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The First Seven Days of a Quit Attempt Predicts Relapse: Validation of a Measure for Screening Medications for Nicotine Dependence

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Abstract

Objectives—There is a critical need for the development of novel treatments for nicotine dependence. Since the majority of smokers who make a quit attempt fail within seven days, medication screening procedures which focus on this early cessation period may provide an indicator of treatment efficacy. To establish the clinical validity of this paradigm, it is critical to demonstrate the association of early abstinence with longer-term abstinence. We tested the number of days abstinent during the first week following the target quit date (TQD) as a predictor of point-prevalence abstinence in three independent pharmacotherapy trials for nicotine dependence.

Methods—This was a secondary data analysis of three randomized clinical trials: a placebo-controlled trial of transdermal nicotine (n=545); an open-label nicotine replacement therapy (patch vs. spray) trial (n=566); and a bupropion placebo-controlled trial (n=538). In separate logistic regression models, the maximum number of consecutive days of abstinence during the first week following the TQD was used to predict biochemically-verified 7-day point prevalence abstinence at end-of-treatment and six months post-TQD.

Results—Across the three trials, number of days abstinent significantly predicted abstinence at end-of-treatment and six months (ORs>1.4, p s<0.0001). Likewise, not having any lapse during the first week predicted abstinence at end-of-treatment and six months (ORs>4.7, p s<0.0001).

Conclusions—The first week of abstinence was highly predictive of end-of-treatment and long-term abstinence. Medication screening procedures which focus on this early abstinence period (i.e., six or seven days of consecutive abstinence) represent a valid tool for assessing the presence of a signal for medication efficacy.

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Keywords

Smoking cessation; nicotine dependence; medication screening; relapse

Despite the fact that cigarette smoking continues to be the greatest preventable cause of morbidity and mortality in the US, there are currently only three US Food and Drug Administration (FDA)-approved medications for smoking cessation: nicotine replacement therapy (NRT), bupropion, and varenicline. With varenicline, the most efficacious of these medications (Nides, 2008), fewer than 50% of smokers remain abstinent by the end of treatment and 75% of smokers relapse within 12 months (Cahill et al., 2011). Medication development is hampered by the enormous cost and time associated with bringing new drugs to market (Chong and Sullivan, 2007). Traditional drug development strategies can cost up to \$2 billion and take up to 14 years to bring a new drug to market (Paul et al., 2010). Early medication screening procedures reduce the resources necessary to evaluate a medication's potential as a cessation aid and may ultimately increase the availability of treatments to help more smokers quit (Perkins and Lerman, 2011; Perkins et al., 2006).

To provide a more efficient method of assessing treatment efficacy, early screening procedures need to demonstrate clinical validity. Recent medication screening paradigms have focused on the first seven days of a quit attempt to evaluate treatment efficacy because early abstinence is a vulnerable period for most smokers (Patterson et al., 2009; Perkins and Lerman, 2011; Perkins et al., 2006). Each year, 40% of smokers try to quit, but 50–75% relapse within the first week of a quit attempt (Garvey et al., 1992; Hughes et al., 2004). Further, withdrawal symptoms peak during the first few days of abstinence (Hughes, 2007; Shiffman et al., 2006), and these symptoms, in turn, predict relapse (Killen and Fortmann, 1997; Patterson et al., 2010; Rukstalis et al., 2005). These laboratory-based models of medication screening provide smokers with a medication and assess the number of days abstinent during a 7-day simulated quit attempt as the primary endpoint. Initial studies with FDA-approved smoking cessation treatments (e.g., nicotine patch (Perkins et al., 2008) and varenicline (Perkins et al., 2010)) suggest that this procedure is sensitive in detecting efficacy among treatment-seeking smokers. However, to establish this paradigm as a valid tool for screening novel drugs, it is critical to demonstrate that early abstinence predicts longer-term abstinence (i.e., odds of relapse).

Several studies have examined the relationship between early quit success and relapse. For example, quit date abstinence and any smoking during the first two weeks following the target quit date (TQD) are significantly related to abstinence at end of treatment and 6 months (Kenford et al., 1994; Westman et al., 1997). Compared to smokers who maintained continuous abstinence for two to four weeks following the TQD, those who did not were less likely to be abstinent at follow-up (Ferguson et al., 2009; Heffner et al., 2010; Romanowich and Lamb, 2010). In addition, 12 or more days of abstinence following the TQD predicted abstinence at 6 months (Baker et al., 2011). To our knowledge no studies have specifically tested the relationship between the number of days abstinent during the first week following a quit attempt and subsequent relapse. Using data from a large, phase III clinical trial of nicotine patch therapy for smoking cessation (Schnoll et al., 2010), we examined whether the total number of days abstinent during the first seven days following the target quit date (TQD) predicted abstinence following eight weeks of treatment and at 6-month follow-up. We then sought to replicate our findings using data from two independent clinical trials: a randomized open-label trial of nicotine patch vs. nicotine spray and a randomized placebo-controlled trial of bupropion (Lerman et al., 2006). These data could provide critical support for using laboratory models of short-term abstinence to evaluate treatment efficacy.

METHODS

Participants and Procedures (Study 1: Nicotine Patch Open-label Trial)

Treatment-seeking smokers responding to advertisements were screened for eligibility from 2004 to 2008 at the University of Pennsylvania. Eligibility criteria were: ages 18–65 and a smoking rate of >10 cigarettes per day for the previous 12 months. Exclusion criteria included a history of DSM-IV Axis I psychiatric disorders (except nicotine dependence), seizure disorder, current use of psychotropic medications, and pregnancy or lactation.

The study protocol was approved by the University of Pennsylvania institutional review board ([Clinicaltrials.gov](https://clinicaltrials.gov) registration number NCT00364156) and all procedures were conducted in accordance with the Declaration of Helsinki. Participants completed pretreatment assessments of demographics, smoking rate, depression, and nicotine dependence. Once eligibility was confirmed, participants were randomized to receive standard nicotine patch therapy (21mg transdermal nicotine for eight weeks and placebo for 16 weeks) or extended therapy (21mg transdermal nicotine for 24 weeks). After a pre-quit counseling session, transdermal nicotine-patch therapy was initiated on the TQD and continued for eight weeks (end-of-treatment; EOT). For the following 16 weeks, those in the extended treatment condition continued using nicotine patches while those in the standard treatment condition were given placebo patches. For this secondary data analysis, we used data collected to six months. During the first eight weeks, all participants received NRT and three sessions of behavioral counseling (Schnoll et al., 2010). In total, 269 (49%) participants were randomized to the extended nicotine patch condition, and 276 (51%) to the standard nicotine patch condition.

Participants and Procedures (Study 2: Nicotine Replacement Therapy Open-Label Trial [Patch vs. Spray]; NRT Trial)

Treatment-seeking smokers were recruited at Georgetown University (Washington, DC) and the University of Pennsylvania (Philadelphia, PA), from February 2000 to August 2003, using methods and inclusion criteria similar to those described above.

The study was approved by the institutional review boards from both universities ([Clinicaltrials.gov](https://clinicaltrials.gov) registration number NCT00326781) and all procedures were conducted in accordance with the Declaration of Helsinki. The procedures and outcome assessments were identical to those described above, except that participants were randomized to nicotine patch or nicotine nasal spray. Abstinence criteria were identical to those described above. In total, 284 (50%) participants were randomized to the nicotine patch condition, and 282 (50%) to the nicotine spray condition.

Participants and Procedures (Study 3: Bupropion Placebo Controlled Trial)

Treatment-seeking smokers responding to advertisements were screened for eligibility from April 1999 to October 2001 at Georgetown University and SUNY Buffalo (New York). Inclusion criteria were similar to those described above.

The study was approved by the institutional review boards from both universities ([Clinicaltrials.gov](https://clinicaltrials.gov) registration number NCT00322205) and all procedures were conducted in accordance with the Declaration of Helsinki. Participants at both sites received identical assessments of demographics, smoking rate, and nicotine dependence (FTND) (Heatherton et al., 1991). In this double-blind placebo controlled study, participants were randomized to receive 10 weeks (EOT) of bupropion or matched placebo. Bupropion was administered according to the standard dosing regimen (150 mg/day for the first three days, followed by 300 mg/day). Participants were instructed to quit on a TQD two weeks after initiating

treatment. All participants received seven sessions of standardized cessation counseling during the medication phase. For this secondary data analysis, we used data collected to six months. There were 265 (49%) participants randomized to the placebo condition, and 274 (51%) to the bupropion condition.

Measures and Outcomes

Covariates—Questionnaires to collect socio-demographic (e.g., age, education, etc.) and smoking history information (e.g., cigarettes per day, FTND) as well as the CES-D scale were completed.

First Week of Abstinence—Self-reported abstinence during the first week following the TQD was assessed via timeline followback methods as in previous work (Brown et al., 1998; Schnoll et al., 2010). The maximum number of consecutive days of abstinence was recorded. Participants who did not report at least one 24-hour period of abstinence were included in analyses and coded as “0” days abstinent.

We were interested in whether the relationship between early abstinence and subsequent relapse was being driven by those who maintained abstinence for all seven days during the first week following the TQD. For all three studies, we conducted additional models including only those subjects who smoked during the first week. Finally, we tested whether the dichotomous measure of any smoking during the first week predicted point-prevalence abstinence.

Point-prevalence abstinence—The primary outcomes were 7-day point-prevalence abstinence at EOT (eight weeks for Studies 1 and 2 and 10 weeks for Study 3) and at 6-month follow-up. Self-reported smoking for the seven days prior to these assessments was biochemically verified. Participants who were lost to follow-up, could not provide bioverification of abstinence, had exhaled breath carbon monoxide (CO) levels greater than 8ppm (Studies 1 and 2) (Benowitz et al., 2002), or had saliva cotinine >15 ng/ml (Study 3) were assumed to be smoking.

Statistical Analysis

Separate logistic regression models examined whether the maximum number of consecutive days of abstinence (out of seven) following the TQD predicted point-prevalence abstinence at EOT and at 6-month follow-up in the nicotine patch open-label trial. To provide support for the predictive validity of the number of days abstinent following the TQD, identical models were conducted in two independent samples: the nicotine replacement therapy (patch vs. spray) trial and the bupropion placebo-controlled trial. Sex, nicotine dependence, baseline depression scores, and race (white vs. other) were covariates in the models. For the nicotine patch therapy and NRT trial, treatment arm was only included for the models testing abstinence at six months because all participants were using treatment through week 8 and no significant treatment arm effects were found at EOT (Lerman et al., 2006; Schnoll et al., 2010). Drug condition (bupropion vs. placebo) was included in both models for the bupropion placebo-controlled trial.

In addition, we examined models predicting point-prevalence abstinence including only those who smoked at least once during the first week following the TQD. We also examined models using the dichotomous measure (i.e., any smoking during the first week) as a predictor of point-prevalence abstinence. Finally, we tested the assumption of linearity of the predictor based on methods described by Box and Tidwell (1962) using the `boxtid` command in Stata.

RESULTS

Participant Characteristics

Table 1 depicts demographic and smoking characteristics for all participants across the three clinical trials. For the nicotine patch therapy trial, 23 of the 568 participants in the intent-to-treat analysis were missing timeline followback data during the first week after the quit attempt. Thus, the sample for the current analysis consisted of 545 smokers. One of the 567 participants in the intent-to-treat analysis for the NRT trial and 8 of the 546 participants in the intent-to-treat analysis for the bupropion trial were missing values on one or more covariates. Thus, the samples for these analyses were 566 and 538, respectively.

Abstinence in the Nicotine Patch Open-Label Trial (Study 1)

Table 2 depicts the point-prevalence abstinence rates by the maximum number of consecutive days of abstinence during the first week following the TQD for each clinical trial. Out of 545 smokers, 180 (33%) and 146 (27%) met criteria for point-prevalence abstinence at EOT and at six months, respectively. Logistic regression models predicting point-prevalence abstinence at EOT and at six months were significant ($p < 0.001$). Each additional day of abstinence during the first week increased the odds of being abstinent by 1.6 (95% CI 1.45–1.81, $p < 0.0001$) and by 1.4 (95% CI 1.27–1.57, $p < 0.0001$) at EOT and at six months, respectively. There were no other significant predictors at EOT, $p > 0.13$. At six months, the extended patch group was more likely to be abstinent (ORs=1.8, 95% CI 1.22–2.80, $p = 0.004$) as were those with lower baseline depression scores (ORs=0.96, 95% CI 0.92–0.99, $p = 0.01$). There were no significant interactions with the number of days abstinent.

Not surprisingly, not having any lapse during the first week following the TQD significantly predicted abstinence at EOT and six months (OR=7.4, 95% CI 4.8–11.4, $p < 0.0001$ and OR=4.8, 95% CI 3.1–7.5, $p < 0.0001$, respectively).

Abstinence in the Nicotine Replacement Therapy Open-Label (Patch vs. Spray) Trial (Study 2)

Out of 566 smokers, 189 (33%) and 114 (20%) met criteria for point-prevalence abstinence at EOT and at six months, respectively. Both logistic regression models predicting point-prevalence abstinence were significant ($p < 0.001$). At EOT and at six months, each additional day of abstinence during the first week increased the odds of being abstinent by 1.65 (95% CI 1.48–1.85, $p < 0.0001$) and by 1.4 (95% CI 1.26–1.60, $p < 0.0001$), respectively. There were no other significant predictors, $p > 0.11$.

Those who were abstinent all seven days during the first week were 9.4 (95% CI 6.1–14.7, $p < 0.0001$) times more likely to be abstinent at EOT and 6.1 (95% CI 3.7–10.2, $p < 0.0001$) times more likely to be abstinent at six months compared to those who reported any lapse during the first week.

Bupropion Placebo Controlled Trial (Study 3)

Out of 538 smokers, 150 (27%) and 117 (22%) met criteria for point-prevalence abstinence at EOT and at six months. Both logistic regression models predicting point-prevalence abstinence were significant ($p < 0.001$). At EOT and at six months, each additional day of abstinence during the first week increased the odds of being abstinent by 1.7 (95% CI 1.5–1.9, $p < 0.0001$) and by 1.6 (95% CI 1.43–1.82, $p < 0.0001$), respectively. There were no other significant predictors, $p > 0.08$. Because the bupropion group had significantly higher abstinence rates at end-of-treatment and at six months (Lerman et al., 2006) and had significantly more days abstinent during the first week compared to the placebo group (4.7

vs. 3.4 days, respectively, $p<0.0001$), we tested whether treatment group interacted with number of days abstinent. The interaction was not significant at either EOT or six months ($ps>0.06$).

Not having any lapse during the first week significantly predicted point-prevalence abstinence at EOT (OR=9.0, 95% CI 5.7–14.2, $p<0.0001$) and at six months (OR=7.2, 95% CI 4.4–11.8, $p<0.0001$), compared to those who were abstinent all seven days.

Excluding Smokers Who Maintained Abstinence All Seven Days During the First Week

For the models including only participants who lapsed during the first week, the number of days abstinent significantly predicted point-prevalence abstinence in the nicotine patch trial ($n=286$) at EOT (ORs=1.4, 95% CI 1.15–1.71, $ps=0.001$) and at six months (ORs=1.2, 95% CI 1.01–1.48, $ps=0.03$). For the NRT trial ($n=292$), the number of days abstinent was a significant predictor at EOT (ORs=1.2, 95% CI 1.02–1.5, $ps=0.03$), but not at six months, $p=0.66$. For the bupropion trial ($n=321$), the number of days abstinent significantly predicted abstinence at EOT (OR=1.6, 95% CI 1.4–2.0, $p<0.0001$) and at six months (OR=1.6, 95% CI 1.3–1.9, $p<0.0001$).

Test of Linearity of Predictor

For the nicotine patch and bupropion trials, the test of nonlinearity was not significant at either follow-up timepoint ($ps>0.27$), suggesting the assumption of linearity was met. For the NRT trial, the test of nonlinearity was significant at both timepoints ($ps<0.01$), suggesting the assumption of linearity was not met.

CONCLUSIONS

This study provides evidence that abstinence during the first week of a quit attempt is highly predictive of abstinence at follow-up. Using data from a randomized controlled trial of transdermal nicotine, we showed that continuous abstinence of the first six or seven days following the TQD corresponded to an increased likelihood of being abstinent following eight weeks of treatment. In other words, compared to those whose initial lapse occurred within 24 hours (i.e., zero days of abstinence), those who were completely abstinent for the first seven days were 32 times more likely to be abstinent after eight weeks of treatment. Importantly, this effect was evident at six months post-TQD and was consistent across three separate pharmacotherapy trials for smoking cessation. These findings suggest that abstinence during the first week may be a useful indicator of the efficacy of novel treatments for nicotine dependence. Although our hypothesis that the number of days of abstinence predicts relapse was supported, the data also indicated that any smoking during the first week may be a stronger predictor of longer-term abstinence.

We provide evidence that six or seven days of abstinence, compared to zero days, during the first week of a quit attempt significantly improves a smoker's odds of being abstinent at EOT. Although slightly weaker at six months post-TQD, this index of early abstinence remained a robust predictor of abstinence at follow-up across all three clinical trials. The majority of participants abstinent at follow-up were abstinent for all seven days following the TQD, suggesting that any occurrence of a lapse during early abstinence may be more important to capture than our continuous measure. Indeed, when individuals who were abstinent all seven days were excluded from analyses, the effect size for number of days abstinent predicting treatment success at EOT was substantially smaller, though statistically significant. At six months post-TQD, the patterns were similar in the nicotine patch and bupropion trials, but not the NRT trial. For example, those who were abstinent for one day during the first week were more likely to be abstinent at follow-up compared to those with

zero days. In contrast, those who were consecutively abstinent for five days did not appear to have an increased likelihood of success compared to those who were abstinent for two days during the first week. In general, patterns were consistent across three independent pharmacotherapy trials, supporting the clinical validity and generalizability of any smoking during the first week as an indicator of subsequent treatment success.

Our findings may provide novel information regarding how a particular treatment promotes abstinence. For example, prior analysis of the bupropion trial revealed significantly higher abstinence rates in the bupropion group compared to the placebo group (Lerman et al., 2006). In the current analyses, when number of days abstinent was included in the model predicting point-prevalence abstinence at six months, the effect of bupropion was not significant. While we were not testing mediating effects of treatment, bupropion may be efficacious, in part, by reducing early lapses, which in turn promotes long-term abstinence. Although it is unclear as to why these results differed, this may be a question for future research and may be addressed by more sophisticated models predicting abstinence (e.g., Li et al., 2011; Wileyto et al., 2004).

Identifying smokers at high risk for early relapse (i.e., within the first week) may be a useful tool to adjust treatments to maximize a smoker's likelihood of successfully quitting. Recently, the notion of adaptive treatments has gained traction, including treatments for nicotine dependence (Hughes, 2008; Murphy and McKay, 2004). These treatments utilize data as they are collected to adjust the dose, duration, or type of treatment (Brown et al., 2009). Our data indicate that the occurrence of any lapse during the first week may be a useful index of failure to respond to treatment. Across treatments, less than 1% of smokers who failed to maintain at least 24 hours of abstinence during the first week were abstinent at EOT or 6-month follow-up. This information may enable characterization of individual differences related to relapse as well as groups of smokers who may be "hard-to-treat" (Japuntich et al., 2011; Morral et al., 1997). We propose that this dichotomous measure may have utility in clinical settings where clear rules regarding continuation of treatment may be necessary. Collecting information regarding the number of days abstinent may be useful in research settings by providing more fine grained information, but six or seven days of abstinence during the first week following the TQD may be more useful as a proxy of a smoker's success. Thus, these data provide direct validation that laboratory-based screening studies may be used to identify novel therapeutics for nicotine dependence.

We have been developing initial screening procedures to evaluate treatment efficacy at earlier stages of development to reduce the burden associated with developing new medications and increase the likelihood that effective new drugs will be brought to market. These procedures, which focus on the first seven days of abstinence, combine the practical advantages of human laboratory studies with the clinical validity of clinical trials (Perkins and Lerman, 2011; Perkins et al., 2006). For instance, these early screening procedures require smaller sample sizes and fewer resources because the primary outcome is sensitive to treatment effects at the early stages of abstinence. Although findings from the current clinical trials may not extend to acute laboratory studies, initial validation studies suggested that, compared to placebo, transdermal nicotine and varenicline increased the number of days abstinent during the first week among smokers with high motivation to quit (Patterson et al., 2009; Perkins et al., 2010; Perkins et al., 2008). Indeed, motivation to quit may represent an important difference between smokers in clinical trials and those in laboratory studies. Thus, our screening studies recruit treatment-seeking smokers. Although our findings were consistent across two of the three FDA-approved treatments for nicotine dependence, it would be useful to replicate these results with varenicline. Nevertheless, our data suggest that the first week of abstinence represents a valid marker for assessing the presence of a signal for medication efficacy.

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Table 1

Demographic and Smoking Characteristics Across Three Pharmacotherapy Trials for Nicotine Dependence

	Nicotine Patch Open- Label Trial N=545	Nicotine Replacement (Patch vs. Spray) Trial N=566	Placebo-controlled Bupropion Trial N=538
Sex (n, % female)	245, 45%	303, 54%	305, 56%
Race (n, % Caucasian)	463, 85%	377, 67%	424, 79%
Age (years)	45.6 (10.3)	45.7 (10.7)	45.0 (11.2)
Baseline Depression	9.0 (6.7)	11.8 (8.6)	12.2 (8.3)
CPD	21 (9.2)	21.8 (9.9)	21.0 (9.5)
FTND	5.3 (2.1)	5.5 (2.1)	5.2 (2.1)

Note: Except where indicated, all the values represent mean and standard deviation (SD).

FTND=Fagerstrom Test for Nicotine Dependence; CPD=cigarettes per day

Table 2

Point-prevalence abstinence rates by the maximum number of consecutive days of abstinence during the first week following the TQD for each clinical trial.

Point-prevalence Abstinence Rates									
Days	Nicotine Patch Trial			Nicotine Replacement Therapy Trial			Bupropion Trial		
	Total n	# (%) Abstinent EOT	# (%) Abstinent 6 months	Total n	# (%) Abstinent EOT	# (%) Abstinent 6 months	Total n	# (%) Abstinent EOT	# (%) Abstinent 6 months
0	82	3 (3.7)	4 (4.9)	69	4 (5.8)	6 (8.7)	122	3 (2.5)	4 (3.3)
1	23	3 (13.0)	4 (17.4)	23	3 (13.0)	3 (13.0)	34	3 (8.8)	1 (2.9)
2	38	1 (2.6)	4 (10.5)	33	4 (12.1)	2 (6.1)	33	2 (6.1)	2 (6.1)
3	43	9 (20.9)	5 (11.6)	57	7 (12.3)	4 (7.0)	45	5 (11.1)	4 (8.9)
4	52	9 (17.3)	9 (17.3)	42	5 (11.9)	1 (2.4)	37	8 (21.6)	4 (10.8)
5	23	5 (21.7)	3 (13.0)	37	6 (16.2)	2 (5.4)	25	2 (8.0)	2 (8.0)
6	25	8 (32.0)	7 (28)	31	7 (22.6)	5 (16.1)	24	11 (45.8)	10 (41.7)
7	259	142 (54.8)	110 (42.5)	274	153 (55.8)	91 (33.2)	218	116 (53.2)	90 (41.3)