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Experimental Evidence for a Causal Relationship Between Smoking Lapse and Relapse

Laura M. Juliano
American University

Eric C. Donny, Elisabeth J. Houtsmuller, and Maxine L. Stitzer
Johns Hopkins University School of Medicine

In this study, the authors prospectively evaluated the impact of a smoking lapse on relapse probability. After 4 days of smoking abstinence, 60 smokers were randomly assigned to smoke 5 nicotine-containing or 5 denicotinized cigarettes, or to remain abstinent (no lapse) during a 4-hr time period. Afterward, smoking abstinence was encouraged with monetary incentives, and smoking behavior was tracked for 6 days. Relative to the no-lapse condition, exposure to either of the cigarette types more than doubled the probability of subsequent smoking. Smoking outcomes did not differ between nicotine-containing and denicotinized cigarettes. The data suggest that stimulus factors may play an important role in lapse to relapse processes.

Keywords: smoking, lapse, relapse, denicotinized, nicotine

Relapse continues to be the most likely outcome of an attempt to quit smoking. As many as 85%–90% of individuals who attempt to quit return to regular smoking within 1 year (Baer, Kamarck, Lichtenstein, & Ransom, 1989; Brandon, Tiffany, Obremski, & Baker, 1990; Garvey, Bliss, Hitchcock, Heinold, & Rosner, 1992). The relapse process begins with a single smoking episode, which may appear at the outset to be a *lapse* or a *slip*. Although it is possible that an individual could achieve long-term abstinence despite having had a smoking lapse, this is rarely the case. Rather, 79%–97% of individuals who experience a smoking lapse subsequently return to some pattern of regular smoking (e.g., indicated by 3 or more consecutive days of smoking; Baer et al., 1989; Brandon et al., 1990; Garvey et al., 1992; Kenford et al., 1994; Shiffman et al., 1996). The apparent inevitability of a smoking lapse leading to full relapse is of great concern because initial smoking lapses are common and cannot always be avoided, and the mechanisms underlying the lapse–relapse association have not been elucidated.

A number of explanations in the addictions research literature point to a direct and causal role of lapse in increasing relapse probability. It has been suggested that negative cognitive and affective reactions to a lapse, referred to as abstinence violation effects (AVEs; e.g., feelings of defeat, guilt), undermine quitting success by promoting further drug taking (Marlatt & Gordon, 1985). At present, studies relating AVE reactions to relapse have reported mixed findings (Shiffman et al., 1996).

Reexposure to the pharmacological effects of the drug during the lapse is also believed to directly promote relapse. A rich body of preclinical research has demonstrated that after operant responding for drugs has been acquired and subsequently extinguished, a single injection of a drug, but not saline, will reinstate drug-seeking behavior (de Wit, 1996; Shaham, Shalev, Lu, de Wit, & Stewart, 2003). Such reinstatement, or *priming effects*, have been shown to occur in animals across a wide variety of drugs, including nicotine (Chiamulera, Borgo, Falchetto, Valerio, & Tessari, 1996; Shaham, Adamson, Grocki, & Corrigall, 1997).

There is also a growing appreciation of the importance of nonpharmacological factors and associative mechanisms in drug self-administration and relapse dynamics (Bouton, 2002; Caggiula et al., 2001). Drug-associated stimuli have also been shown to reinstate drug-seeking behavior in animals when presented after extinction in the absence of the drug (reviewed in Shaham et al., 2003). For example, a recent study demonstrated that contingent presentation of stimuli previously associated with nicotine was sufficient to reinstate nicotine-seeking behavior in rats (Paterson, Froestl, & Markou, 2005). Furthermore, stimulus effects may be critically important for nicotine reinforced behavior. Stimuli associated with nicotine delivery have been shown to potentiate acquisition, retard extinction, and facilitate the reacquisition of nicotine self-administration in rodent models of nicotine self-administration (Caggiula et al., 2001, 2002; Donny et al., 1998). These data suggest that the drug-associated cues present during a lapse may also play an important and direct role in increasing the motivation to use drugs.

At this time, variations of the drug reinstatement model have been used to a limited extent with humans. Doses of alcohol,

Laura M. Juliano, Department of Psychology, American University; Eric C. Donny, Elisabeth J. Houtsmuller, and Maxine L. Stitzer, Behavioral Pharmacology Research Unit, Johns Hopkins University School of Medicine.

Eric C. Donny is now at the Department of Psychology, University of Pittsburgh.

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Correspondence concerning this article should be addressed to Laura M. Juliano, Department of Psychology, American University, 4400 Massachusetts Avenue, NW, Washington, DC 20016. E-mail: juliano@american.edu

cocaine, or heroin have been shown to increase drug craving in users of the particular drug after a short period of abstinence (de Wit, 1996). Studies have also shown that priming doses of alcohol increase alcohol self-administration in alcoholics (Bigelow, Griffiths, & Liebson, 1977; Ludwig & Wikler, 1974) and social drinkers (de Wit & Chutuape, 1993). Cocaine users are also more likely to choose cocaine over money after a priming dose of cocaine (Donny, Bigelow, & Walsh, 2004).

Only one published study to date has directly and prospectively examined the effects of smoking reexposure after a brief abstinence period in humans (Chornock, Stitzer, Gross, & Leischow, 1992). In this study, after 3 days of required smoking abstinence, participants were randomly assigned to either smoke five of their own cigarettes or remain abstinent during a discrete time period. Afterward, all participants were free to return to smoking during a 4-day observation period. Participants who experienced the programmed lapse returned to smoking more rapidly than those who did not. This study provides important empirical evidence that smoking exposure after abstinence increases the probability of subsequent smoking. However, this study cannot help to discern whether smoking exposure led to subsequent smoking because of exposure to nicotine in the cigarette smoke or to the other familiar stimulus properties of smoking.

Nicotine is believed to be the main pharmacologically active ingredient in cigarette smoke responsible for maintaining smoking behavior (Stolerman & Jarvis, 1995). However, it has been hypothesized that nonnicotine smoking-associated stimuli may also play a crucial role in smoking maintenance and relapse, presumably because of learned associations with nicotine (Caggiula et al., 2001; Rose, Behm, Westman, & Johnson, 2000). Previous research has demonstrated that both nicotine and denicotinized cigarettes are capable of alleviating craving and withdrawal symptoms (Gross, Lee, & Stitzer, 1997; Juliano & Brandon, 2002; Pickworth, Fant, Nelson, Rohrer, & Henningfield, 1999), and that denicotinized cigarettes function as a reinforcer (Shahan, Bickel, Madden, & Badger, 1999). However, no published study to date has evaluated the impact of cigarettes with varying nicotine contents on lapse exposure effects.

The goal of the current study was to evaluate the effects of a smoking-lapse episode on relapse outcomes and to determine the importance of nicotine in smoking-lapse exposure effects. Smokers who were not seeking cessation treatment participated in a 10-day study that involved a temporary quit attempt during which a smoking-lapse episode was experimentally manipulated. Monetary incentives were used to introduce uniform levels of pre- and postmanipulation abstinence motivation. We compared the effects of smoking nicotine-containing cigarettes, smoking denicotinized cigarettes, or not lapsing on subsequent smoking likelihood. It was hypothesized that individuals in the two smoking-lapse conditions (i.e., exposed to nicotine or denicotinized cigarettes) would have shorter latency to self-initiated smoking than those in the no-lapse condition. Predictions concerning the comparison of nicotine and denicotinized cigarettes were less straightforward. On one hand, it is possible that smoke containing nicotine would more effectively activate brain reward systems (Balfour, Wright, Benwell, & Birrell, 2000; Di Chiara, 2000) or more closely approximate smoking conditioning histories and thus be more likely to reinstate subsequent drug taking. On the other hand, the similarity of subjective and reinforcing effects between nicotine and denicotinized cigarettes in previous studies suggests that exposure to smoking stimuli in the absence of nicotine may be sufficient to motivate subsequent drug taking via conditioning or other mechanisms, effectively overshadowing any effect of nicotine.

Method

Participants

Cigarette smokers ($N = 87$) were recruited from the community through newspaper advertisements and flyers. During a screening telephone call, potential volunteers were told that this was not a stop-smoking program but that the research would involve a "practice quit attempt." They were informed that they would be asked to stop smoking for several days but that they may also be asked to smoke several cigarettes as part of the study following a few days of abstinence. Those who indicated they wished to make a permanent quit attempt within the next 30 days were screened out of the sample at this point. Other inclusion criteria were as follows: 18–65 years of age, history of smoking at least 10 cigarettes per day for the past year, negative pregnancy and illicit drug screen tests, and medically healthy. A subset of participants ($n = 60$; 69%) achieved the required 4 days of continuous abstinence and were randomly assigned to the experimental manipulations. The characteristics of participants who did and did not achieve the initial 4 days of continuous abstinence are described in Table 1.

Materials

The experimental cigarettes were developed by Ultratech (Lafayette Hills, Pennsylvania). The denicotinized cigarettes contained a subpharmacological dose of nicotine (0.07 mg), and the nicotine cigarettes contained 0.6 mg nicotine. The two cigarettes had equivalent tar levels (11 mg). To maintain double-blind experimental conditions, experimenters who had no contact with the participants set out cigarettes ahead of time.

Table 1
Participant Characteristics

Characteristic	Randomly assigned ($n = 60$)	Discharged[a] ($n = 27$)
Gender		
% Women	48	52
% Men	52	48
Race (%)		
Caucasian	55	41
African American	40	48
Asian	5	4
Other	0	7
Age (years)	37.25 (13.97)	40.15 (13.14)
Cigarettes per day	20.29 (9.83)	20.13 (9.75)
Years smoked	17.99 (13.42)	22.02 (13.08)
FTND (0–10)	5.12 (2.10)	5.81 (2.18)
CO at baseline (ppm)	17.65 (10.50)	18.93 (11.86)
Contemplation Ladder (0–10)	7.67 (2.63)	7.88 (2.47)
Beck Depression Inventory (0–63)	9.61 (8.73)	6.42 (7.63)
Previous serious quit attempts	3.39 (5.01)	3.74 (6.19)
Abstinence confidence (0–6)	5.05 (1.66)	5.15 (1.69)
Desire to quit (0–6)	5.50 (1.73)	5.92 (1.26)

Note. Values are means and standard deviations (in parentheses) unless otherwise noted. FTND = Fagerström Test for Nicotine Dependence; CO = carbon monoxide.
[a] Participants were discharged from the study if they smoked during the first 4 days of required abstinence.

Procedure

Participants who passed the brief phone screening attended a baseline visit to determine final eligibility (i.e., medical, drug, and pregnancy screen), complete baseline assessments, and receive study instructions. Participants were told that their practice quit attempt would last 10 days and that they must remain completely abstinent for the first 4 days (compensated $80.00 for doing so) to continue participation in the study. They were told that the purpose of the study was to examine responses to smoking after a brief period of abstinence and that there was a two out of three chance that they would be asked to smoke cigarettes (that could contain either nicotine or no nicotine) on the 4th day of the abstinence period.

Participants chose a quit day, which always occurred on a Sunday (usually within 1 week of the baseline screening visit) and were instructed to quit smoking at 4:30 p.m. Participants visited the laboratory the following day (Monday—Day 1) and were given a brief (about 45 min) individual smoking cessation counseling session that included information about how to anticipate and prepare for high-risk situations and tips for dealing with nicotine withdrawal symptoms. All participants were also given a smoking cessation booklet that was developed by our laboratory on the basis of empirically validated principles of effective smoking cessation. The purpose of these interventions was to help as many participants as possible achieve the required 4 days of smoking abstinence necessary to participate in the experimental phase of the study. Participants returned to the laboratory on Tuesday (Day 2), Wednesday (Day 3), and Thursday (Day 4) to complete measures, submit smoking self-monitoring forms, sign a statement that they have not smoked, and provide breath carbon monoxide (CO) and salivary cotinine samples to validate self-reported smoking abstinence. Participants who reported smoking or had a carbon monoxide reading greater than six parts per million or a salivary cotinine reading greater than 1 on a NicAlert (Nymox Pharmaceutical, Maywood, New Jersey) strip (>30 ng/μl) during Visits 2–4 were discharged from the study and paid $5.00 for each of their visits to the laboratory. The cotinine criterion was not applied to Day 1 because there may have been residual elevations from prior smoking. Participants who demonstrated continuous abstinence at the morning Day 4 visit were randomly assigned to one of three experimental manipulations: (a) smoke five nicotine-containing cigarettes, (b) smoke five denicotinized cigarettes, or (c) no lapse. For participants assigned to the smoking conditions, the first cigarette was smoked in the laboratory through a puff topography device (data not reported). Heart rate and time spent smoking the cigarette were recorded. Afterward, participants provided a carbon monoxide sample and completed the cigarette rating questionnaire as well as measures of craving, mood, withdrawal, confidence, and desire to quit. Participants in the smoking conditions were then provided with four additional cigarettes of the same type to smoke in their natural environment over the next 4 hr. They were instructed to smoke the four experimental cigarettes on an ad libitum basis and to refrain from smoking any other cigarettes. Participants in the no-lapse condition were instructed to continue to abstain. When participants returned to the laboratory later that afternoon, they submitted four cigarette butts (smoking conditions only), provided salivary cotinine and expired air carbon monoxide samples, and completed measures described below. All participants reported having complied with the instructions, and carbon monoxide readings were consistent with self-reports.

At that time, all participants were instructed to abstain from smoking for the next 6 days and were reminded that they could receive abstinence incentives if they did so. The abstinence incentive schedule was modeled after a procedure developed by Donny et al. (2004) and used a series of daily choices between smoking versus money. The series began with $12.00 per day payment for confirmed smoking abstinence on Days 5 and 6. The pay amount then decreased to $9.00 per day for Days 7 and 8, and to $6.00 per day for Days 9 and 10. As the payment for abstinence declined, it was anticipated that participants would be more inclined to smoke. Participants were informed that the chance to earn abstinence-contingent payments would stop as soon as smoking was detected. To ensure that follow-up requirements were not a factor in the decision to smoke or remain abstinent, we told participants that if they smoked, they would still be required to attend all remaining laboratory visits at a pay rate of $5.00 per visit. Although *relapse* was defined as detection of the first smoking episode after the final Day 4 visit, the first instance of smoking generally marked a return to daily smoking. For example, among 18 participants who initiated smoking within 72 hr of the manipulation, 17 continued to smoke on at least the next 3 consecutive days.

Participants returned to the laboratory on Days 5, 6, 8, and 10 to complete measures, submit self-monitoring forms, sign a statement that they had or had not smoked, and provide breath carbon monoxide and salivary cotinine samples. Smoking was implicated by a breath carbon monoxide greater than 6 ppm, saliva cotinine dipstick reading greater than 1 (i.e., 30 ng/μl), or self-report of any smoking. A maximum of $184.00 could be earned for study participation: $5.00 for each of 10 laboratory visits, $80.00 for the first 4 days of continuous abstinence, and $54.00 for postmanipulation abstinence.

Measures

Breath carbon monoxide. Breath carbon monoxide samples were collected (Vitalograph, Lenexa, Kansas) to verify smoking status at every study visit. Pre- to postsmoking changes in carbon monoxide level also provided a measure of the amount of smoke inhaled during the experimental manipulation.

Salivary cotinine. We assessed cotinine during each of the laboratory visits using the NicAlert Strip Test Kit (Nymox Pharmaceutical, Maywood, New Jersey). Test strips provide a reading between 0 and 6 that indicates the level of recent smoking exposure. Test strip readings have been shown to reliably differentiate smokers and nonsmokers and correlate with gas chromatography cotinine analysis. Smoking abstinence was indicated by a reading of 0 (1–10 ng/μl cotinine concentration) or 1 (10–30 ng/μl cotinine concentration). Additional saliva samples were collected under the guise that they would be sent out for a more sensitive analysis of whether the participant smoked. This type of bogus pipeline procedure has been shown to increase the accuracy of self-reported smoking behavior (Aguinis, Pierce, & Quigley, 1993).

The following three self-report measures were administered at baseline only:

Smoking history questionnaire. This questionnaire contained questions about smoking history and included a standardized measure of nicotine dependence, the Fagerström Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991).

Beck Depression Inventory. The Beck Depression Inventory (Beck, Steer, & Brown, 1996) is a well-validated measure of depression severity that measures the intensity of 21 depressive symptoms on a 4-point scale ranging from 0 to 3, with higher scores reflecting progressively more severe symptomatology.

Contemplation Ladder. The Contemplation Ladder assesses readiness to quit smoking by having respondents circle a number between 0 (*no thoughts of quitting*) and 10 (*taking action to quit*). It has been shown to predict subsequent participation in smoking cessation programs (Biener & Abrams, 1991) and quitting success (Abrams, Herzog, Emmons, & Linnan, 2000).

An additional battery of self-report measures described below was administered at baseline, during each study visit, and before and after the experimental manipulation.

Confidence/desire to quit. This measure was developed for this study. Participants were asked how confident they were that they could "quit smoking at this time," "abstain from cigarettes for the next 24 hours," "abstain from cigarettes until the end of the study," and that they would "not be smoking one month from today." Confidence was

rated on a 7-point scale ranging from 0 (*not at all confident*) to 6 (*extremely confident*). The four items demonstrated very high internal consistency ($\alpha = .90$) and were averaged to form a single confidence score. Participants were also asked to rate their "desire to quit smoking at this time" on a 7-point scale ranging from 0 (*no desire at all*) to 6 (*extreme desire*).

Positive and Negative Affect Schedule. The Positive and Negative Affect Schedule (Watson, Clark, & Tellegen, 1988) is a reliable ($\alpha > .85$) and valid measure of positive and negative affect. It lists 20 adjectives that participants rate on a 5-point Likert scale ranging from 1 (*not at all*) to 5 (*extremely*) indicating how they feel "at this moment." Ten adjectives assess positive affect, and 10 adjectives assess negative affect. Total scores for positive affect and negative affect were used in the analysis, as well as the single item "guilt."

Craving scale. This scale consisted of five items that assessed craving to smoke. Items were as follows: "How pleasant would a cigarette be right now?," "How much of an urge or desire do you have to smoke right now, just for the pleasure of smoking?," "How much do you need to smoke right now, just for relief?," "How much do you want to smoke right now?," and "How much do you crave a cigarette right now?" Items were presented on a 100-mm visual analogue scale anchored on the left with *not at all* and on the right with *an awful lot*. The first four items of this scale have been shown to be sensitive to smoking abstinence under controlled conditions (Schuh & Stitzer, 1995). The fifth item was added to the scale in the current study to improve reliability. The five items demonstrated very high internal consistency (mean $\alpha = .95$) and were averaged to form a total craving score.

Nicotine withdrawal. Participants rated nicotine withdrawal symptoms on a 4-point scale ranging from 0 (*none*) to 3 (*severe*). A total withdrawal score (Hughes, 1992) was calculated by summing ratings for the following six *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; American Psychiatric Association, 1994) items: depression, irritability, anxiety, difficulty concentrating, restlessness, and increased appetite. The six items demonstrated high internal consistency (mean $\alpha = .85$).

Finally, a cigarette ratings questionnaire was administered one time to assess responses to the initial test cigarette during lapse exposure. Ratings were made on a 100-mm visual analogue scale anchored on the left with *not at all* and on the right with *extremely*. The items were as follows: pleasant, tasted good, harsh, strong, tasted different than my usual brand, enjoyable sensations on lips, enjoyable sensations on throat, smelled good, reduced craving, reduced irritability, dizzy, relaxing, buzzed, nauseous, liked, and stimulating.

Statistical Analytic Strategy

Analysis of variance (ANOVA) was used to compare reactions to nicotine-containing and denicotinized cigarettes after smoking the first lapse cigarette and after all five lapse cigarettes. ANOVA was also used to make postmanipulation comparisons among all three conditions, which were followed up with simple comparison *t* tests. Smoking behavior was tracked for 6 days after the experimental manipulation, and thus the maximum time abstinent was 144 hr, at which point data were censored. We analyzed progressions to self-initiated smoking using Cox regression with the number of hours from the end of the final Day 4 visit to the first instance of self-initiated smoking as the unit of time. We compared abstinence survival rates between the nicotine and denicotinized conditions and between each of the smoking conditions and the no-lapse condition. Because of strong a priori predictions about the direction of the findings, a one-tailed alpha of .05 was used as the significance criterion when the nicotine or denicotinized group was compared with the no-lapse group. A two-tailed alpha of .05 was used as the significance criterion for all other comparisons.

Results

Baseline Data

A series of ANOVAs revealed no differences among the three groups at baseline on expired air carbon monoxide, age, smoking rate, number of years smoked, nicotine dependence, cravings, withdrawal, abstinence confidence, desire to quit, and depression. There were also no significant differences on the above variables between participants who achieved the initial 4 days of required abstinence and those who did not (see Table 1). There were also no differences between groups on any measures during each of the first 4 days of required abstinence.

Manipulation Check Data

As can be seen in Table 2, a number of indicators of smoking exposure suggest that the two types of experimental cigarettes were smoked similarly. For the first lapse cigarette, there were no significant differences between the nicotine and denicotinized conditions in total smoking time, carbon monoxide boost, or cigarette butt weights. The first lapse cigarette produced significantly greater heart rate boost in the nicotine condition relative to the denicotinized condition, confirming that a pharmacological active dose of nicotine was ingested only in the nicotine condition. Verbal reports and objective measures (carbon monoxide and cigarette butt weights) indicated that participants in the nicotine and denicotinized conditions equally complied with instructions to smoke four additional cigarettes in their natural environments. At the end of the manipulation, both conditions produced significantly greater carbon monoxide boost than the no-lapse condition.

Subjective Reactions to the Lapse Manipulation

Subjective reactions to the lapse manipulation are summarized in Table 2. On the cigarette ratings questionnaire, there was a trend for nicotine cigarettes to produce greater reports of dizziness than the denicotinized cigarettes. Denicotinized cigarettes produced significantly greater ratings on "harsh" and "tastes different than usual brand" items. There were no other differences between the two types of cigarettes on the remaining cigarette rating scale items. There was a trend for the first lapse nicotine cigarette to produce greater craving reduction from premanipulation levels than the denicotinized cigarette. However, there was no difference in craving reduction between the cigarette types after all five lapse cigarettes were smoked, with the nicotine and denicotinized cigarettes producing nearly equivalent reductions in craving. Participants in both the nicotine and denicotinized smoking conditions experienced significantly greater craving reduction after smoking the first lapse cigarette and after smoking all five lapse cigarettes compared with participants in the no-lapse condition. There were no differences between the nicotine and denicotinized condition in withdrawal ratings after the first lapse cigarette or after all five cigarettes. After the manipulation, participants in both the nicotine and denicotinized conditions had significantly lower ratings of nicotine withdrawal than those in the no-lapse condition.

There were no differences among the conditions in postmanipulation ratings or pre- to postmanipulation changes in positive or negative affect, guilt, abstinence confidence, or desire to quit.

Table 2
Reactions to the Experimental Manipulation

Variable	Nicotine	Denicotinized	No lapse	Significance
CO boost after first cigarette (ppm)	4.45 (2.31)	4.05 (2.67)	—	(2, 37) *ns*
CO boost after experimental manipulation (ppm)	9.15 (6.67)$_a$	7.20 (4.66)$_a$	−0.40 (1.35)$_b$	$F(2, 37) = 22.42$, $p < .001$
Smoking time (s)	408.65 (96.77)	363.65 (93.31)	—	*ns*
Cigarette butt weights				
First cigarette	0.42 (0.11)	0.44 (0.14)	—	*ns*
Four cigarettes	1.75 (0.48)	1.59 (0.80)	—	*ns*
Heart rate boost (beats per minute)	9.05 (6.09)	1.01 (5.86)	—	$F(1, 38) = 12.68$, $p < .001$
Dizzy (0–100)	54.26 (37.27)	33.95 (31.44)	—	$F(1, 38) = 3.40$, $p = .073$
Harsh (0–100)	32.47 (35.80)	59.10 (36.38)	—	$F(1, 38) = 5.30$, $p = .027$
Tastes different than usual brand (0–100)	68.16 (38.71)	89.05 (21.46)	—	$F(1, 38) = 4.40$, $p = .043$
Craving change				
After first cigarette	−24.22 (32.77)	−8.20 (26.89)	—	$F(1, 38) = 2.77$, $p = .105$
After all five cigarettes	−15.09 (13.28)$_a$	−15.20 (21.93)$_a$	.14 (11.23)$_b$	$F(2, 53) = 5.08$, $p = .010$
Withdrawal ratings				
After first cigarette	3.55 (3.38)	3.44 (3.11)	—	*ns*
After all five cigarettes	3.40 (3.03)$_a$	3.65 (2.91)$_a$	6.70 (4.82)$_b$	$F(2, 59) = 4.95$, $p = .010$

Note. Values are means and standard deviations (in parentheses). A dash indicates that there was no measurement of the variable. Significant overall analyses of variance among the three conditions were followed up with simple comparison *t* tests; dissimilar subscript letters indicate a significant difference between groups at $p < .05$ (two-tailed). There were no significant differences between the nicotine and denicotinized cigarettes on the following visual analogue scale items: pleasant, tasted good, strong, enjoyable sensations on lips, enjoyable sensations on throat, smelled good, reduced craving, reduced irritability, relaxing, buzzed, nauseous, liked, and stimulating. There were no significant postmanipulation differences among the three conditions in positive affect, negative affect, desire to quit, or confidence.
CO = carbon monoxide.

Latency to Smoke

As shown in Figure 1, the percentage of participants abstinent at the end of the 6-day follow-up period was 70% for the no-lapse group, relative to 45% and 40% among those who smoked nicotine-containing and denicotinized cigarettes, respectively. As is shown in Figure 1, when compared with the no-lapse condition, the denicotinized condition produced a significantly more rapid return to smoking (Wald = 4.09, $p = .022$, hazard ratio [HR] = 2.755, 95% confidence interval [CI] = 1.031–7.358), whereas the nicotine condition revealed a strong trend (Wald = 2.08, $p = .075$, HR = 2.081, 95% CI = 0.769–5.634). The effects appear to be substantial as individuals in both the denicotinized and nicotine conditions were more than twice as likely to smoke during the 6-day follow-up period compared with those in the no-lapse con-

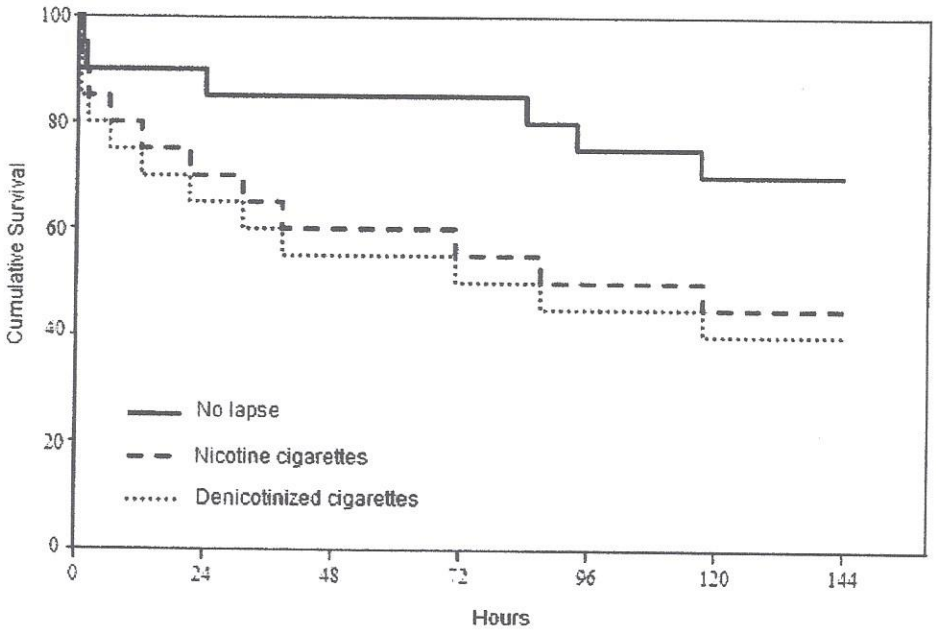

Figure 1. Survival curves showing time (hours) to self-initiated smoking for the three experimental conditions.

dition. Cox regression analysis comparing the nicotine and denicotinized conditions revealed no significant difference in survival distributions (Wald = 0.450, p = .502, HR = 0.756, CI = 0.333–1.714), suggesting that the nicotine content of the cigarettes had no impact on survival probabilities.

Discussion

Using a short-term prospective model of smoking cessation and relapse, we attempted in this study to disentangle critical components of a smoking-lapse episode to better understand lapse mechanisms that drive the motivation for subsequent smoking. To this end, we compared the effects of lapsing with nicotine-containing cigarettes, lapsing with denicotinized cigarettes, or not lapsing on subsequent smoking likelihood. Smoking outcomes did not significantly differ between the nicotine and denicotinized conditions (see Figure 1). Relative to the no-lapse condition, exposure to either of the cigarette types more than doubled the probability of subsequent smoking during the 6-day follow-up, with the denicotinized condition producing a significantly different relapse curve, and the nicotine condition revealing a strong trend (see Figure 1). The current findings are consistent with an earlier study that demonstrated that an experimentally induced smoking lapse with one's own brand of cigarettes after 3 days of abstinence promoted a subsequent return to smoking (Chornock et al., 1992). The data are also consistent with prospective clinical studies showing an association between lapse and relapse (Shiffman et al., 1996) and with drug reinstatement effects that have been widely demonstrated with animal models (Shaham et al., 2003). The first instance of smoking after abstinence appears to play a direct and potentially causal role in the relapse process and has significant detrimental effects on quitting success. However, the lack of difference between the nicotine-containing and denicotinized cigarettes suggests that the acute delivery of nicotine in cigarette smoke may not be a necessary causal factor underlying the lapse to relapse process but rather that other factors such as conditioning and/or expectancies may also play a critical role.

The lack of difference in smoking outcomes between the nicotine and denicotinized conditions may not be that surprising considering that the two cigarette types produced similar effects across various subjective outcomes, including reductions in craving and withdrawal. Previous studies have also reported that nicotine and denicotinized cigarettes produce similar reductions in craving and withdrawal, presumably because of conditioned effects (e.g., Butschky, Bailey, Henningfield, & Pickworth, 1995; Dallery, Houtsmuller, Pickworth, & Stitzer, 2003; Pickworth et al., 1999).

There are a number of possible conceptualizations that could account for the ability of cigarette smoke without nicotine to promote subsequent smoking. First, the stimulus components of denicotinized cigarette smoke or the act of smoking (e.g., puffing, inhaling) may produce conditioned responses because of previously learned associations with nicotine. Regardless of different conceptualizations about the nature of such conditioned reactions (e.g., compensatory, appetitive), they are believed to increase drug-taking motivation. It is also possible that the nonnicotine components of cigarette smoke have direct rewarding effects and that the exposure to such components motivated subsequent smoking. The findings from this study may or may not generalize to a scenario in which a smoker smokes only denicotinized cigarettes prior to quitting (undergoing extinction) and then lapses with a denicotinized cigarette. Future research on reactions to denicotinized cigarettes both in the context of acute administration and extended administration (i.e., sufficient time for possible extinction to occur) may shed light on the mechanisms by which they influence smoking motivation.

It is also possible that the denicotinized cigarettes may have produced frustration because of lack of reward and thus motivated smoking; however, there were no detectable differences across the groups in positive or negative affect. There were also no group differences in guilt, abstinence confidence, or desire to quit. These results may not be surprising given that the lapse was dictated by the experimental protocol and not self-initiated. Negative cognitive and emotional reactions to a lapse (i.e., AVEs) are more likely to have an influence during self-initiated smoking lapses in the natural environment. However, it is notable that, unlike the current study, Chornock et al. (1992) found increased guilt among participants who were assigned to lapse. The inconsistent findings across studies may be due to differences between the studies such as the type of lapse cigarettes (experimental cigarettes vs. own brand) or the incentives provided for abstinence (monetary vs. verbal encouragement).

Latency to self-initiated smoking across the 6-day follow-up period varied from 30 min to 118 hr. For some individuals, the first point of self-initiated smoking occurred as late as Day 5 of the 6-day follow-up period, and thus we were unable to evaluate time to relapse, which would have required a more extended period of observation. Among participants who were classified as relapsed, abstinent days rarely occurred after the first point of self-initiated smoking, and thus the classification appeared valid for these participants. Nevertheless, the limited length of follow-up after the lapse limits to some extent the conclusions that can be drawn about the lapse to relapse process.

The volunteers in this study were not trying to quit smoking permanently, and this characteristic of participants may limit the generality of findings. All participants in the study were aware that the maximum time of abstinence was 10 days and thus may have had different cognitive and/or affective reactions to the experimental manipulation than individuals embarking on a permanent abstinence attempt. Participants who were actively seeking smoking treatment and/or who were planning to quit smoking in the next 30 days were excluded so as not to jeopardize their cessation efforts with a lapse, which we felt would have created an ethical conflict. Rather, monetary incentives were used to increase participants' motivation for abstinence both before and after the experimental manipulation. The abstinence incentives used in the current study were successful in delaying return to smoking relative to Chornock et al.'s (1992) study. In that study, no monetary incentives were used and participants were simply encouraged to remain abstinent after the experimental manipulation. Under those conditions, more than 70% of the participants smoked within 5 hr of the experimental manipulation, and only 9% were abstinent at the end of the 4-day follow-up period. In the current study, only 12% of participants smoked within the first 5 hr of the manipulation, and more than 50% were still abstinent at the end of the 6-day follow-up period. Thus, the use of monetary incentives appears to have increased the sensitivity of the model for detecting experimentally induced lapse exposure effects by prolonging the average latency to relapse (i.e., preventing floor effects). This model, which uses

monetary incentives to motivate abstinence, may prove useful for examining effects of medications and behavioral interventions or for identifying individual differences in relapse propensity. Furthermore, replication of the findings with a sample of smokers with intrinsic motivation to quit would be desirable because this would help to validate the use of what appears to be a sensitive and useful short-term model of cessation and relapse.

Another potential limitation to the generality of findings is that experimental cigarettes were used and lapse effects may differ in the context of smoking one's usual brand of cigarette. Compared with the nicotine cigarettes, the denicotinized cigarettes produced greater ratings of harsh and tastes different than usual brand. Such taste differences could be a function of the absence of nicotine or other distinctive qualities of the denicotinized cigarettes resulting from the process used to eliminate the nicotine. However, participants had no prior exposure to either of the experimental cigarettes used in this study, and both were rated as tasting different than their usual brand. It would be interesting to evaluate the effects of lapsing with one's own brand of cigarettes in the context of the current experimental model. We would predict that own brand cigarettes, by virtue of their more potent conditioning effects, would produce even stronger lapse exposure effects than those observed with nicotine-containing cigarettes in the current study.

Participants had to initially demonstrate 4 days of continuous smoking abstinence to be eligible to participate in the study. This may have created a selection bias in that only those who were capable of abstaining for 4 days were exposed to the experimental manipulation. However, it is encouraging that there were no differences in baseline characteristics between individuals who did and did not achieve abstinence during the first 4 days of the study (see Table 1), suggesting that the participants exposed to the manipulation were not substantively different from the larger body of potential research participants. Furthermore, the elimination of smokers who find it difficult to quit in the first place should result in a relatively conservative assessment of lapse exposure phenomenon (i.e., those eliminated may be even more sensitive to lapse exposure effects).

Part of the experimental manipulation (i.e., smoking four additional cigarettes or remaining abstinent) was not under direct observation of the researchers, nor was smoking behavior during the follow-up period. These design strategies provided a more naturalistic experience for participants and thus increased external validity of the study. However, they limit internal validity to some extent by increasing reliance on self-report data. This is countered to a large extent by the corroboration of self-report with objective measures of smoking abstinence (e.g., carbon monoxide).

Finally, although the effects observed were convincing in magnitude (see Figure 1), the study had limited power to detect statistical differences because of the small sample size. The difference between the nicotine and no-lapse group would have likely reached traditional levels of significance with a larger sample size. A power analysis indicated that we would have achieved statistical significance ($p < .05$, one-tailed) with a sample size of 25 per group given the event rate of 48.3% and HR (effect size) of 2.08.

Additional research is needed to extend the generality of findings reported here. The lapse in this study was scheduled after 4 continuous days of abstinence, because the lapse rate has been shown to be highest in early abstinence (e.g., Shiffman et al., 1997), and early lapse (i.e., within 1–2 weeks of quitting) has been shown to be a strong predictor of relapse (Kenford et al., 1994; Smith et al., 2001). Nevertheless, under naturalistic conditions, the time to first lapse varies widely across individuals. Future research should evaluate lapse exposure effects after other more prolonged periods of abstinence. In the current study, participants smoked five cigarettes as part of the lapse exposure manipulation. Five cigarettes were chosen to increase the salience of the manipulation. However, it would be interesting in future studies to evaluate the effects of a range of smoking reexposure doses to simulate the variability in smoking-lapse doses encountered in the natural environment. In light of the extensive animal literature showing reinstatement of drug-seeking behavior after exposure to stress (Shaham, Erb, & Stewart, 2000) or drug-associated environmental cues (Shaham et al., 2003), it would be of interest to examine the effects on smoking relapse of exposure to these other provocative stimuli.

In summary, this study demonstrated under controlled conditions that smoking lapse has a direct detrimental effect on subsequent abstinence outcomes. The nicotine in cigarette smoke did not appear to play a vital immediate role in the lapse to relapse process. Future studies should continue to evaluate the mechanisms by which cigarette smoke exposure, both with and without nicotine, promotes subsequent smoking relapse. The data especially suggest a need for further examination of nonnicotine components of smoking in lapse to relapse mechanisms. After these mechanisms are better understood, they may aid in development of treatments that can prevent the progression from first lapse to relapse.

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