Developing human laboratory models of smoking lapse behavior for medication screening

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Abstract

Use of human laboratory analogues of smoking behavior can provide an efficient, cost-effective mechanistic evaluation of a medication signal on smoking behavior, with the result of facilitating translational work in medications development. Although a number of human laboratory models exist to investigate various aspects of smoking behavior and nicotine dependence phenomena, none have yet modeled smoking lapse behavior. The first instance of smoking during a quit attempt (i.e. smoking lapse) is highly predictive of relapse and represents an important target for medications development. Focusing on an abstinence outcome is critical for medication screening as the US Food and Drug Administration approval for cessation medications is contingent on demonstrating effects on smoking abstinence. This paper outlines a three-stage process for the development of a smoking lapse model for the purpose of medication screening. The smoking lapse paradigm models two critical features of lapse behavior: the ability to resist the first cigarette and subsequent ad libitum smoking. Within the context of the model, smokers are first exposed to known precipitants of smoking relapse (e.g. nicotine deprivation, alcohol, stress), and then presented their preferred brand of cigarettes. Their ability to resist smoking is then modeled and once smokers ‘give in’ and decide to smoke, they participate in a tobacco self-administration session. Ongoing and completed work developing and validating these models for the purpose of medication screening is discussed.

Keywords

Alcohol; human laboratory models; medication development; nicotine dependence; smoking lapse; stress

INTRODUCTION

Cigarette smoking is the single most preventable cause of morbidity and mortality in the United States, accounting for 440,000 annual deaths (nearly one of every five deaths), and $157 billion in annual health-related economic losses in the United States alone (CDC 2002, 2004). Nicotine dependence, as with other substance use disorders, is a chronic relapsing condition. Although the majority of smokers are motivated to quit smoking (70%), very few successfully quit on a yearly basis (less than 2%; CDC 2002).

Clinical practice guidelines for treating tobacco dependence state that pharmacotherapy is a vital element of a multi-component treatment approach (Fiore et al. 2000). The US Food and Drug Administration (FDA)-approved treatments for smoking cessation attenuate relapse rates (see George & O'Malley 2004 for review), however, there is much room for improvement.
Nicotine-replacement therapies (i.e. patch, gum, lozenge, spray) and bupropion (a monoamine oxidase inhibitor) are generally found to double quit rates by the end of treatment (Fiore et al. 2000; Silagy et al. 2004), but long-term follow-up rates are poor. Although varenicline (a partial nicotinic agonist), the most recently approved FDA medication, has been found to increase the rate of smoking cessation by almost fourfold over placebo by the end of treatment (Jorenby et al. 2006), the majority (70%) will have relapsed within the first year.

Identifying medications that will improve abstinence rates is difficult as the process of relapse to smoking is multiply determined and complex in nature. Factors known to increase the risk of relapse include, but are not limited to: younger age; nicotine dependence; low self-efficacy; weight concerns; previous quit attempts; negative mood; smoking cues; social modeling; cigarette availability; heavy drinking; post-cessation craving; psychiatric status; and withdrawal symptoms (e.g. Shiffman et al. 1996; Killen & Fortman 1997; Ockene et al. 2000; Piasecki et al. 2000).

One way to facilitate medication development for smoking cessation is through the use of human laboratory paradigms. There has been much discussion among the scientific community about the need to develop human laboratory models to provide a bridge between pre-clinical studies and more costly clinical trials. ‘Such investigations can accelerate the search for effective clinical interventions by bridging the gap between analog laboratory studies . . . and large-scale, costly, and time consuming clinical trials’ (Monti 1997; as cited in Monti et al. 1999; p. 1392). Use of human laboratory analogues of smoking behavior can provide an efficient, cost-effective mechanistic evaluation of a medication signal on smoking behavior (see Perkins, Stitzer & Lerman 2006; Lerman et al. 2007 for reviews).

A number of available human laboratory models have been designed to investigate the various aspects of smoking behavior and nicotine-dependence phenomena (see Lerman et al. 2007 for review) including nicotine discrimination (Perkins et al. 1997, 1999), nicotine reinforcement and tolerance (Perkins et al. 2001, 2002), deprivation effects (Hatsukami et al. 1984) and self-administration behavior (Hatsukami et al. 1998; Perkins et al. 1997). Probably the best studied human laboratory paradigm examining smoking behavior is the cue-reactivity paradigm. Based on theories of classical conditioning (Poulos, Hinson & Siegel 1981), motivation (Cox & Klinger 1986), information processing (Tiffany 1990) and dual affect (Baker, Morse & Sherman 1987), researchers have examined psychological and physiological reactivity to stimuli associated with smoking behavior. Stimuli, or cues, are typically drug-specific (e.g. holding a cigarette) or affect-related (e.g. inducing negative affect). Much of this research has focused on assessing craving states arising from the presentation cues (see Carter & Tiffany 1999) for review), however, some research has extended this model to examine indices of smoking behavior (e.g. latency to access a cigarette; Carter & Tiffany 2001). Examining reactivity to specific cues allows for the assessment of the degree to which cues exert stimulus control over drug-use behavior.

Although existing evidence suggests that assessment of cue-reactivity is a useful analogue for drug-use behavior, including relapse situations (Niaura et al. 1989; Rohsenow et al. 1994; Litt, Cooney & Morse 2000), limited work has examined how pharmacological agents alter cue-reactivity (Kranzler & Bauer 1992; Robbins et al. 1992; Hersh, Bauer & Kranzler 1995; Modesto-Lowe et al. 1997; Hutchison et al. 1999; Monti et al. 1999; Rohsenow et al. 2000; Tiffany, Cox & Elash 2000; Shiffman et al. 2003; Fonder et al. 2005). For example, Shiffman et al. (2003) demonstrated that nicotine gum attenuated craving in response to standard smoking cues after 3 days of abstinence. Hutchison et al. (1999) demonstrated that an acute administration of naltrexone (combined with nicotine patch) altered craving response to standard smoking cues in smokers who had been deprived of cigarettes for 9 hours. Although these two examples demonstrated medication effects on craving in smokers, the relationship
to actual smoking behavior is unknown. Failure to assess smoking behavior in cue-reactivity studies has been identified as a limitation of the model's sensitivity in detecting medication effects (Tiffany et al. 2000).

Other researchers have examined a human analogue of reinstatement as a model of relapse (see Bickel & Kelly 1988 for review). The reinstatement model has been commonly used with animals and involves a non-contingent drug presentation after an extinction period, with the typical finding that drug re-exposure reinstates self-administration behavior (de Wit & Stewart 1983). Reinstatement models of smoking relapse have been investigated in humans (Chornock et al. 1992; Juliano et al. 2006). Following three days of abstinence, participants smoked five cigarettes (re-exposure) in their natural environment. Results demonstrated that all re-exposed participants relapsed within 2 days (Chornock et al. 1992). Medication effects have been investigated with reinstatement models. For example, King & Meyer (2000) examined the effect of naltrexone in a human laboratory paradigm designed to resemble the initial period of smoking cessation. After overnight abstinence, participants smoked a single cigarette (to model a lapse episode). Participants were then able to smoke up to four additional cigarettes to model subsequent relapse. Results demonstrated that naltrexone attenuated craving after the first cigarette and reduced the number of cigarettes smoked during the ad-lib period.

In reviewing the available models, an important gap in the literature was identified. None of the human laboratory paradigms had modeled the ability to resist the first cigarette (i.e. a smoking lapse episode). The cue-reactivity models described earlier do not assess smoking behavior. In the reinstatement models, participants are re-exposed at a set time to the drug after a period of abstinence and then subsequent self-administration behavior is examined. However, modeling the first instance of smoking (i.e. smoking lapse) is an important target for medication development. One of the best predictors of relapse is a ‘slip’ or ‘first lapse’ (Marlatt, Curry & Gordon 1988; Brandon et al. 1990; Garvey et al. 1992; Norregaard, Tonnesen & Petersen 1993; Kenford et al. 1994; Nides et al. 1995). Lapses typically occur soon after quitting, and are typically defined as any smoking, even one puff (e.g. Brandon et al. 1990; Shiffman et al. 1996), whereas relapses are defined as a return to regular smoking (e.g. smoking on 7 consecutive days; Hughes et al. 2003). Although lapses are highly predictive of relapse episodes, very little work has examined whether lapses themselves confer increased risk for relapse, or are a marker for other identified predictors of relapse. Factors such as stress, greater nicotine dependence and lower self-efficacy have been identified as facilitating the transition between lapses and relapses (Brandon et al. 1990; Shiffman et al. 1996).

With regard to the strength of the association between lapses and relapses, Shiffman et al. (1996) found that lapses occurred, on average, 5 to 6 days after quitting, and among those that had lapsed 70% had relapsed by the 3-month follow-up appointment. Brandon et al. (1990) examined a subsample of 129 smokers who were able to achieve complete abstinence during a 2-week treatment period. During the follow-up period, 92 (71%) participants had smoked, of which 88% had fully relapsed. In a sample of self-quitters, Garvey et al. (1992) demonstrated that in those who had any smoking in the post-cessation period, 95% returned to regular smoking. Conversely, Westman et al. (1997) found that smokers who maintained abstinence on the quit day were 10 times more likely to be abstinent in the long term. ‘The importance of the first lapse is obvious: it represents a transition from abstinence to smoking’ (Shiffman et al. 1996, p. 366).

On this basis, a human laboratory analogue of early lapse behavior was developed for the purpose of medication screening. The first occurrence of smoking during a cessation attempt is a critical transition, and represents an important target for medication development. However, currently available models examining tobacco-related phenomena have not yet modeled the ability to resist the first cigarette. The smoking lapse model described in the
following section is the only currently available human laboratory paradigm, examining two critical features of lapse behavior; the ability to resist the first cigarette and subsequent smoking. Focusing on an abstinence outcome is critical for medication screening as FDA approval for cessation medications is contingent on demonstrating effects on smoking abstinence.

MODELING SMOKING LAPSE BEHAVIOR

The basic paradigm used to model smoking lapse behavior is presented in Fig. 1. The general procedure is that smokers are first exposed to known precipitants (or primes) of smoking relapse behavior (e.g. nicotine deprivation, alcohol, stress). Following the prime, their preferred brand of cigarettes is placed in front of them with a lighter and an ashtray. Smokers are then instructed that they have the option to initiate a tobacco self-administration session or to delay initiation for up to 50 minutes in exchange for monetary reinforcement. A fixed level of monetary reinforcement is provided for each 5-minute increment that they can resist smoking during the 50-minute delay period. This delay period models their ability to resist smoking. Once participants ‘give in’ and decide to smoke, they then participate in a 60-minute tobacco self-administration session, in which they can choose to smoke their preferred brand of cigarettes or receive monetary reinforcement for cigarettes not smoked.

This model may be conceptualized as an extension of cue-reactivity paradigms. Similar to cue-reactivity paradigms, smokers are first exposed to various primes (i.e. nicotine deprivation, smoking availability, alcohol) that are associated with relapse behavior. However, unlike cue-reactivity paradigms, which typically assess craving as the primary outcome, the primary outcomes are the length of the delay period (i.e. ability to resist smoking), and second, the number of cigarettes smoked during the ad-lib period.

Cigarette availability and the opportunity to smoke are key components of the model. As cigarettes must be available for smoking to occur, it is not surprising that smoking availability is strongly related to lapse and relapse behavior (e.g. Shiffman et al. 1996). Cigarette availability has also been investigated in cue-reactivity studies (see Wertz & Sayette 2001 for review). In general, studies that have manipulated perceived availability of the drug have demonstrated stronger effects on craving (Juliano & Brandon 1998; Dols et al. 2000) and decreased latency to access a cigarette (Carter & Tiffany 2001). This follows from animal learning models demonstrating that approach behavior is strengthened if reinforcement is immediately available (e.g. Grice 1948). Within the context of the model, smokers are presented with standard smoking cues (preferred brand of cigarettes, lighter, ashtray) as they are trying to resist smoking. Smokers are instructed that they have the option to ‘give in’ and smoke at any time during the delay procedure.

The availability of alternative reinforcers is another important component of the smoking lapse model. The incorporation of money as an alternate reinforcer during the delay period and self-administration session was designed to increase the likelihood that the relative reinforcing value of smoking would be detected. The availability of alternative reinforcers can provide a sensitive test of the relative reinforcing value of an abused substance (see Higgins 1997; Rodefer et al. 1997). Within the context of the smoking lapse model, money is provided as an alternative reinforcer in order to provide some incentive for not smoking and to enhance the likelihood that the effects of medications on the relative reinforcing value of smoking will be detected.

THREE STAGES OF DEVELOPING SMOKING LAPSE MODELS

Development of the smoking lapse models occurs in three stages.
Stage 1: developing the model parameters

The goal of the first stage is to develop the parameters of the smoking lapse model such that ‘target model behavior’ is demonstrated.

Target model behavior is defined as delaying for 50% of the delay period (which models ability to resist smoking) and choosing 50% of the cigarette options during the self-administration period. This ‘target model behavior’ will then allow us to examine whether a medication increases or decreases the ability to resist smoking and to examine its effect on subsequent ad-lib smoking behavior in future investigations examining medication effects (see Fig. 2). The aim of this stage is to identify the level of alternative monetary reinforcement necessary to balance out the incentive value to smoke produced by the precipitants of relapse. Thus, to identify which level of monetary reinforcement is necessary so that smokers, on average, delay for approximately half of the delay window (i.e. ~25 minutes). To date, parameters for smoking lapse models incorporating alcohol and nicotine deprivation as precipitants of relapse have been developed. Developing the parameters for a model incorporating stress as the precipitant of relapse is underway.

Modeling alcohol-precipitated smoking lapse behavior—Across several studies using different methodologies, alcohol has been implicated as a risk factor for relapse to tobacco use (Shiffman 1986; Baer & Lichtenstein 1988; Zimmerman et al. 1990; Shiffman et al. 1996). We have completed a study to develop the parameters of the alcohol–smoking lapse model (McKee et al. 2006). This study used a within-subject design enrolling daily smokers who were also heavy social drinkers. Subjects were not seeking treatment for smoking. Subjects received a priming drink (0.03 g/dl or taste-masked placebo) and then had the option of initiating a tobacco self-administration session or delaying initiation by 5-minute increments for up to 50 minutes in exchange for monetary reinforcement. Subsequently, the tobacco self-administration session consisted of a 1-hour period, in which subjects could choose to smoke their preferred brand of cigarettes using a smoking topography system or receive monetary reinforcement for cigarettes not smoked. A schematic overview of the laboratory procedures is provided in Fig. 3. Results demonstrated that after consuming the alcohol beverage, subjects were less able to resist the first cigarette and initiated their smoking sessions sooner, and smoked more cigarettes compared with the placebo beverage. The level of monetary reinforcement provided in the context of this study was $1.00 per 5-minute delay. Thus, subjects could earn up to $10 over the course of the 50-minute window if they were able to resist for the entire delay period. Results demonstrated that the $1.00 reinforcement level produced ‘target model behavior’ for the delay period in that subjects resisted for approximately 50% of the delay window (i.e. approximately 25 minutes; see Fig. 4).

Modeling nicotine deprivation–precipitated smoking lapse behavior—Effects of nicotine deprivation, particularly craving, have been identified as risks factors for relapse to smoking (Brandon, Tiffany & Baker 1987; Baer & Lichtenstein 1988; Doherty et al. 1995; Killen & Fortman 1997; Piasecki et al. 2000, 2003). We have completed a study developing the parameters of the nicotine deprivation–smoking lapse model (McKee et al. unpublished). Using a within-subject design, daily smokers (not seeking treatment) were nicotine deprived for either 0, 6 or 18 hours and then had the option of initiating a tobacco self-administration session or delaying initiation by 5-minute increments for up to 50 minutes in exchange for monetary reinforcement. Three levels of monetary reinforcement were provided ($0.25, $0.50, $1.00) as nested between subject variables. Subsequently, the tobacco self-administration session consisted of a 1-hour period, in which subjects could choose to smoke their preferred brand of cigarettes using a smoking topography system or receive monetary reinforcement for cigarettes not smoked. A schematic overview of the laboratory procedures is presented in Fig. 5. Results demonstrated that lapse behavior varied significantly as a function of both the level
of nicotine deprivation and the level of monetary reinforcement. Increasing levels of nicotine deprivation decreased the ability to resist smoking and facilitated subsequent smoking. For the 6-hour deprivation window, designed to target increases in craving responses, the $0.25 condition (per 5-minute delay) demonstrated target model behavior. The 18-hour deprivation window, designed to target increases in other tobacco withdrawal symptoms including craving, demonstrated target model behavior with a $1.00 level of reinforcement (per 5-minute delay; see Fig. 4).

Modeling stress-precipitated smoking lapse behavior—Stress has been implicated as a primary mechanism in drug relapse, including relapse to smoking. Smokers (35 to 100%) cite stress and associated negative affect states as causal factors in accounts of relapse episodes (O’Connell & Martin 1987; Baer & Lichtenstein 1988; Baer et al. 1989; Borland 1990). Shiffman & Waters (2004) prospectively examined the role of stress in smoking lapse episodes and found that rapid increases in negative affect (triggered by a specific stressor such as an argument) were predictive of smoking lapse episodes. We are currently developing the parameters for a stress-smoking lapse model. Using a within-subject design, smokers are first exposed to either personalized stress imagery (designed to produce rapid increases in negative affect) or neutral-relaxing imagery (see Sinha, Catapano, O’Malley 1999; Sinha et al. 2000). Similar to the paradigms described earlier, we then model their ability to resist smoking and subsequent self-administration behavior. We are currently determining which level of monetary reinforcement to provide following the stress imagery, such that subjects will delay for approximately half of the delay window (i.e. demonstrate target model behavior).

Stage 2: validating the models with known medications
To validate the smoking lapse models, we are in the process of screening known medications with proven efficacy for attenuating the effect of the model’s primes on smoking relapse. Whereas other options for validating these models exist (e.g. assessing predictive validity during an actual quit attempt), screening known medications through the model presents an efficient method of validation that directly bears on the model’s sensitivity to detect medication effects. To test the sensitivity of the alcohol–smoking lapse model, we are currently examining the effect of naltrexone, a long-acting opiate antagonist, as this medication is known to attenuate the reinforcing effects of alcohol. Clinical investigations of naltrexone demonstrate reductions in drinking frequency and heavy drinking in detoxified alcoholics (O’Malley et al. 1992, 1995; Volpicelli et al. 1992, 1997). Laboratory studies have demonstrated that naltrexone reduced craving for alcohol (McCaul et al. 2000), and ad-lib drinking behavior (O’Malley et al. 2002; Drobes et al. 2003). We hypothesize that naltrexone will attenuate the ability of alcohol to prime smoking lapse behavior. For the nicotine deprivation–smoking lapse model, we are currently examining the effect of varenicline and bupropion. For each of these medications, we are using the clinically recommended doses and titration schedules so that smokers are at steady state levels for the laboratory session, mirroring conditions of a ‘quit day’. Given the efficacy of these medications to attenuate withdrawal symptoms (Durcan et al. 2002; Jorenby 2002; Jorenby et al. 2006) and to increase abstinence rates, we expect that the ability to resist smoking within the context of the laboratory paradigm will be increased, relative to smokers receiving placebo.

Stage 3: examining novel agents
The ultimate goal for these models is to facilitate translational work in medication development by providing an intermediary step between pre-clinical studies and clinical trials. Once models have demonstrated their sensitivity with known medications, we plan to extend our investigations to begin screening novel agents with these smoking lapse models. For example, the alcohol–smoking lapse model could be used to screen medications that have shown some efficacy in a general population of smokers, but have not as yet been tested in a sample of
smokers who are drinkers (a population typically excluded from pharmaceutical company trials), or which have promise based on known effects on alcohol consumption.

**Mechanistic evaluations**

In addition to the smoking lapse models being used as translational tools for medication development, these models could be utilized to investigate mechanisms underlying smoking lapse behavior. It would be possible to change the parameters of the model depending on the question of interest. The nature (and combinations) of the primes could be changed (e.g. smoking availability + stress + alcohol) to examine their effect on subsequent lapse behavior. The study samples could be changed to examine group differences in lapse behavior (e.g. light versus heavy smokers, presence versus absence of various clinical syndromes). The laboratory procedures also allow for careful mechanistic evaluations of smoking lapse behavior. In the alcohol smoking lapse model we demonstrated that increased nicotine dependence was associated with reduced ability to resist smoking following alcohol consumption (McKee et al. 2006). This finding suggests that those with greater nicot ine dependence were more reactive to tobacco following alcohol consumption. Within the context of the various smoking lapse models we are currently investigating craving, mood reactivity, cardiovascular reactivity, neuroendocrine levels, neuropeptides and endocannabinoids as possible mechanisms of smoking lapse behavior.

Additionally, the ‘ability to resist’ aspect of the smoking lapse model can be viewed as a laboratory marker of self-control. Recent models of addiction identify self-control mechanisms as critical in driving the compulsive nature of addiction (Jentsch & Taylor 1999; Goldstein & Volkow 2002; Brady & Sinha 2005). Further, there is growing awareness both clinically and scientifically that as addicted individuals are more likely to be impulsive, self-control problems are often exacerbated in high challenge states (Volkow & Li 2004; Kelley, Schiltz & Landry 2005; Sinha 2005). Within the context of the smoking lapse model, exposure to various precipitants of relapse poses a challenge to the subject to exert self-control by resisting the desire to smoke. Using the nicotine deprivation–smoking lapse model, we have found that various measures of state and trait impulsivity were predictive of the ability to resist smoking (Harrison, Coppola, McKee 2008). Finally, it may also be possible to model the ability to resist smoking and to examine the effect of medications on the ability to resist smoking, at the same time using brain-imaging techniques such as functional magnetic resonance imaging. This approach would highlight which brain regions are involved when smokers are actively resisting smoking and may also serve to elucidate possible medication effects.

**SUMMARY AND CONCLUSIONS**

The smoking lapse models described earlier have the potential to facilitate translational work in medication development. Smoking lapse behavior represents a critical transition in a quit attempt, and currently available human laboratory paradigms had not yet modeled the ability to resist smoking. Modeling the ability to resist smoking is important from a medications development perspective as FDA approval for smoking cessation medications is contingent on demonstrating abstinence effects. Further, the smoking lapse models can be viewed as a logical extension of the cue-reactivity paradigm with the flexibility to model the effect of singular or compound cues on smoking lapse behavior. Although developing the models requires careful parametric investigations, across our two developed models we see evidence that known precipitants of relapse (i.e. alcohol, nicotine deprivation) facilitated smoking lapse behavior in a similar manner to what is demonstrated clinically.

Although the smoking lapse model has some identified advantages over other available models, no one model can provide a sufficient test of a medication signal on smoking behavior. To evaluate the potential complexity of a medication effect on cognitive, affective and behavioral...
components of smoking, it is likely that multiple screening models will be required (see Lerman et al. 2007). As the smoking lapse paradigms are currently being validated by examining model behavior to known medications, it will be critical to demonstrate external validity; that medications with known efficacy increase the ability to resist smoking within the context of the smoking lapse model (i.e. varenicline attenuates the ability of nicotine deprivation to facilitate smoking lapse behavior). To be effective, a translational model needs to demonstrate medication effects on markers or predictors of clinical response (Lerman et al. 2007). Modeling smoking lapse behavior holds promise for its potential utility to facilitate translational research in smoking cessation medication development.

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Figure 1.
Schematic of the smoking lapse model

Precipitants of relapse + cigarette availability

Decision to smoke

Ability to resist
Smoking behavior
Figure 2.
Developing the smoking lapse model parameters to demonstrated ‘target model behavior’. Target model behavior is defined as delaying for 50% of the delay period (which models ability to resist smoking) and choosing 50% of the cigarette options during the self-administration period.
*Within-subject design (0.03 g/dl or placebo)*

+0 minutes  +180 minutes  Termination of delay (0 to 50 minutes)  +60 minutes

- Nicotine deprivation
- Last cigarette

- Delay period
  - $1 per 5 min
  - Cigs/lighter/ashtray

- Ad-lib period
  - $1 per 1/2 cigarette
  - Smoking topography

- Priming drink (0.03 g/dl or placebo)

**Figure 3.**
Schematic overview of the procedures for developing the parameters of the alcohol–smoking lapse model
Figure 4.
Monetary reinforcement conditions by primes (alcohol or nicotine deprivation) which demonstrated ‘target model behavior’ for the ability to resist smoking. Target model behavior is defined as delaying for 50% of the delay period (which models ability to resist smoking).
• Within-subject design (0 hour, 6 hour, 18 hour nicotine deprivation)

Figure 5.
Schematic overview of the procedures for developing the parameters of the nicotine deprivation–smoking lapse model