above; withdrawal growth was modeled as a function of an intercept and linear and quadratic trend components. The sole Level 2 predictor of variance in individual growth was the average number of cigarettes per day reported by lapsed subjects during the Post-lapse period. Average smoking rate during the Post-lapse window was entered as a Level 2 predictor rather than using a time-varying smoking covariate in the Level 1 model, in keeping with the general strategy of organizing withdrawal data according to smoking outcomes. PL (12 missing) and TL group (5 missing) means were substituted for subjects with missing smoking ratings, according to their group membership. Results were nearly identical when these individuals were omitted. Results were also similar when lapse group was entered as a Level 2 predictor.

## Results

### *Predicting Relapse From 8-Week Withdrawal Parameters*

*Predicting relapse in the full sample.* In the full sample, the overall relapse rate by 6 months posttreatment using the continu-

[1] Thus, the Level 1 model was a linear regression equation of the form:

$$Y_{ti} = \beta_{0i} + \beta_{1i}(L_t) + \beta_{2i}(Q_t) + r_{ti}$$

where $Y_{ti}$ is the withdrawal score of individual $i$ at time $t$, the $\beta$s are estimated coefficients that describe the growth of individual $i$'s withdrawal across the window, $L_t$ is the value of the linear trend function at time $t$, $Q_t$ is the value of the quadratic trend function at time $t$, and $r_{ti}$ is a random error term. Orthogonal polynomials were used to represent the linear (−2, 1, 0, 1, 2) and quadratic (2, −1, −2, −1, 2) trends. As a consequence of using orthogonal polynomials, the intercept term ($\beta_{0i}$) represents an estimate of individual $i$'s symptom elevation or mean withdrawal severity across the 5-day period.

Level 2 models were of the form:

$$\beta_{0i} = \gamma_{00} + \gamma_{01}(\mathrm{TL}) + \gamma_{02}(\mathrm{PL}) + u_{0i}$$

where $\beta_{0i}$ is the array of withdrawal intercepts estimated for all smokers at Level 1, $\gamma_{00}$ is an estimate of the average intercept for MA controls, $\gamma_{01}$ is a coefficient estimating the magnitude of the TL group's deviation from the MA average intercept, $\gamma_{02}$ is a coefficient estimating the magnitude of the PL group's deviation from the MA average intercept, and $u_{0i}$ is a random effect term. Analogous equations were constructed to predict individual-level variance in linear and quadratic trends in symptom growth.

ous abstinence measure described above was 72%. The top portion of Table 2 summarizes the findings at the final step of the logistic regression model. The set of withdrawal parameters significantly improved the logistic model when added at Step 2, $\chi^2(4, N = 795) = 101.48$, $p < .001$. Higher withdrawal intercepts, positive linear slopes, and greater volatility each made significant independent contributions to predicting relapse. All effects were in the predicted direction. As expected, quadratic coefficients were not predictive of relapse. Serum cotinine, FTQ scores, and baseline withdrawal scores were also significantly related to relapse.

*Predicting relapse in lapsers.* In the subgroup of participants counted as lapsing during the first 8 weeks of the cessation attempt, the rate of ultimate relapse was 89%. The middle portion of Table 2 summarizes the findings at the final step of the logistic model. Again, the set of withdrawal parameters significantly improved the logistic model at Step 2, $\chi^2(5, N = 514) = 43.17$, $p < .001$. Higher intercepts, positive linear slopes, greater volatility, and negative cigarette coefficients (associated with lowered withdrawal on lapse days) were associated with relapse. In this model, smoking rate and baseline withdrawal scores were also significant predictors of relapse.

*Predicting relapse in abstainers.* In the subgroup of participants who maintained continuous abstinence during the first 8 weeks of the cessation attempt, the relapse rate was 37.0% by 6 months postcessation. The bottom portion of Table 2 summarizes the findings at the final step of the model. The set of withdrawal parameters did not improve the logistic model, $\chi^2(4, N = 244) = 7.46$, $p = .11$, but positive linear slope remained associated with relapse. None of the baseline variables significantly predicted relapse among the abstainer subgroup.

Table 2
*Results of Logistic Regression Analyses Predicting Relapse in Each Subsample, Controlling for Treatment, Study Site, and Baseline Variables*

| Predictor | Wald | OR | 95% CI |
|---|---|---|---|
| Mixed Lapsers and Abstainers ($n = 795$) | | | |
| Baseline measure | | | |
| Sex | 2.01 | 0.77 | 0.53, 1.11 |
| History of depression | 0.49 | 0.84 | 0.51, 1.38 |
| Smoking rate | 2.78 | 0.85 | 0.70, 1.03 |
| Carbon monoxide | 0.52 | 0.93 | 0.76, 1.14 |
| Serum cotinine | 5.63* | 1.30 | 1.05, 1.61 |
| FTQ | 8.68** | 1.35 | 1.11, 1.65 |
| NPANAS | 2.53 | 0.85 | 0.69, 1.04 |
| Baseline symptom severity | 7.24** | 0.74 | 0.59, 0.92 |
| Withdrawal parameter | | | |
| Intercept | 12.74** | 1.62 | 1.24, 2.12 |
| Linear | 39.07** | 1.86 | 1.53, 2.27 |
| Quadratic | 0.14 | 1.04 | 0.85, 1.26 |
| Volatility | 14.97** | 2.05 | 1.43, 2.95 |
| Lapsers only ($n = 514$) | | | |
| Baseline measures | | | |
| Sex | 0.49 | 0.79 | 0.41, 1.53 |
| History of depression | 0.51 | 0.74 | 0.33, 1.68 |
| Smoking rate | 5.15* | 0.70 | 0.51, 0.95 |
| Carbon monoxide | 0.40 | 1.13 | 0.78, 1.63 |
| Serum cotinine | 0.33 | 1.12 | 0.77, 1.62 |
| FTQ | 3.59 | 1.40 | 0.99, 1.97 |
| NPANAS | 1.23 | 0.84 | 0.61, 1.15 |
| Baseline symptom severity | 8.42** | 0.61 | 0.43, 0.85 |
| Withdrawal parameter | | | |
| Intercept | 4.26* | 1.61 | 1.02, 2.51 |
| Linear | 18.48** | 1.97 | 1.45, 2.68 |
| Quadratic | 0.93 | 1.20 | 0.83, 1.72 |
| Volatility | 6.91** | 2.52 | 1.27, 5.01 |
| Cigarette effect | 4.66* | 0.73 | 0.54, 0.97 |
| Abstainers only ($n = 244$) | | | |
| Baseline measure | | | |
| Sex | 0.93 | 0.74 | 0.41, 1.36 |
| History of depression | 0.08 | 1.12 | 0.50, 2.50 |
| Smoking rate | 0.19 | 0.93 | 0.66, 1.31 |
| Carbon monoxide | 1.78 | 0.79 | 0.55, 1.12 |
| Serum cotinine | 3.36 | 1.38 | 0.98, 1.95 |
| FTQ | 2.00 | 1.28 | 0.91, 1.81 |
| NPANAS | 1.99 | 0.75 | 0.50, 1.12 |
| Baseline symptom severity | 0.02 | 0.98 | 0.66, 1.45 |
| Withdrawal parameter | | | |
| Intercept | 0.57 | 1.19 | 0.76, 1.84 |
| Linear | 4.33* | 1.43 | 1.02, 2.01 |
| Quadratic | 0.67 | 0.88 | 0.65, 1.19 |
| Volatility | 0.24 | 1.17 | 0.63, 2.18 |

*Note.* The reference category for sex is female; for depression, it is negative history. For all measures, higher values of the odds ratio (OR) indicate increased risk of relapse (any smoking between 10 weeks and 6 months after baseline). ORs for continuous measures reflect the effect of a 1-standard deviation unit increase. Significant ORs < 1 indicate a negative relationship between the predictor and relapse. These results reflect estimates with all variables entered simultaneously. Effects of treatment and study site are included in the models but are not listed here to simplify presentation. 95% CI = 95% confidence interval. FTQ = Fagerström Tolerance Questionnaire; NPANAS = Negative subscale of the Positive and Negative Affect Schedule.
* $p < .05$. ** $p < .01$.

## *Patterns of Withdrawal Before and After Smoking Lapse*

*Subgroup characteristics.* Table 3 presents baseline and demographic data for each of the analyzed subgroups, along with results of post hoc comparisons between groups. The PL group contained more placebo-assigned subjects and fewer patch-only and combination therapy participants than the MA group. The PL group also included significantly fewer combination therapy patients than the TL group. There were a higher proportion of women in the TL group than in the MA group. The PL group had higher FTQ scores than the MA group. The TL group was significantly younger than the MA group.

*Growth model results.* Fixed effects estimates from the growth models for each window are summarized in Table 4 and group symptom trends for each window are plotted in Figure 1. In all post-quit growth models, significant residual variability in all growth parameters was left unexplained by group membership.

*Baseline model.* The intercept, linear slope, and quadratic trend for MA participants were significantly different from zero. PL and TL participants were not significantly different from the MA participants at baseline, with the exception of a slope difference between MA and PL participants. The PL group showed a more negative linear slope over the baseline period.

*Early model.* In the first 5 days of the quit attempt, MA participants had a mean withdrawal severity of 10.3, with a statistically significant, descending linear slope across the 5 days. Each lapse group reported withdrawal that was more severe than

Table 3
*Baseline and Demographic Characteristics of Smoking Outcome Subgroups*

| Measure | Matched abstainers (MA) ($n$ = 152) | Transient lapsers (TL) ($n$ = 124) | Protracted lapsers (PL) ($n$ = 28) |
|---|---|---|---|
| Treatment group | | | |
| Placebo* | | | |
| % | $9.9_{a}$ | $16.9_{a,b}$ | $28.6_{b}$ |
| *n* | 15 | 21 | 8 |
| Bupropion | | | |
| % | 34.9 | 31.5 | 21.4 |
| *n* | 53 | 39 | 6 |
| Patch* | | | |
| % | $21.1_{a}$ | $24.2_{a,b}$ | $42.9_{b}$ |
| *n* | 32 | 30 | 12 |
| Combination* | | | |
| % | $34.2_{a}$ | $27.4_{a}$ | $7.1_{b}$ |
| *n* | 52 | 34 | 2 |
| Race (White) | | | |
| % | 91.4 | 93.5 | 92.9 |
| *n* | 139 | 116 | 26 |
| Sex (female)* | | | |
| % | $43.4_{a}$ | $58.1_{b}$ | $50.0_{a,b}$ |
| *n* | 66 | 72 | 14 |
| History of depression | | | |
| % | 17.1 | 17.7 | 10.7 |
| *n* | 26 | 22 | 3 |
| Age (years)* | | | |
| *M* | $45.4_{a}$ | $41.5_{b}$ | $42.2_{a,b}$ |
| *SD* | 10.8 | 11.4 | 7.8 |
| Cigarettes per day | | | |
| *M* | 25.5 | 25.6 | 27.5 |
| *SD* | 9.5 | 9.4 | 6.1 |
| Cotinine | | | |
| *M* | 328.5 | 371.9 | 374.7 |
| *SD* | 147.8 | 209.3 | 218.4 |
| Carbon monoxide exhaled | | | |
| *M* | 27.9 | 27.2 | 32.6 |
| *SD* | 11.9 | 12.9 | 11.4 |
| FTQ** | | | |
| *M* | $6.8_{a}$ | $7.3_{a,b}$ | $7.8_{b}$ |
| *SD* | 1.8 | 1.8 | 1.8 |
| NPANAS | | | |
| *M* | 1.4 | 1.5 | 1.5 |
| *SD* | 0.4 | 0.5 | 0.4 |
| Baseline withdrawal severity | | | |
| *M* | 4.2 | 4.7 | 4.4 |
| *SD* | 4.1 | 5.0 | 4.4 |

*Note.* In each row where a significant omnibus effect was observed, cells that do not share a common subscript were significantly different from one another. Omnibus effects were followed by pairwise post hoc tests (either focused chi-square analyses or Bonferroni-protected *t* tests). Percentages refer to the prevalence of a characteristic within a subgroup and should be compared across columns (e.g., 9.9% of MA participants were assigned placebo vs. 16.9% and 28.6% rates of placebo treatment in the TL and PL groups, respectively). FTQ = Fagerström Tolerance Questionnaire; NPANAS = Negative subscale of the Positive and Negative Affect Schedule.
* Omnibus effect, $p < .05$. ** Omnibus effect, $p < .01$.

MA participants, as indicated by significant intercept effects, but neither trend component distinguished lapse groups from the MA growth pattern.

*Pre-lapse model.* In the 5 days prior to the first lapse, the MA group reported a mean withdrawal severity of 8.1, with a statistically significantly, descending linear slope. Both the PL and TL groups reported significantly more severe withdrawal than MA participants over this period, as indicated by significant intercept effects. TL members' symptom reports were further distinguished from MA controls in having a significantly different, slightly positive linear slope and a statistically significant quadratic trend, with both trends summating to yield an increase in symptomatology across the 2 days immediately preceding the lapse event.

Lapse day ratings were not included in the analyses because of the possibility that smoking influenced withdrawal ratings on those days, but the mean ratings for each group are provided in Figure 1

Table 4
*Results of Growth Models Before and After the First Lapse to Smoking*

| Effect | Coefficient |
|---|---|
| Baseline model | |
| Intercept (MA) | 4.87** |
| TL effect | 0.58 |
| PL effect | −0.40 |
| Linear slope (MA) | 0.46** |
| TL effect | −0.04 |
| PL effect | −0.57** |
| Quadratic trend (MA) | 0.13* |
| TL effect | −0.10 |
| PL effect | 0.09 |
| Early model | |
| Intercept (MA) | 10.32** |
| TL effect | 1.49* |
| PL effect | 3.34** |
| Linear slope (MA) | −0.48** |
| TL effect | 0.19 |
| PL effect | −0.21 |
| Quadratic trend (MA) | −0.13 |
| TL effect | 0.20 |
| PL effect | 0.10 |
| Pre-lapse model | |
| Intercept (MA) | 8.07** |
| TL effect | 1.62* |
| PL effect | 2.88* |
| Linear Slope (MA) | −0.34** |
| TL effect | 0.37* |
| PL effect | 0.05 |
| Quadratic trend (MA) | −0.10 |
| TL effect | 0.29** |
| PL effect | 0.07 |
| Post-lapse model | |
| Intercept (MA) | 7.04** |
| TL effect | 1.81* |
| PL effect | 5.69** |
| Linear slope (MA) | −0.22* |
| TL effect | 0.05 |
| PL effect | −0.44 |
| Quadratic trend (MA) | −0.02 |
| TL effect | 0.11 |
| PL effect | −0.14 |

*Note.* Baseline, early, and pre-lapse: $n = 304$ (PL = 28, TL = 124, MA = 152); post-lapse: $n = 298$ (PL = 24, TL = 124, MA = 150). MA = matched abstainers; TL = transient lapsers; PL = protracted lapsers. "TL effect" or "PL effect" connotes that the coefficient must be summed with the corresponding MA estimate to yield the predicted effect for the lapser subgroup. For example, the PL effect of −0.40 for the intercept in the baseline model suggests that PL group members had an average intercept of 4.47 (.40 points lower than the MA intercept of 4.87). Number of participants differs across analyses as a function of missing data.
* $p < .05$. ** $p < .01$.

for context. As can be seen, both lapse groups reported withdrawal ratings on the lapse day that were higher than the preceding day, whereas the MA group reported withdrawal that was consistent with the previous day's report.

*Post-lapse model.* In the 5 days following the lapse, the MA group reported a mean withdrawal severity of 7.0, and their withdrawal experience was again characterized by a significant, descending linear slope. Both lapse groups were distinguished from MA controls in reporting significantly more severe withdrawal over this period, indicated by significant intercept effects, but neither trend component discriminated these groups from MA controls. Aggregated across the 5-day window, PL participants who provided ratings reported smoking an average of 3.4 cigarettes per day ($SD = 2.6$, range = 0.6–11.6, $Mdn = 2.4$). TL participants reported an average of 0.5 cigarettes per day ($SD = 1.7$, range = 0–12; $Mdn = 0.0$).

*Post-lapse smoking and withdrawal.* Results of the model testing the relationship between withdrawal parameters and the number of cigarettes smoked during the post-lapse period are presented in Table 5. The parameter estimates indicate that increased smoking during the post-lapse period was associated with significantly more severe withdrawal during the post-lapse window and a significantly more rapid linear decline in symptomatology across the period. Taken together, these effects suggest that those participants with the worst withdrawal smoked more cigarettes. This increased smoking resulted in dose-dependent withdrawal reduction across the immediate post-lapse period.

## Discussion

The analyses presented here replicate and extend our prior cluster-based studies of withdrawal heterogeneity and smoking relapse. Logistic regression analyses linking withdrawal parameters to follow-up smoking status represent a conceptual replication of the earlier studies. In contrast to earlier research, the present analyses used a different set of statistical indices of withdrawal dynamics (continuously scaled parameters) and a different outcome criterion (continuous abstinence beyond Week 10). Moreover, data were drawn from a sample in which withdrawal–relapse connections had not yet been characterized. Despite these differences, the results generally accorded with the main findings of earlier cluster-based studies. Variables indexing individual differences in withdrawal symptom dynamics were associated with relapse. Similar to the findings of Piasecki et al. (2000), symptom slopes were good predictors of relapse likelihood, but other facets of the symptom profile contributed additional information that improved prediction further.

In the present analyses, withdrawal parameters were robust predictors of relapse in the mixed sample of lapsers and abstainers and in the subset of lapsers only. Remarkably, although many studies have been unable to find any consistent relation between withdrawal and relapse likelihood (Patten & Martin, 1996), we found that several different dimensions of withdrawal—the elevation, variability, and trajectory of symptoms—showed strong predictive relations with relapse in both the full sample and in lapsers. Moreover, the predictive relations were of substantial magnitude; in all analyses, a withdrawal dimension proved to be the best predictor of outcomes (as judged by Wald coefficients and ORs). Finally, these dimensions of symptom experience were related to relapse, even though a host of variables known to account for relapse likelihood (e.g., affective intensity, dependence, treatment, smoking rate) were statistically controlled at prior model steps. This strategy is quite conservative, in fact, because some of the control variables might influence relapse via withdrawal. Thus, use of these control variables would reduce meaningful variance in withdrawal symptoms to the extent that symptoms mediate the baseline influences.

The robust prediction of relapse from withdrawal measures in this research and our past studies of withdrawal heterogeneity

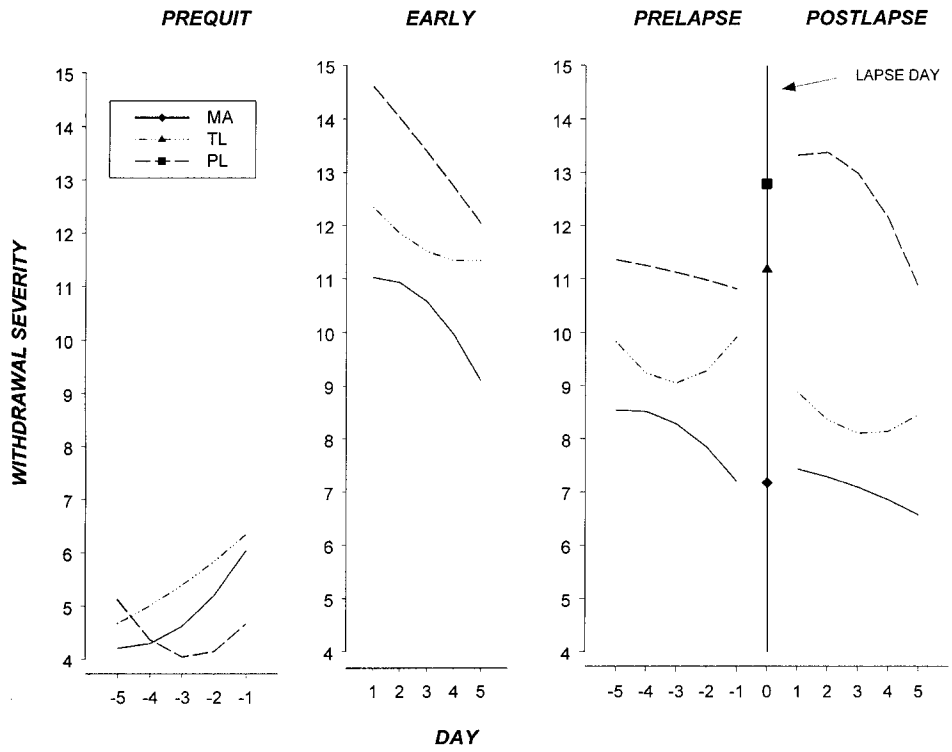


*Figure 1.* Predicted withdrawal growth functions from protracted lapsers (PL; $n = 28$), transient lapsers (TL; $n = 124$), and matched abstainers (MA; $n = 152$) across the four modeled epochs. Note that the dependent variable in the growth models was the raw sum of item scores on the Minnesota Nicotine Withdrawal Scale (MNWS; resulting in a possible score range from 0 to 36); these values can be divided by 9 to convert them to the more conventional range for MNWS scores. Raw means for each group on the lapse day are provided for context and use the same modified MNWS metric. The mean latency to first lapse among lapsers was 16.7 ($SD = 10.4$) days; for TL, $M = 16.7$ ($SD = 10.0$), and for PL, $M = 16.8$ ($SD = 11.9$).

(Piasecki et al., 1998, 2000) begs the question, Why has past research failed to reveal strong, consistent linkages between withdrawal and relapse? Previous studies used differing measurement instruments, sample compositions, and the intervals in which withdrawal is assessed prior to being summarized for entry into prediction models (Patten & Martin, 1996). Despite such methodological diversity, existing withdrawal–relapse research has been unified in one critical respect: It has focused on individual differences in withdrawal symptom *severity*, summarized in a single score (e.g., Gritz, Carr, & Marcus, 1991; Hughes, 1992; Hughes, Gust, Skoog, Keenan, & Fenwick, 1991; Kenford et al., 1994). These scores are often constructed to represent severity differences occurring during a relatively short epoch occurring early in the quit attempt (e.g., Week 1 post-quit).

The focus of previous research on individual differences in early severity probably stems from investigators' implicit acceptance of a simple physical dependence model of withdrawal score production (cf. Kenford et al., 2002). This practice makes sense if one assumes that withdrawal scores are chiefly influenced by cellular processes that follow a fixed time course for all individuals, such that symptoms always peak within the first week or so of quitting. Under this set of assumptions, simple measures of early symptom severity would be expected to adequately index all relapse-relevant variation in withdrawal scores. This is because individuals would be expected to only differ along a severity dimension, and the peak level of symptoms (presumably the point of maximal withdrawal-related relapse risk) would be captured by measures collected relatively early in the quit attempt.

Our withdrawal heterogeneity research has differed methodologically from much previous withdrawal–relapse research because we have adopted a different conceptual model of symptom score production, one that emphasizes broader affective processes in preference to a narrower physical dependence mechanism. Because affects are expected to be influenced by a host of both pharmacologic and nonpharmacologic factors, affect-laden symptom scales should vary considerably across both persons and time. Owing to this variability, individual differences in early withdrawal severity cannot be expected to sufficiently index all of the potentially relapse-relevant information contained in a set of withdrawal scores. To capture more information, statistical techniques that provide a relatively richer representation of individual differences in symptomatic experience are needed. Withdrawal heterogeneity research has used estimates of symptom pattern (e.g., cluster shape, slopes, volatility) to supplement individual differences in symptom severity in relapse prediction models and has integrated symptom data collected over a much longer postcessation span (e.g., 8 weeks). To the extent that this additional information is motivationally important and statistically independent of

Table 5
*Tests of the Moderation of Withdrawal Growth by Smoking Intensity in the Post-Lapse Period*

| Effect | Coefficient |
|---|---|
| Intercept | 8.33** |
| Cigarette effect | 1.16** |
| Linear slope | −0.09 |
| Cigarette effect | −0.15** |
| Quadratic trend | 0.07 |
| Cigarette effect | −0.02 |

*Note.* Total $n = 148$ (protracted lapsers $n = 24$, transient lapsers $n = 124$). "Cigarette effect" quantifies the strength of the moderating effect of cigarettes on each growth parameter. The cigarette effect coefficient must be multiplied by the number of cigarettes smoked, and the resulting quantity must be summed with the corresponding parameter estimate to yield the predicted effect for an individual (see Footnote 1 in text). For example, a person who smoked 10 cigarettes in the post-lapse period would be predicted to have an intercept of 19.93 [(10 × 1.16) + 8.33], a linear slope of −1.59 [(10 × −0.15) − 0.09], and a quadratic parameter of −0.13 ([10 × −.02] + .07).
** $p < .01$.

early severity differences, it enhances prediction of relapse from withdrawal data.

Another factor that has been cited as potentially hampering past research on withdrawal–relapse relations is *exclusion bias* (Jorenby et al., 1996; Patten & Martin, 1996)—limiting analyses to persons who were completely abstinent during the period when withdrawal ratings were collected. Exclusion bias may retard detection of withdrawal–relapse relations by eliminating from analyses precisely those subjects undergoing the most severe, motivationally potent withdrawal processes.

In this research, prediction from withdrawal parameters was substantially weaker in the analysis limited to the subsample of 8-week continuous abstainers, and withdrawal variables failed to improve these logistic models when added at a final step. These findings may indicate that relapse among long-term abstainers is simply not due to withdrawal- or treatment-related casual factors. However, this finding may also reflect the sorts of metric difficulties that can arise when lapsers are discarded from studies of withdrawal symptomatology. Only 257 participants maintained continuous abstinence over the 8 weeks during which symptoms were modeled. This represents a significant reduction in statistical power for prediction analyses. The relatively low relapse rate (37% vs. 71% in the mixed sample) and the relatively restricted range of withdrawal severity/patterning in abstainers compound the power problem and illustrate how distorted the resulting sample is, relative to clinical realities. To be sure, the present research represents an exaggerated version of exclusion bias. Fewer participants would have been eliminated and a higher ultimate relapse rate would have been observed if we had only limited the analyses to persons abstaining over the first 1–2 weeks of quitting (although Kenford et al., 1994, found that the great majority of those who ultimately relapse begin smoking in the first 1–2 weeks of the quit attempt). Although the present abstainer-only analyses may represent an extreme case, this sort of "worst-case scenario" is useful as an illustration of the potential hazards of exclusion bias. Treatment effects and other potential relapse predictors are commonly tested in mixed samples of lapsers and abstainers. In contrast, owing to investigators' fears that postcessation smoking will contaminate withdrawal reports, very high hurdles have been unintentionally erected for uncovering withdrawal–relapse relations.

Although prediction of relapse from withdrawal parameters was greatly weakened in the abstainer-only model, positive linear slope continued to predict relapse in this model, as it did in both models involving lapsers. Linear slope is clearly an integrative metric that could reflect the influence of myriad variables or processes. For instance, a positive linear slope might arise from either a chronic, cumulative psychological process or because numerous stressful experiences amass near the end of the measured period, driving late symptoms acutely higher. Although we can say relatively little definitively at present about the mechanisms that give rise to linear slope differences, the motivational impact of a positive slope seems easily apprehended: If symptoms generally seem to be getting worse over the quit attempt, then this should seriously undermine motivation to remain abstinent. The findings suggest that there may be a need to track symptom experiences in clinical settings and to adjust treatment strategy or intensity when symptoms worsen. The fact that positive linear slope foreshadowed relapse even in continuous abstainers suggests a need to perform such monitoring for all participants, regardless of the apparent stability of abstinence.

The logistic regression analyses did not crisply address the critical question of which comes first—unusual withdrawal patterning or smoking? If symptom swings motivate smoking to achieve symptom relief, then a trying pattern of symptoms should precede smoking lapses. In a second sequence of exploratory models, we addressed this question by keying withdrawal observations around the first lapse back to smoking, a moment when any motivational impact of withdrawal would presumably be translated into action. These analyses showed that at least some of relapsers' more severe symptomatology arises prior to any post-quit smoking and suggests a causal role of symptoms in precipitating relapse.

The lapse groups displayed somewhat distinctive patterns of withdrawal symptomatology over the cessation period; these hint at diverse paths to relapse. The PL group, who smoked on each of the 3 days following the first lapse, reported the most severe withdrawal in the Early and Pre-lapse windows but reported that their symptoms were improving at a rate that was equivalent to that of MA controls. On the lapse day, their ratings jumped considerably, and after the first lapse event, their symptoms were higher than in abstinence. These descriptive findings raise fascinating questions about the translation of severe withdrawal into protracted lapse. One possibility is that the sheer grind of enduring severe withdrawal takes a motivational toll, eventually prompting PL individuals to smoke the first cigarette. Smoking a cigarette after a period of abstinence has been shown to trigger acute increases in some withdrawal symptoms (Chornock, Stitzer, Gross, & Leischow, 1992), and perceived cessation failure may induce negative affect (Marlatt, 1985); the increased withdrawal severity reported on the lapse day by PL group members may reflect these effects. Alternatively, it may be the case that the acute rise in symptoms on the lapse day is attributable to situational events, such as stressors or exposure to smoking cues (Shiffman et al., 1996). Whatever the mechanism, it is interesting that despite continued smoking and a negative withdrawal slope, PL smokers' withdrawal scores remained higher than those reported by other groups for at least the first 5 days after the lapse.

The TL group, who re-established abstinence for at least 1 day shortly after the first lapse, reported withdrawal of intermediate severity during the Early and Pre-lapse intervals. Notably, however, this group was characterized by a significant quadratic trend in the pre-lapse period, the only statistically significant upswing in symptoms detected for any group. This worsening of symptomatology in the 1–2 days prior to the first lapse suggests that local dynamic changes in withdrawal are associated with the transition from abstinence to smoking (cf. Patten & Martin, 1996; Shiffman et al., 1997). The TL group's symptoms were lower after the lapse day than before it. This may have permitted the renewed attempts at abstinence that differentiated this group from the PL smokers. Nonetheless, a large percentage of TL members were counted as smoking at long-term follow-up assessment. A challenge for future withdrawal research will be to determine how smokers who survive the first lapse and re-establish abstinence eventually slip back into a pattern of regular smoking.

A focused growth model examining the relation between post-lapse smoking heaviness and symptom patterning showed that withdrawal symptoms decreased as a direct function of the amount smoked after the first lapse event. This finding is important for two reasons. First, it suggests the operation of negative reinforcement processes thought to contribute to relapse under many classic models of addictive behavior (e.g., Benowitz, 1991; Schachter, 1978). This observation, combined with the results of the early- and pre-lapse models, helps us to understand how an isolated lapse can trigger full-blown relapse to smoking. That is, the combination of both relatively high early symptoms and the availability of dose-dependent withdrawal relief would seem to be a particularly potent formula for relapse.

Second, the findings join with other data from this study (e.g., Piasecki et al., 2003) to illustrate the complicated relations between lapsing and withdrawal measures in clinical data. The present data provided three different representations of smoking and lapse, and these yielded different superficial associations with withdrawal parameters. In a companion article (Piasecki et al., 2003), we showed that lapse status, defined as any smoking during the first 8 weeks of the quit attempt, was associated with more extreme withdrawal parameters—higher intercepts, more positive linear slopes, and greater symptomatic volatility. Those findings were echoed in the exploratory piecewise analyses; TL and PL smokers showed, for example, higher withdrawal intercepts than MA participants in the Early, Pre-lapse, and Post-lapse periods. However, because they are focused on shorter time frames, the piecewise data can demonstrate finer-grained relations between smoking and withdrawal. Thus, in these analyses, symptom patterning differed as a function of both the duration of the lapse (number of consecutive days smoked after lapsing), the severity of the lapse (number of cigarettes smoked in the post-lapse period), and the time window under consideration. The modeled cigarette coefficient in the subsample of lapsers provided a third, complementary view of the relations between smoking and withdrawal symptoms. The cigarette coefficient captured any stable individual differences in the impact of smoking relative to the expected score derived from a fitted quadratic prediction function. These coefficients were related to the extensity of smoking during the 8-week post-quit period and to ultimate relapse, such that individuals with negative coefficients (acutely lowered withdrawal indicating reliable symptom relief occasioned by smoking) smoked more heavily and more often and were more likely to be smoking at long-term follow-up.

Taken together, the present data suggest that lapse–withdrawal relations are complex and that different functional relations will be obtained depending on the specific construction of a lapse variable. Different representations of lapse status are likely to be useful for distinct research purposes. The potential for exclusion bias requires that lapsers be included in withdrawal–relapse research. The complexity of lapse–withdrawal relations seen in our analyses argues for careful handling of lapse information in future withdrawal research.

What is the clinical and theoretical significance of our systematically replicated findings—findings showing that withdrawal symptoms are substantially predictive of a smoker's likelihood of relapse? It is important to recognize that most recent models of drug motivation adopt as a critical premise the notion that negative reinforcement mechanisms cannot account for cardinal features of addiction such as relapse (e.g., Robinson & Berridge, 1993; Stewart et al., 1984; Wise & Bozarth, 1987). Recent theorists have cited evidence that addicts typically report that withdrawal symptoms typically do not precipitate relapse and that correlational analyses suggest little association between withdrawal severity and relapse. Such theorists have made powerful arguments that alternative motivational models must be accorded importance by default. Our data suggest, however, that negative reinforcement mechanisms may have been given short shrift. If it is indeed the case that the extent of misery is the most telling and predictive setting event for relapse, this must be taken into account by modern models of addiction. Such models need not invoke a negative reinforcement mechanism per se to account for such findings; for instance, they might invoke the notion that aversive states inflate incentive effects (e.g., Robinson & Berridge, 1993). Nevertheless, they must accommodate the growing evidence that distress appears to characterize the prototypic relapse context and appears to index most sensitively the processes that yield relapse vulnerability (Kenford et al., 2002; Shiffman, 1982; Shiffman et al., 1996).

As implied earlier, the data presented here and in a companion article (Piasecki et al., 2003) do not necessarily implicate pharmacologic withdrawal specifically as a causal mechanism. The symptomatic dimensions that are tapped by the withdrawal assessments could reflect interpersonal stressors or other nonpharmacologic factors. Such factors, for instance, might be reflected especially in the volatility index. Theories need to take into account the link between distress and relapse, whether or not pharmacologic withdrawal per se is invoked as an explanation. Data such as those presented here, suggesting a significant link between symptoms and relapse, add to the importance of identifying the causal determinants of assessed symptoms.

This research could have clinical significance. First, it agrees with suggestions that negative affect should be a primary target of smoking cessation interventions (Hall, Muñoz, Reus, & Sees, 1993; Seidman & Covey, 1999). Second, it suggests that relapse might be anticipated and possibly be derailed through the tracking of symptomatic trajectories. The measure of symptomatic volatility was especially notable with respect to its substantial associations (e.g., ORs) with relapse. This suggests that information on the variable course of postcessation symptoms might be incorporated into treatment and used to help individuals steel themselves for the possibility of a prolonged or fluctuating withdrawal.

Limitations of the present studies should be noted. First, exposure to environmental stimuli that might have influenced the withdrawal syndrome was not assessed. Thus, the present findings yield relatively little information about the mechanisms of unremitting or exacerbating withdrawal symptoms. Moreover, although we attribute the diverse relations between withdrawal symptoms and lapsing to a motivational impact of withdrawal, other factors (e.g., third variables) could conceivably play a role as well. Second, we examined scores on a conventional self-report questionnaire that comprises primarily psychological complaints. Different findings might be obtained with objective measures (e.g., Brandon, Wetter, & Baker, 1996; Wetter, Fiore, Baker, & Young, 1995) or by scrutinizing other withdrawal signs. Furthermore, the self-reports were gathered nightly using paper-and-pencil measures. One major limitation of paper diaries is that they have the potential to be "back-filled." That is, some participants may complete a series of daily ratings immediately prior to visiting the study center so as to avoid embarrassment at having failed to complete the diaries as scheduled. In cases in which lapse events occurred prior to back-filling, participants' symptom ratings could have been adjusted to "explain" the lapse. It will be important to replicate these findings using time-stamped, real-time data collection strategies (e.g., Shiffman et al., 1996).

It is important to note that the analyses keyed around first lapses depict the reliable "signal" in subgroup withdrawal reports, and this necessarily conceals individual differences. Subgroup membership predictors did not completely account for variability in the pattern and level of symptoms, and the extensity and duration of smoking after the lapse event varied within the PL and TL groups. Although the TL–PL distinction is conceptually useful for depicting the relations between symptom dynamics and the severity of a lapse, the criterion used to form these groups was somewhat arbitrary and resulted in a PL group that was formed by a relatively small number of participants. Finally, to strengthen inference in the first-lapse analyses, we built models that permitted us to depict withdrawal after at least 5 days of continuous abstinence within each group. This necessitated eliminating a large number of participants who smoked within the first 5 days of the quit date.

Such limitations notwithstanding, the present data clearly extend the literature on linkages between withdrawal heterogeneity and smoking relapse in important directions. They demonstrate that distinct dimensions of postcessation symptom experience make independent contributions to relapse likelihood and demonstrate that unusual symptom dynamics, most notably positive linear slopes and symptom volatility, precede postreatment smoking. The results should encourage further research using multiple analytic strategies to understand the determinants of symptom dynamics and their translation into relapse.

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Received November 1, 2000
Revision received March 1, 2002
Accepted July 29, 2002 ■