Chapter 8
New Findings on Nicotine Addiction and Treatment

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Introduction

Over the last 10 years, we have witnessed a rapid expansion in both the scientific understanding of tobacco addiction and in the range of pharmacotherapies available for smoking cessation treatment. These recent developments will be reviewed below, emphasizing the link between basic research and the development of new treatments. This link is bidirectional: increased knowledge gained from basic animal and human laboratory research informs the development of new treatments; in addition, however, findings from treatment studies help us test and refine hypotheses about underlying mechanisms. We will consider three main areas of treatment research: (1) pre-cessation administration of therapeutic agents, including nicotine, varenicline, mecamylamine and bupropion; (2) development of nicotine vaccines; and (3) progress towards tailoring cessation treatments based on a smoker's genetic make-up.

Pre-cessation Administration of Pharmacologic Agents

Pre-cessation use of Nicotine Replacement Therapy

Since the advent of nicotine replacement therapy (NRT) in the 1980 s, an assumption has often been made that its main mechanism of action was the alleviation of smoking withdrawal symptoms (e.g., Peters & Morgan, 2002). In that case, it has been a rational strategy to begin NRT upon quitting smoking. However, a different rationale for substitution therapy generally – and NRT specifically – is to attenuate the reinforcing effects of the abused substance, in this case cigarettes (Henningfield & Jasinski, 1988). By using NRT to establish a level of nicotine in the smoker's blood

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(and brain), and continuing smoking for a prescribed period of days or weeks, cigarettes may be less reinforcing (Levin et al., 1994). This reduction of reinforcement may be due to either satiation or tolerance: satiation refers to the reduction in the motivation to obtain additional positive or negative reinforcement from smoking; tolerance refers to the attenuation of the effect of nicotine such as through receptor desensitization (temporary inactivation of nicotinic receptors after continuous exposure to nicotine). Either mechanism will result in a cigarette being less reinforcing if it is smoked when plasma nicotine levels are elevated, as compared to smoking after a period of deprivation.

It is therefore reasonable to hypothesize that administration of NRT during the weeks leading up to a target quit date might present the smoker with many occasions of smoking when reinforcement is attenuated. This in turn may both lessen a smoker's dependence on cigarettes and facilitate cessation. Indeed, several studies have now discovered this to be the case; there is a robust increase in abstinence rates after 2-week pre-cessation treatment with NRT, during which smokers use both NRT and cigarettes concurrently. For example, two published articles have reported a significant enhancement in quit rates after pre-cessation nicotine skin patch administration (Rose, Behm, Westman, & Kukovich, 2006; Schuurmans, Diacon, van Biljon, & Bolliger, 2004). In these studies, pre-quit nicotine patch administration approximately doubled abstinence rates. Moreover, a large-scale (n = 400) replication trial has recently replicated these findings, also finding a doubling in abstinence rates over conventional NRT (Rose, Herskovic, Behm, & Westman, 2007).

A similar trial using pre-cessation nicotine chewing gum also reported a trend for increased abstinence relative to conventional NRT (Herrera, Franco, Herrera, Partidas, Rolando & Fagerstrom, 1995). Although there is not sufficient information to determine whether pre-cessation nicotine chewing gum is as effective as pre-cessation skin patch treatment, an ad lib dosing regimen of nicotine gum might, in theory, not be as effective. The reason is that if subjects alternated between smoking and using gum, nicotine levels just prior to smoking a cigarette might not be adequate to attenuate its reinforcing effects. If on-demand nicotine formulations are used in a pre-cessation context, it will be important to compare ad lib dosing with fixed-time dosing (e.g., once/hr).

An additional line of evidence supporting the rationale behind pre-cessation NRT is the analysis of post-quit date "lapses" during conventional NRT. Smokers often lapse, that is, smoke a cigarette, while on "post-quit" nicotine patch treatment. We would expect that the reinforcing effects of these cigarettes would be reduced relative to placebo patch treatment. Indeed, in some clinical trials evaluating nicotine patch treatment subjective ratings of reward were lower in the active nicotine patch condition (Levin et al., 1994; Rose & Behm, 2004). If extinction of the reinforcing value of cigarettes depends on the number of "nonreinforced trials," one would predict that as the number of lapses increases, NRT should have a greater effect in terms of suppressing the progression to a full-blown relapse. A recent analysis of lapse episodes by Shiffman, Scharf, Shadel, Gwaltney, Dang, Paton, & Clark (2006) supports this conclusion: the odds ratio for success after (post-quit) NRT increased after the first lapse. Although lapses often led to relapse, lapses were

more predictive of relapse in the placebo NRT condition. Thus, NRT may have helped reduce the resumption of smoking by attenuating the reinforcing effects of the cigarettes smoked during lapses (see also Shiffman, Ferguson, & Gwaltney, 2006, for alternative explanations).

This learning-theory analysis might also help explain why not all studies have reported a reduction in the rewarding effects of smoking during NRT. For example, Cardenas, Busto, MacDonald, & Corrigall (2002) found no difference between the subjective rewarding effect of smoking two test cigarettes after wearing active vs. placebo nicotine patches in an acute laboratory study; however, a critical difference between that study and the clinical trials reporting an attenuation of smoking reward by concurrent NRT is that the clinical trials allowed subjects to learn, over time, that cigarette-related sensory cues were less rewarding.

Sensory cues, such as taste, aroma, and airway sensations accompanying inhalation provide much of the immediate rewarding effect of smoking (Rose, 2006; Rose, Westman, Behm, Johnson, & Goldberg, 1999). The rewarding value of these cues may be enhanced by the pharmacologic effects of nicotine, operating through multiple processes. One of these processes does not rely on contingency, or pairing, of cues and nicotine (Palmatier, Matteson, Black, Liu, Caggiula, Craven, & Sved, 2007), and is thus a nonassociative facilitation of reward value by nicotine.

However, in addition to this nonassociative effect, it is likely that, over many years of pairing cigarette cues with nicotine administration, these cues also become conditioned reinforcers through Pavlovian conditioning (Rose & Levin, 1991). Thus, in order to devalue these cues, it may be necessary to present numerous learning trials in which the cues are not reinforced. A clinical trial extending over days or weeks, in which frequent smoking episodes occur during NRT, may thus provide the best opportunity to observe an attenuation of cigarette reward.

The rate of ad lib smoking might also influence whether a reduction in cigarette reward rating occurs during NRT. If smokers reduce their rate of smoking, then each cigarette will be smoked after a longer period of deprivation; this factor would tend to increase reward ratings and could offset the reduction in reward due to NRT. Hence, if rates of smoking decline during NRT but reward ratings remain constant, it does not necessarily mean that NRT had no effect on reward. An effective procedure for revealing the effect of NRT on cigarette reward might be to pace smoking behavior; by maintaining a constant rate of smoking, the diminished rewarding effects of each cigarette might be more clearly shown without being offset by a possible increase in cigarette deprivation resulting from cigarettes being spaced farther apart.

It is somewhat surprising that only 2 weeks, and possibly less time, is needed to have a discernible impact on ratings of cigarette reward, given that the behavior of smoking has years of previous conditioning. However, this may be an example of the "overtraining extinction effect" (Ishida & Papini, 2007), analogous to the "overtraining reversal effect" (Orona, Foster, Lambert, & Gabriel, 1982; Valles, Rocha, & Nation, 2006), according to which overlearning can in some situations facilitate subsequent extinction. One explanation for this effect is that extended training results in such a strong and specific expectation of reinforcement that it

is especially surprising when reinforcement does not occur. This increased salience of omitted reinforcement may promote more rapid extinction.

Another factor that bodes well for a smoking cessation therapy based on extinguishing the rewarding properties of cigarettes is that, unlike laboratory-based cue-extinction approaches, extinction will take place in the diverse contexts of a smoker's life. Thus, there is less likelihood of the "renewal effect" (Bouton & Swartzentruber, 1991), according to which extinction disappears and the previously reinforced response returns when the context in which extinction occurs is changed.

In a complementary approach to pre-cessation NRT, nicotine reinforcement of smoking can also be reduced using denicotinized cigarettes. Denicotinized cigarettes have been shown to promote extinction of smoking behavior (Donny, Houtsmuller, & Stitzer, 2007; Rose & Behm, 2004), and in principle these cigarettes can be used with or without concurrent NRT. However, in one published study, concurrent NRT enhanced compliance with use of denicotinized cigarettes; subjects reported smoking significantly fewer nicotine containing cigarettes in the active NRT condition (Rose, Behm et al, 2006). Possibly NRT prevented nicotine withdrawal symptoms that might otherwise have driven subjects to smoke nicotine containing cigarettes; alternatively, the attenuation of the rewarding effects of nicotine cigarettes by NRT reduced the temptation to smoke them instead of the denicotinized cigarettes. In any case, use of denicotinized cigarettes in conjunction with NRT during the weeks leading up to a quit date provides a compelling approach. Nicotine delivery is dissociated from the act of smoking in two ways: first, smoking denicotinized cigarettes is not reinforced by nicotine delivery; and second, nicotine is provided at times when smoking does not occur. Although it may be argued that the continuous delivery of nicotine from a skin patch does at times accompany cigarettes, nonetheless the behavioral contingency is broken between the act of smoking and nicotine delivery: the nicotine level in the bloodstream (and brain) is not changed from pre- to post-smoking.

The use of denicotinized cigarettes during pre-cessation NRT has another potential advantage in terms of allaying concerns about receiving excessive nicotine from cigarettes in addition to receiving nicotine from a skin patch. Although studies have not found any acute danger associated with smoking cigarettes while wearing nicotine patches, concerns nevertheless remain in the minds of many smokers and clinicians alike. These concerns would likely be reduced if denicotinized cigarettes were used during pre-cessation nicotine patch treatment. Further clinical trials will be needed to evaluate the potential efficacy of this approach.

The discussion thus far has assumed that the relevant association to be broken is the association between the act of smoking and receipt of nicotine reinforcement. However, one should also consider the role of other learned associations. For example, there is an association between environmental cues and the act of smoking; this association may be weakened as subjects smoke fewer cigarettes per day leading up to the target quit date. In fact, in studies we have conducted thus far, the reduction in cigarettes per day and craving during the 2 weeks of pre-cessation NRT were better predictors of subsequent smoking abstinence than was the reduction in ratings of the subjective rewarding properties of cigarettes (unpublished data). However, it

is likely that an attenuation of reward leads to reduced smoking; as discussed above, if smokers space cigarettes farther apart, the rewarding effects of smoking may be maintained because each cigarette will be smoked after a greater degree of deprivation than when smoking occurs at the usual rate. Nonetheless, the reduced nicotine reward initially obtained from smoking while receiving NRT may be important in leading to a reduced frequency of smoking, and ultimately to a weakening of the association between environmental stimuli and smoking behavior.

It may be difficult in practice to disentangle the effects of weakening the association between external environmental cues and smoking behavior from the effects of weakening the association between smoking and obtaining a rewarding effect. As mentioned above, studies controlling the frequency of smoking during the pre-quit NRT treatment might be informative. If the frequency of smoking is held constant (e.g., by appropriate instructions), then one could test the hypothesis that the therapeutic effect of pre-cessation NRT depends on weakening the stimulus–response association between environmental cues and smoking behavior. According to this hypothesis, one would predict that no enhancement in quit rates will be observed if the rate of smoking is maintained at baseline levels. In contrast, if breaking the association between smoking behavior and obtaining a rewarding effect from nicotine is the critical element in enhancing quit rates, then the usual therapeutic effect should be obtained even when rates of smoking leading up to the target quit date are held constant. The therapeutic effect of pre-cessation NRT might actually be enhanced because the number of "extinction" trials would be greater than when subjects decrease their smoking rates during the pre-cessation period.

Varenicline

Cigarette reward may be attenuated not only by administering nicotine itself prior to a quit-smoking date, but also by administration of other nicotinic agents. One such agent is varenicline, a nicotinic receptor partial agonist. Varenicline activates – but also blocks – nicotinic receptors of the $\alpha 4\beta 2$ subtype (Coe et al., 2005), and in addition it may act on other subtypes of nicotinic receptors (Mihalak, Carroll, & Luetje, 2006). Varenicline has received FDA approval as a smoking cessation pharmacotherapy; treatment guidelines recommend initiating treatment 1 week before a target quit date (Lam & Patel, 2007). Although the usual rationale provided is that this period is required to attain therapeutic blood levels of varenicline, the discussion in the previous section suggests that it may be important for the patient to experience an attenuation of the rewarding effects of cigarettes for some time while on varenicline treatment. Whether quit rates could be further improved by prolonging the pre-cessation treatment period beyond 1 week has not been determined.

It is also not yet known how varenicline treatment would compare with NRT when NRT is initiated before the target quit-smoking date. The odds ratio of success for varenicline relative to placebo is approximately 4:1 (Oncken et al., 2006), which is similar to the estimated effect of pre-cessation NRT (abstinence rates twice that of conventional NRT, which in turn doubles abstinence rates relative to placebo).

Unfortunately, a clinical trial directly comparing varenicline and pre-cessation NRT would be very costly, potentially requiring well over a thousand participants to achieve adequate statistical power to detect what may be a small difference in efficacy.

Pre-cessation Mecamylamine Treatment

Might there be other strategies for clearly augmenting success rates beyond pre-cessation NRT? We think there is such a strategy: administering a nicotinic receptor antagonist concurrently with NRT. In a large-scale Phase III clinical trial, the nicotinic receptor antagonist mecamylamine, used in combination with pre-cessation NRT, was found to be more efficacious than pre-cessation NRT alone (Rose, 2006). It may be noted that not all trials have been sufficiently powered to detect the modest increment in abstinence rates obtained when mecamylamine is added to pre-quit NRT (Glover et al., 2007). However, given that the comparison condition of pre-cessation (plus post-cessation) NRT is possibly twice as effective as standard NRT, it is significant that combined pre-cessation nicotine + pre-cessation mecamylamine treatment surpassed this highly active "control" condition.

Pre-cessation Bupropion Treatment

Bupropion is another approved smoking cessation treatment, and like varenicline, it is recommended that treatment be initiated at least 1 week before the target quit date (Martinez-Raga, Keaney, Sutherland, Perez-Galvez, & Strang, 2003). Again, the rationale often given is that this period is needed to achieve therapeutic drug levels. However, a behavioral extinction effect may also be operative, whereby bupropion could attenuate nicotine reinforcement. This attenuation of nicotine reinforcement might result from two mechanisms (Damaj et al., 2004): first, bupropion has been shown to block nicotinic receptors, and thus its effects might to some extent resemble those of varenicline or mecamylamine; second, bupropion has dopaminergic and possibly noradrenergic stimulant effects that could substitute for the psychological stimulant or reward-enhancing effect (Mays et al., 2007) that is sought by some smokers, thereby inducing partial satiation. The role of extinction in pre-cessation bupropion treatment could be evaluated by studies that vary the duration of pre-cessation treatment or the number of cigarettes smoked during this period.

Nicotine Vaccine

We turn now to nicotine vaccines, which several companies are attempting to develop as smoking cessation treatments. The idea behind a nicotine vaccine is simple: if nicotine can be intercepted before reaching the brain, its reinforcing

effects should be attenuated. This, in turn, should facilitate smoking cessation, analogous to the treatments discussed above for reducing nicotine reinforcement. Nicotine is not an antigen; by itself it is not thought to elicit an antibody reaction; however, by conjugating nicotine with various molecules that are recognized by the immune system as "foreign," an antibody response can be elicited (LeSage et al., 2006).

Although the strategy behind a nicotine vaccine appears straightforward, one puzzle is that the amount of antibody likely to be present in the blood stream is relatively small compared to the dose of nicotine inhaled from a cigarette. That is, animal studies have reported an antibody concentration on the order of 1 μM (Heading, 2007). In a human smoker, this antibody concentration, assuming a plasma volume of 2.75 l, is only sufficient to bind approximately 445 μg nicotine, less than the dose delivered in five puffs of a typical cigarette. It is puzzling that a nicotine antibody in such concentrations would be effective, for if an antibody has extremely high affinity for nicotine (e.g., an equilibrium binding constant of less than 50 nM), then the antibody would quickly become saturated with nicotine from the first few puffs of smoke. In that case nicotine inhaled from subsequent puffs of cigarette smoke will simply "bypass" the saturated antibody and reach the brain just as quickly as it would without vaccination.

A possible resolution to this puzzle is that nicotine antibodies might have only moderate affinity for nicotine, thereby avoiding saturation of antibody binding sites. In this case, the nicotine in arterial blood will partition between an antibody-bound and an unbound (free) fraction. The reduction in free nicotine concentration will reduce the rate at which nicotine crosses the blood–brain barrier. Then, as the nicotine bound to the antibody dissociates and slowly enters the brain, antibody molecules will be freed up to bind to additional nicotine; the same process could be repeated for each puff (or cigarette). Ultimately, significant amounts of nicotine may reach the brain; however, by reducing the rate with which nicotine enters the brain, reinforcement for smoking may be attenuated.

The feasibility of nicotine vaccines has been supported in Phase II clinical trials (e.g., Hatsukami et al., 2005). In addition, the rationale is indirectly supported by recent studies of the kinetics of nicotine inhaled into the lungs. In a recent study of lung-to-brain nicotine in our laboratory, the radiotracer C-11 nicotine was added to the tobacco of a cigarette. After inhalation of a single puff of smoke, the radioactive tracer was detected in the lung, and subsequently in the brain. We found that brain nicotine levels peaked approximately 1–2 minutes after inhalation (Rose et al., 2006) – much longer than the 7-seconds frequently quoted based on early speculations (Russell & Feyerabend, 1978). The reason for this delay is that nicotine distributes into lung tissue and some time is required for it to be eliminated into the bloodstream (Brewer, Roberts, & Rowell, 2004; Rose, Lokitz et al., 2006). The slower-than-expected kinetics is good news for the potential efficacy of nicotine vaccines, because it allows more time for the vaccine to bind a portion of the nicotine before it reaches the brain. Indeed, perhaps individual differences in lung retention of nicotine could be used to predict which smokers will respond favorably to vaccine therapy. Future research is needed to evaluate this possibility.

Tailoring Smoking Cessation Treatment Based on Genetics

It has been known for some time that quit-smoking success has a substantial heritable component, on the order of 50% (Xian, Scherrer, Madden, Lyons, Tsuang, True, & Eisen, 2003). However, until now the specific genetic underpinnings of this component have not been identified. Recently, a genome-wide association study has identified genetic variants associated with quit-smoking success. In this study, conducted as a collaboration between our research center and the laboratory of Dr. George Uhl at the National Institute on Drug Abuse (NIDA), many genes were found to contribute to quitting outcome (Uhl, Liu, Drgon, Johnson, Walther, & Rose, 2007). Each gene had a small influence, but cumulatively accounted for a substantial fraction of the variance in clinical outcome.

This genetic information can be applied to both research and treatment settings. In clinical research, using genotype as a covariate in clinical trials will increase the power to detect the effects of pharmacotherapy or other treatments. In clinical practice, genetic information might have the following applications: (1) more intensive treatment can be given to smokers who have a high genetic liability for relapse; (2) treatment can be tailored further by ascertaining which smokers are likely to respond more favorably to specific treatments such as NRT, varenicline or bupropion. Some preliminary findings in this regard have been reported using a candidate gene approach (Lerman et al., 2006), and genome-wide information should prove even more useful; and (3) information about the protein products of the genes identified may lead to novel interventions. For example, several genes identified as predictors of quitting outcome involved cell adhesion molecules (e.g., cadherin 13) that may be involved in synapse formation and memory-like processes (Uhl et al., 2007). This finding is in accord with the view that cigarette addiction involves learning and memory processes such as reinforcement of cues and behavior; quitting smoking involves cue extinction, a form of learning, and also involves learning new behaviors and coping techniques to substitute for smoking. Additional targets for smoking cessation treatment development will hopefully be identified from a better understanding of these genetic mechanisms.

Conclusion

We have reviewed several recent innovative smoking treatment approaches and the potential mechanisms underlying their efficacy. We have seen that learning theory, receptor mechanisms, pharmacokinetics, and genetic influences all have demonstrable implications for treatment development. If the next 10 years of research prove as fruitful as the previous ones, we can anticipate a growing armamentarium of ever more successful treatments to combat cigarette addiction.

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